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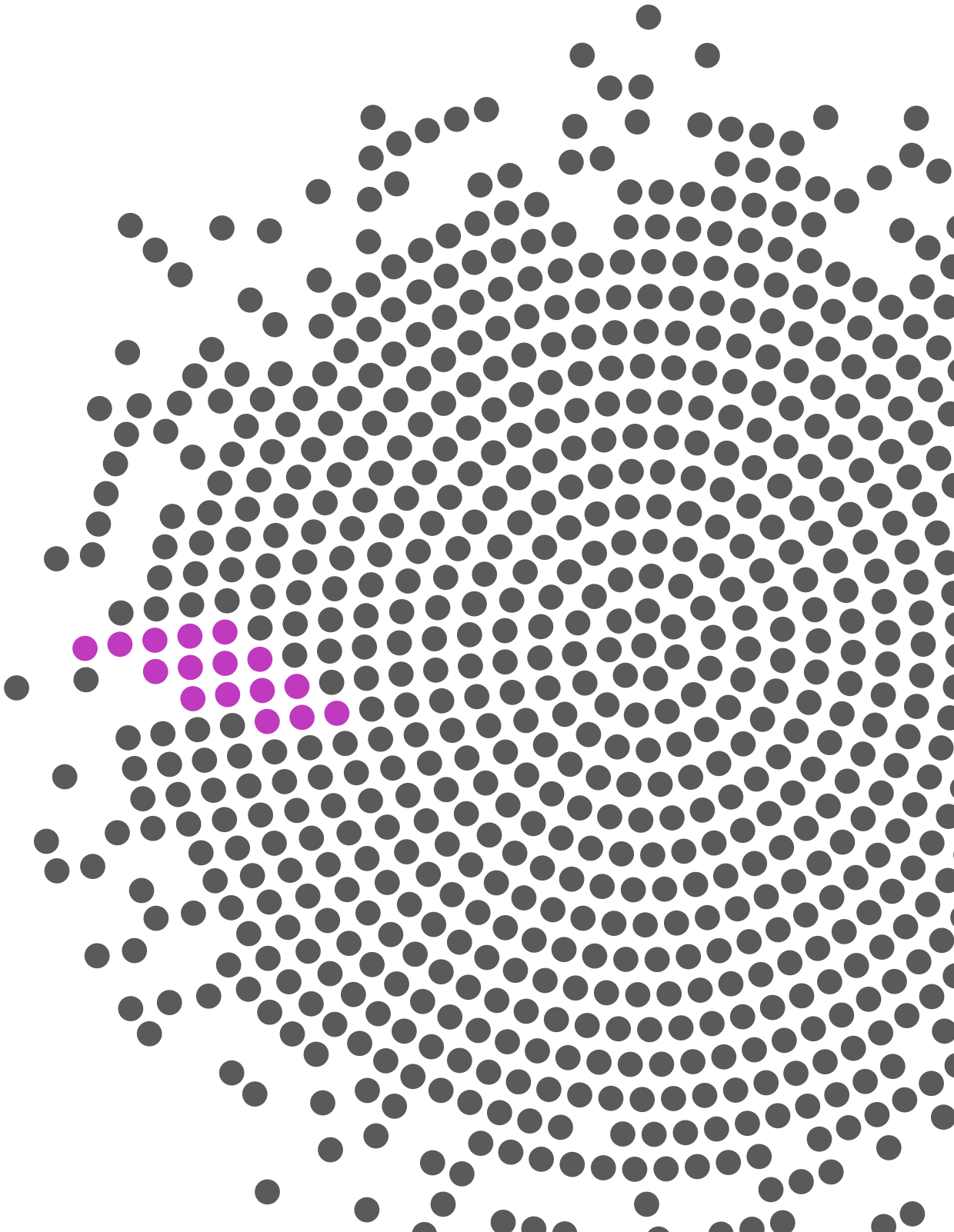

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Overcome the invisible – new treatment opportunities for triple negative breast cancer

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ABSTRACT

Breast cancer is considered a disease of civilization. It is diagnosed in approximately 1.7 million women each year, and more than 500,000 people die. Among the diagnosed neoplasms, 15-20% are TNBC (triple negative breast cancer) characterized by weak expression of estrogen and progesterone receptors and overexpression of the human epidermal growth factor 2 receptor. TNBC is a very heterogeneous group cancers. TNBCs are considered aggressive as they are usually diagnosed at higher stages, often appear in younger patients, and develop faster than some other breast cancers. Moreover, when these tumors do not respond to chemotherapy in the early stages, they have a great tendency to spread to other parts of the body. The aim of the study is to present data on the modern application of immunotherapy in the treatment of patients with triple negative breast cancer. The topics of effectiveness and the mechanism of action were discussed. The latest scientific reports have been taken into account.

Inhibition of ICI (immune checkpoint) is a new and effective method of treatment in several types of solid tumors. Unfortunately, for TNBC, the use of monotherapy targeting PD-1, PD-L1 or CTLA-4 showed little effect. Still many types of immunotherapy are questionable as to their effectiveness. However, in 2019 The Food and Drug Administration (FDA) has approved the use of atezolizumab in combination with the protein – paclitaxel in the treatment of adult patients with inoperable, locally advanced TNBC. Results from a multicentre randomized trial of 902 patients showed a higher median PFS (progressive-free survival) in patients receiving atezolizumab with paclitaxel. The PFS was 7.4 months in patients receiving atezolizumab plus paclitaxel protein-bound and 4.8 months in patients receiving placebo plus paclitaxel protein. ORR (objective response rate) was 53% and 33%, respectively. Unfortunately, in the 2022, a case report was reported describing the adverse reaction of sarcoidosis caused by atezolizumab in a patient with metastatic breast cancer. It turns out, therefore, that while immunotherapy is a hope for TNBC patients, it is not free from undesirable side effects.

The work is of a review character. A review of the scientific literature was made using the PubMed NCBI database and other sources and materials related to the topic of the work.

Keywords: TNBC, breast cancer, immunotherapy

THE AIM OF THE STUDY

The aim of the study is to present new possibilities of treating triple negative breast cancer (TNBC). This type of cancer is discussed in this paper. Issues such as TNBC immunotherapy, immune checkpoint inhibitors (ICI), the use of combined therapy with atezolimumab with paclitaxel or the case of adverse reaction after atezolimumab were also addressed. The targets of TNBC immunotherapy have been given particular attention. The knowledge of immuno-oncology may translate into the development of effective and relatively safe therapies for patients.

The aim of the study is to present new treatment options for triple-negative breast cancer (TNBC). This type of cancer is discussed in this article. Issues such as TNBC immunotherapy, immune checkpoint inhibitors (ICI), the use of therapy with atezolimumab in combination with paclitaxel, or an adverse events after atezolimumab were also discussed. Particular attention has been paid to the goals of TNBC immunotherapy. Knowledge of immuno-oncology may translate into the development of effective and relatively safe therapies for patients.

METHODOLOGY

The review of the scientific literature was carried out using the PubMed NCBI database (National Center of Biotechnological Information) and other sources and materials related to the topic of work, directly or indirectly. The search in the PubMed NCBI database was carried out by entering phrases such as TNBC, Cancer ICI, ICI TNBC, Atezolizumab and Nab-Paclitaxel, hypoxic tumor, cd73 tnbc, cancer lncRNA, microsatellite instability, YAP signaling PD-L1, Wnt singaling cancer, miR-135, PD-1 (AND) TNBC, CTLA-4 (AND) TNBC, next generation immune modulatory (AND) TNBC, TNBC. The date of publication restriction was applied during the search – papers published in the last 10 years were preferentially selected.

BREAST CANCER

The brest cancer is the most common malignant neoplasm in women (about 15% of cancer cases and 15% of cancer deaths worldwide). In the world, including Poland, mortality from breast cancer is decreasing , which is related to the improvement of diagnostic techniques and treatment methods.

In the initial stage, breast cancer is asymptomatic, and the most common visible symptom is a single tumor, which is homogeneous, squamous and not sharply demarcated from other tissues. Imaging techniques such as mammography, ultrasound and magnetic resonance imaging are used in diagnostics. Among the microscopic techniques, there are histopathological and cytological examinations. According to the World Health Organization, there are infiltrating and non-infiltrating tumors. The former, in turn, are divided into infiltrating without a type specification (NST, without a special type), formerly ductal, lobular and special forms. The latter are divided into lobular in situ and intraductal (ductal in situ) (Jassem, 2019).

It is estimated that breast cancer is diagnosed in approximately 12% of women in the United States. In 2017, 25,000 cases of breast cancer were diagnosed in the US. There are 3 main types of breast cancer: hormone receptor positive/ ERBB2 negative (70% of patients), ERBB2 positive (15-20%), and triple-negative (15%). The latter has the worst prognosis of all types of breast cancer. It does not have standard molecular markers.

Median survival for metastatic TNBC is approximately 1 year. For comparison, for the other two subtypes of breast cancer it is 5 years (Waks, 2019).

In recent years, new drugs have been developed that are molecules that antagonize the immune checkpoints, including CTLA-4 (cytotoxic T cell antigen 4), PD-1 (programmed death receptor 1) or PD-L1 (programmed death ligand 1). They significantly influenced the effectiveness of the treatment of many cancers. Recently, they have been used in the treatment of breast cancer (Emens, 2018).

It turns out that the response of TNBC patients to the use of these drugs may be positive and long-term, and the application of this therapeutic strategy is one of the new potential therapeutic solutions. This topic will be discussed in the following sections of this chapter.

TNBC

TNBC accounts for approximately 15-20% of breast cancers. This neoplasm is characterized by an unfavorable clinical course and a poor prognosis. Histologically, such a neoplasm is characterized by a lack of steroid receptors (estrogen and progesterone) and an overexpression of the human epidermal factor type 2 receptor (HER-2). The presence of receptors is tested by immunohistochemical methods using fluorescence in situ hybridization (FISH). Treatment usually includes surgery and chemotherapy as systemic treatment. The problem is, among others however, there are no known specific treatment targets for TNBC. However, efforts are still being made to find targeted therapy (Ryś-Brynarska, 2021).

Among others, poly-ADP-ribose polymerase (PARP), which can bring positive medical results, is increasingly used. Translating research to the clinic is difficult, for example due to the fact that TNBC is a molecularly diverse tumor (differences between the outside and inside of the tumor) (Vagia, 2020).

TNBC is a cancer with a high relapse rate. This is especially true for the first 3 years. The risk of relapse drops sharply after 5 years. The cells of this tumor are characterized by rapid proliferation. An example of a new immunotherapy-based treatment is is the combination of atezolimumab and nab-paclitaxel approved by the Food and Drug Administration (FDA) (Singh, 2021).

IMMUNOTHERAPY IN TNBC

Specifically, TNBC immunotherapy targets include PD-1/ PD-L1 Axis, CTLA-4, and Dual Checkpoint Inhibition, as well as next-generation immunomodulatory targets. The breakthrough in the treatment of melanoma has contributed to the development of immunotherapy in this type of cancer. It is difficult to find specific treatment goals in TNBC, which is why immunotherapy seems to be a good idea (Mediratta, 2021).

PD–1/PD-L1 AXIS

The interaction between programmed death ligand 1 (PD-L1) with programmed death-1 receptor (PD-1) is necessary to escape the host immune system. High PD-L1 expression is a predictor of poor prognosis, although positive PD-L1 tumors respond better to treatment with immune checkpoint inhibitors. In TNBC, 50% of tumors are characterized by lymphocyte infiltration in the tumor core or stroma. Such a histological structure indicates a better prognosis and a better response to treatment (Majidpoor, 2021).

Quin et al. checked whether TNBC has a higher PD-L1 expression than other breast cancer subtypes. PD-L1 expression was shown by 61.5% of TNBC tumors and 18.6% of non-TNBC cancer subtypes. Thus, TNBC has been shown to have higher PD-L1 expression. Additionally, TNBC tumors larger than 20 mm showed higher PD-L1 expression. Researchers also found nucleophosmin (NPM1) specifically binds to the PD-L1 promoter in TNBC cells and activates transcription of the PD-L1 gene and thus inhibits T-cell activity. Study results indicated that NPM1 is a regulator of PD-L1 transcription in TNBC. This may positively translate into the development of new strategies to increase the effectiveness of TNBC immunotherapy. In addition, the study also showed that PARP1 inhibits PD-L1 transcription by binding to the NPM1 nucleic acid binding domain of the PD-L1 promoter. Olaparib, a PARP inhibitor, increases PD-L1 expression in TNBC, which is important for better efficacy of anti-PD-L1 therapy (Qin, 2020).

Kong et al. identified the cell surface CD44 receptor as a key regulator of PD-L1 expression in TNBC and in non-small cell lung cancer. CD44 activated PD-L1 transcription with the involvement of i.a. cleaved intracytoplasmic domain. Research results indicate that CD44 may be a new therapeutic target useful in suppressing the intrinsic function of PD-L1 tumor (Kong, 2020).

CTLA-4 AND DUAL CHECKPOINT INHIBITION

It turns out that there are complementary mechanisms of TNBC's double checkpoint blockade. According to the study results, the combination of anti-PD1 and anti-CTLA4 significantly increased the effectiveness of both therapies. This probably has to do with the fact that anti-CTLA4 increases the expansion of the T-cell receptor (TCR). This combination also activates a daptive anti-tumor immunity in triple-negative breast tumors (Singh, 2021).

NEXT GENERATION IMMUNE MODULATORY DRUGS

The use of immune checkpoint inhibitors is beneficial, but not for all patients. It is important to identify a group of patients in whom such treatment may be the most effective. Wu et al. conducted an analysis the results of which indicate the potential use of a combination of information on CD8, PD-L1 expression and somatic mutations to make decisions about clinical management and treatment (Wu, 2022).

In a study by Ahn et al. TNBC-positive PDL1 tumors were found to be characterized by lymphocytic infiltration. These tumors have relatively good survival rate. This is state on the basis of SP142 test. In the SP142 test, PD-L1 positive tumors also showed the presence of greater numer of CD8 + T cells. The relapse-free survival rate was also higher for the PD-L1 positive tumor (Ahn, 2021).

Not only immunotherapy based on PD1-PDL1 axis blockade may bring therapeutic benefits. Much preliminary research on other immunotherapies has shown promising results. Potential solutions may also be related to the agonism of costimulatory molecules, the interstitial administration of immunotherapy or anti-cancer vaccines. It also seems important to conduct further research on subsequent checkpoint inhibitors. Knowing for which patients which type of immunotherapy will benefit treatment may be useful, therefore it is important to identify and test immunological biomarkers (Tarantino, 2022).

INHIBITION ICI

Immunity checkpoints are part of the regulation of immune system function that protects healthy cells from damage. The mechanism of the action of immune checkpoints is based on the presence of specific proteins on the surface of cells that can be recognized by T cells, thereby suppressing the immune response by these cells. Immune checkpoint inhibitors (ICIs) block these proteins, allowing T cells to kill cancer cells (https://www.cancer.gov/about-cancer/treatment/

types/immunotherapy/checkpoint-inhibitors).

ICI can be used to treat TNBC. One possible treatment option is based on the use of anti-PD-1 or anti-PD-L1 monoclonal antibodies. The tumor-infiltrated lymphocytes express the PD-1 receptor and the tumor cells express the PD-L1 programmed death ligand. This interaction is known as the immune checkpoint. This immune checkpoint is blocked by the antibodies indicated above, which promotes anti-tumor immunity (Lipson, 2015). Pembrolizumab and Atezolizumab, respectively, are examples of investigated and tested antibodies to molecules involved in suppressing the anti-tumor T cell response by a mechanism involving immune checkpoints. (A Study of Atezolizumab (an Engineered Anti-Programmed Death-Ligand 1 [PDL1] Antibody) to Evaluate Safety, Tolerability and Pharmacokinetics in Participants With Locally Advanced or Metastatic Solid Tumors; Study of Pembrolizumab (MK-3475) Monotherapy for Metastatic Triple-Negative Breast Cancer). Only a small part of the patient population benefited from monotherapy with anti-PD-1 / anti-PD-L1 antibodies and such treatment did not bring better outcomes than chemotherapy (Vonderheide, 2017). Additionally, it was observed that such treatment caused a neuro-toxic effect (Vilariño, 2020). The cytotoxic T-cell protein 4 (CTLA-4) is another well-researched mechanism of ICI that can be used in the treatment of TNBC. It is a receptor expressed on Treg lymphocytes and elevated on the surface of Th and Tc lymphocytes, which inhibits the activity of potential autoreactive T lymphocytes (Krummey, 2020). Anti-CTLA-4 antibodies have the same effect as anti-PD-L1 / PD-1 antibodies in that they allow T cells to remain active and exhibit anti-tumor activity. Unfortunately, anti-CTLA-4 monotherapy and the combination of both methods did not have a beneficial therapeutic effect and increased the likelihood of autoimmune diseases (Liu, 2020). While these techniques on their own have not been effective enough, they are nevertheless quite promising.

Research is exploring the possibility of combining ICI monotherapy with other antibo-dies, such as anti-OX40 and chemoterapeutic drugs, for better outcomes. The effectiveness of ICI treatment may be influenced by various factors, such as: tumor dysregulated vascularization, expression of interleukin-8 and CXCR1 / CXCR2, CD73, long non-coding RNA (IncRNA), microsatellite instability (MSI), WNT and YAP signaling pathways, nanoparticle platforms (Mediratta, 2021).

DYSREGULATED TUMOR VASCULATURE

Over time, tumor cells can become extremely hypoxic and endothelial cells may migrate to the tumor core due to increased expression of the angiogenic growth factor. All this inhibits drug entry, lowers T cell activation, and increases PD-L1 expression through INFγ (Schmittnaegel, 2017; Kammertoens, 2017). Combining ICI with anti-angiogenesis therapy may improve the treatment of TNBC. One of the options available is to use a certain class of peptides, for example AXT201. It inhibits VEGF, HGF, IGF1 and some studies indicate that it contributes to the decrease in the number of cells expressing PD-L1 and may also inhibit the pro-angiogenic effect of INFγ (Mirando, 2020).

Additionally, the state of hypoxia can be reversed with the use of oxygen microcapsules, which, in combination with anti-PD-1 antibodies, may increase infiltration of CD45+ cells in the tumor microenvironment (Wu, 2022).

INTERLEUKIN-8 AND CXCR1/CXCR2

Both of them have been shown to be overexpressed in numerous malignant neoplasms, including breast cancer (Cheng, 2019) They bind, changing the status from epithelial to mesenchymal, which promotes migration, invasion, and the regrowth of secondary tumors (Fernando, 2011) The use of IL-8 inhibitors and antibodies anti-CXRC2 may exert anti-tumor activity. Additionally, IL-8 can be used as a biomarker of the benefits of ICI therapy (Sanmamed, 2017).

CD73 EXPRESSION

CD73 converts extracellular AMP to adenosine, which prevents an excessive immune response. CD73 expression is induced in tumors, which contributes to the production of adenosine excess, that inhibits effector T cells by binding to A2A receptors (Sciarra, 2019). In TNBC, adenosine may protect cancer cells from an anti-tumor response and promote cell migration and invasion. Additionally, inhibition of CD73 through APCP reduces cell migration and the EMT proces (Petruk, 2021; Takedachi, 2008). Treatment with a combination of anti-CD73 and anti-PD-1 antibodies shows encouraging results [32].

LONG NON-CODING RNAS

Numerous studies have shown that lncRNAs contribute to resistance to cancer treatment. Additionally, one of the classes of lncRNA – circular RNAs, can act as miRNAs sponges. Multiple circRNA have been identified in TNBC that increase proliferation rates (circGFRA1) and promote epithelial-to-mesenchymal transition (circANKS1B). Moreover, hsa_circ_0072309 has been identified as a potential TNBC risk factor (Magalhães, 2022). However, targeting lncRNAs in therapy is challenging. Combinatorial treatment requires further research (Yan, 2019).

MICROSATELLITE INSTABILITY (MSI)

Microsatellites are short repeated sequences in the genome, that result from the mal-function of DNA repair systems. High MSI status can be associated with patient's senistization to ICIs (Le, 2017). Patients with higher MSI status are more likely to express PD-L1, so, it is also used as a biomarker. The analysis of the MSI status can potentialy help in finding the best treatment (Yoshida, 2022).

WNT AND YAP SIGNALING PATHWAYS

Wnt/β-catenin signaling pathway is associated with the epithelial-mesenchymaln transition (EMT). Activation of this pathway stimulates cell proliferation and has been linked to several cancers, including breast cancer (Jiang, 2019). Moreover, Wnt inhibitors decrease PD-L1 expression, while Wnt agonists increase it. As a result, inhibitors can be used in conjunction with ICIs to improve treatment outcomes (Castagnoli, 2019). One potential candidate for combination therapy may be miR-135. Its overexpression in breast cancer has been shown to reduce cell proliferation, migration, invasion, and metastatic spread. Additionally, it increases the expression of E-cadherin and decreases expression of Snail, Slug, neural-cadherin, Vimentin, which means slowing down EMT. All this is achieved by inhibiting, at least in part, the Wnt/β-catenin signaling pathway (Maeda, 2018).

YAP signaling enhances PD-L1 expression and mediates suppression by regulating T cells [38]. They recruit many cell types such as tumor-associated macrophages by initiating the expression of cytokines and chemokines. An example of the application of this information in practical studies is the combination therapy of ICI with the YAP inhibitor verteporfin, which gave better results than monotherapy with ICI (Yu, 2021).

NANOPARTICLE PLATFORMS

They can be used as an ICI delivery system instead of monoclonal antibodies, that can stimulate self-reactive T cells. Additionally, this approach supports the pharmacokinetics and pharmacodynamics of combinatorial therapies (Gurunathan, 2018).

ATEZOLIMUMAB WITH PACLITAXEL

Atezolizumab attacks PD-L1 present on tumor-infiltrating immune cells by preventing its interaction with PD-1 receptors. Atezolizumab is an example of an ICI. It has been approved as a drug in the treatment of metastatic urothelial carcinoma and non-small cell lung cancer, but it also shows good results in TNBC (Tecentriq (atezolizumab): summary of product characteristics; Emens, 2019) ICI can improve the response to chemotherapy, for example taxanes such as (nab)-paclitaxel. The combination of Atezolizumab and Nab-Paclitaxel used in the study extented progression-free survival (PFS) with TNBC (A Study of Atezolizumab in Combination With Nab-Paclitaxel Compared With Placebo With Nab-Paclitaxel for Participants With Previously Untreated Metastatic Triple-Negative Breast Cancer).

PFS was significantly longer in the atezolizumab plus nab-paclitaxel treatment group (7.2 months) compared to the placebo plus nab-paclitaxel treatment (5.5 months). This was particulary notable in PD-L1-positive group, where atezolizumab-nab-paclitaxel PFS was 7.5 months and placebo-nab-paclitaxel was 5.0 months. Moreover, the objective response rate was much higher: 58.9% vs. 42.6%. The adverse events were identical in both groups, with alopecia being by far the most common. Both groups had equal levels of safety (Jotte, 2020).

This study confirmed the value of including ICI in the first-line treatment of metastatic TNBC

(Schmidt, 2018). Further approval of the drug is dependent on additional studies, showing that treatment has not reached its original PFS value. The FDA reassessed the need for rapid approval, despite the fact that the Oncology Drugs Advisory Committee (ODAC) decided to maintain the accelerated approval of atezolizumab in April 2021 (https://www.cancernetwork.com/view/atezolizumab-tnbc-indication-withdrawn-by-manufacturer-after-talks-with-fda).

CASE REPORT – ADVERSE REACTION AFTER ATEZOLIMUMAB

Immunotherapy is believed to have revolutionized the way cancer is treated. However, be aware that it can also be associated with side effects. An example would be tumor-related sarcoidosis-like reactions (SLR). According to the data, this problem affects 4.4% of malignant tumors. May be related to immunotherapy. However, the exact determination of the cause may be difficult, as it cannot be ruled out that the occurrence of SLR is related to the patient taking other medications (along with immunotherapy). It has been suggested that the efficacy and safety of immunotherapy may be influenced by the use of various medications. Among them there are antimicrobial agents, proton pump inhibitors and steroids. In this section, we present a specific example (case report) to illustrate the problem that may arise after atezolimumab in combination with nab-paclitaxel in TNBC.

A 50-year-old female patient diagnosed with TNBC was treated with atezolimumab in combination with nab-paclitaxel. However, after 5 cycles, lymph node enlargement in the right armpit and the appearance of a subcutaneous tumor in the limbs were observed. The results of the biopsy of this nodule indicated the formation of epithelial granulation tissue with giant Langhans cells. After discontinuation of atezolimumab, the lymph nodes and subcutaneous mass decreased. Let us add that the patient's medical history did not include the use of drugs (mentioned above) that could potentially affect the course of immunotherapy treatment, hence it can be concluded that SLR was related to the use of atezolimumab.

It seems appropriate to thoroughly investigate SLR as a side effect of immunotherapy (Tsunoda, 2022).

SUMMARY

TNBC accounts for approximately 11% of all new cases of breast cancer, the most common malignancy in women. Faced with poor treatments, new therapeutic approaches need to be developed. Part of this process is finding a new generation of immunomodulatory targets as well as the use of immune checkpoint inhibitors in the PD-1 / PD-L1 or CTLA-4 axis. Most studies show that while they are promising therapies, more work is still needed to refine them, especially in the search for effective combinations of chemotherapy and modulation of the immune response. It also demonstrates the importance of an interdisciplinary approach in medicine and how collaboration between scientists and clinicians can improve treatment outcomes.

CONCLUSIONS

TNBC is one of the worse prognosis neoplasms for which it is difficult to find therapeutic targets that would significantly translate into treatment efficacy. A breakthrough in the treatment of melanoma contributed to the development of TNBC immunotherapy. This seems to be a potentially good idea. The goals of immunotherapy in TNBC include: TNBC immunotherapy targets include: PD-1 / PD-L1 axis, CTLA-4 and Dual Checkpoint Inhibition, as well as next generation immune modulatory targets. More research and solutions are needed to support the response to immunotherapy in TNBC patients. It is also worth noting that they may contribute not only to the effectiveness of TNBC immunotherapy, but may also lead to finding potential snake points for treatment in TNBC. Let’s add that medicine is advancing even in difficult-to-treat diseases such as TNBC, and the results of each study are valuable.

General comments/thanks

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Intramedullary Spinal Cord Metastasis in a Patient with Breast Cancer: A Case Report

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ABSTRACT

This 67-year-old patient with breast carcinoma in medical history presented a progressive limitation of superficial and deep sensation below the L4 dermatome, paresis in sole flexion of the left foot, paralysis in flexion of the right foot of a month evolution. The day before admission, urinary retention and abdominal pain occurred. An MRI image (performed privately due to increasing numbness of the lower limbs) revealed a tumour within the spinal cord between the Th12 and L1 vertebral bodies. Postoperatively, improvement in the previous neurological deficit was observed. Tissues obtained during surgery confirmed that it was histopathological low differentiated carcinoma. Metastasis at this level is rare and present less than 6% of all spinal metastases. Most likely, the intramedullar spinal cord lesions are a metastasis of breast cancer.

Keywords: Intramedullary Spinal Cord Metastasis, Metastasis, Breast Cancer, Spinal Cord

INTRODUCTION

Intramedullary Spinal Cord Metastasis (ISCM) are rare complications of cancer (0.1-6% of patients) (Mechtler, 2013; Lv, 2019; Basaran, 2014). However, in contrast to primary spinal cord tumours nowadays they show increasing incidence. Mostly because of advancement made in chemotherapy protocols and surgery therapy of primary cancers, and better diagnostic methods such as (Magnetic Resonance Imaging (MRI). MRI is now considered as the gold standard for the diagnosis of spinal cord tumours (Connolly, 1996; Gasser, 2001). The typical ISCM visualization on MRI is a small, isolated, oval-shaped lesion with or without slight deformation of the spinal cord profile. It is isointense on spin-echo T1 weighted images with a nodular contrast enhancement and pencil shaped hyperintensity on T2-weightes sequences, most frequently extending proximal to the lesion (Castro, 1997). The use of intravenous gadolinium is helpful in demonstrating the typical enhancing central lesion with surrounding T2-weighted signal abnormality pre-sumed to be edema (Fredricks, 1989; Ibrahim, 2021; Mostardi, 2014). ISCMs typically occur in the sixth decade of life, usually 11.9-38 months after primary diagnosis, and have a poor prognosis with a mortality rate after 3-4 months of 80% and a median survival of only 3-11.6 months (Lapolla, 2021). It accounts only 0.85-3.9% of symptomatic metastatic tumors affecting the spinal cord and is found in only 2% of postmortem sections. Breast cancer (11-26%) is the most common cause of spinal metastases after lung cancer (45-54%) (Wewel, 2020) Patients with primary breast cancer have a better prognosis than those with ISCM of other origins. Intramedullary tumours usually cause swelling, distortion and compression of the spinal cord parenchyma, resulting in pain and sensory and motor disturbances and sphincter dysfunction (Ruppert, 2017). Optimistic prognostic factor is patient's general good condition, if it is stable, we can expect relieve in neurology deficiency caused by medullary mass. It rises a hope to oncology patients, as happened in our case.

CASE REPORT

A 67-year-old female was admitted with a progressive worsening of lower limb paresis and sensory disturbances of the perineal region. One month prior to admission, the patient had noticed difficulty in walking and sensory disturbances of the legs, which she reported to her general practitioner doctor. The complaints had increased significantly in the approximately two weeks before admission and include reduced superficial and deep sensation below the L4 dermatome, paresis in sole flexion of the left foot and inflexion of the right foot. The day before hospital admission urinary retention and abdominal pain occurred. These symptoms were associated with a dull aching pain in her midback and numbness in lower extremities. The MRI revealed a tumour within the lumbar intumescence of the spinal cord at the level of the border of the Th12 and L1 vertebrae (Figure 1, 2, 3, 4).

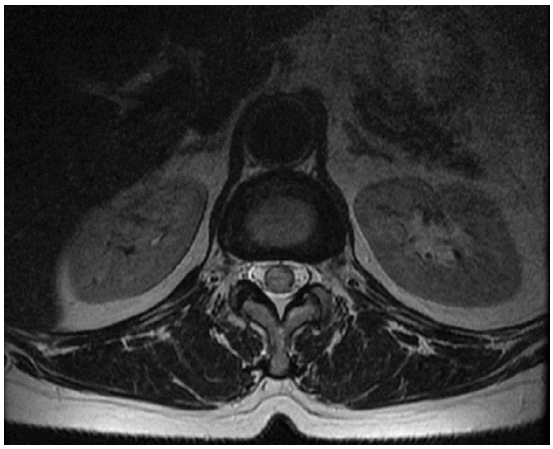

Figure 1. MRI image showing intraspinal metastasis of breast cancer to the spinal cord-axial view

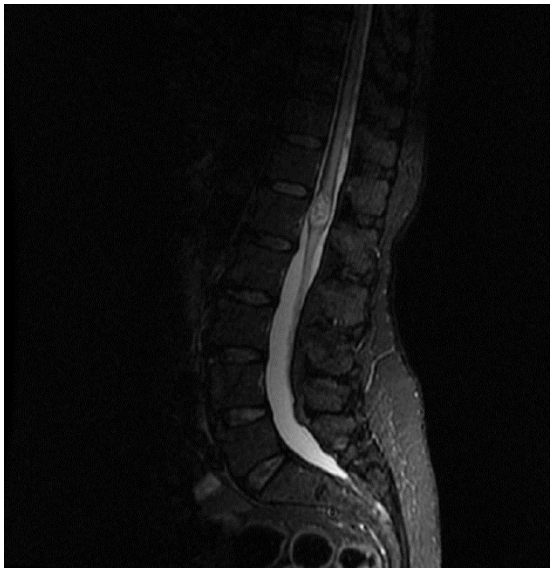

Figure 2. T2-weighted MRI image showing intraspinal metastasis of breast cancer to the spinal cord at Th12-L1 level – sagittal view

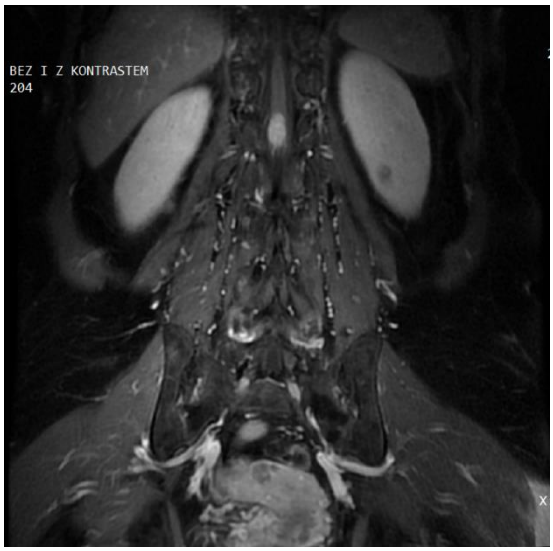

Figure 3. MRI image showing intramedullary metastasis of breast cancer to the spinal cord at Th12-L1 level – sagittal view

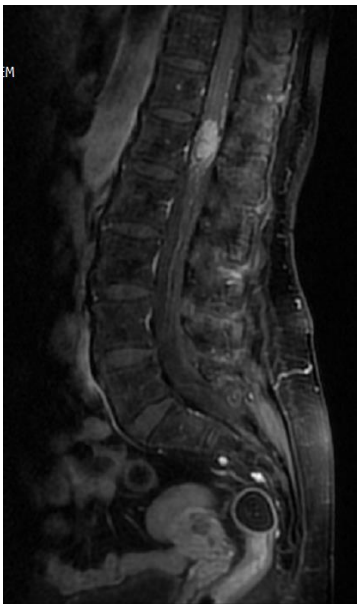

Figure 4. T1-weighted MRI image showing intramedullary metastasis of breast cancer to the spinal cord at Th12-L1 level – frontal view

The patient had a known history of cancer – left breast tumour after mastectomy, with chemotherapy, and sentinel node excision a year earlier. At the time of initial presentation there was already evidence of metastasis to the chest.

The tumour profile was consisted with minimally positive estrogen receptor (ER) and HER-2/neu receptor. The histological picture based on the immunohistochemical findings was consistent with metastatic low-differentiated carcinoma. Most likely, the medullary lesion was a metastasis of breast cancer. The initial medical therapy consisted of a doxorubicin, cyclophosphamide, and doxacel regiment with a partial response. Neurologic examination revealed numbness and reduces motor strength in both lower limbs. There were no pathologic reflexes. During hospitalization, the patient received glucocorticosteroids (Dexamethasone -4x4/d for the first 10 days, then 4+2 mg/d for the next 8 days), non-steroidal anti-inflammatory drugs (NSAID) (Ketoprofen 100 mg 2 times a day, Metamizole 1 g 3 times a day and 100 ml NaCl once a day for the first 10 days of hospitalisation) and, to prevent gastric and duodenal ulcers associated with NSAID intake, proton pump inhibitors (Omeprazole 20 mg once a day). Low-molecular-weight heparin (Dalteparin 5,000 units subcutaneously once a day) was used as thromboprophylaxis associated with surgery.

Surgical treatment included removal of the spinal tumour, through the following procedures: skin incision in the Th-L region, laminectomies, durotomy, and myelotomy. After dissection of the posterior medial fissure, the tumour was visualised and dissected laterally from the spinal cord. Macroscopically, the tumour was removed in its entirety using CUSH bipolar forceps. Multiple motor evoked potentials (MEP) records check during removal – no abnormalities – no spikes in amplitude were noted. TOF monitoring (muscle relaxation control) were also measured. Then it was followed by haemostasis, surgiflo, meningeal sutures and duraplasty. Postoperative course uncomplicated, no neurological deterioration immediately after surgery. The patient was actively rehabilitated. The patient was verticalised and trial bladder stimulation was performed. The postoperative period was uncomplicated, improvement in the previous neurological deficit (her paresis and sphincter control improved), significant pain relief was observed. Although, due to poor differentiation the histopathology did not unambiguously confirm the breast cancer metastasis, based on medical history it was assumed that this was the case.

Psychological history: Oncologically burdened patient, emotionally stable, with depressed mood and sleep difficulties for a year (patient takes half a tablet "for sleep" daily). Supportive dialogue, psychoeducation, and cognitive reinterpretation were performed. Observation of emotional condition and modification of sleep medication was recommended.

The patient was in good condition and transferred to the Rehabilitation Department of the Polyclinic in Zielona Góra for further treatment.

DISCUSSION

Spinal cord compression is the second most common neurologic complication of uncontrolled cancer after brain metastases (Mendez, 2018). It has been well documented that majority of spinal cord metastases arises in the epidural or extradural space (Ziu, 2022). Primary intramedullary spinal cord tumours are uncommon, the represent less than 5% of all spinal cord malignancies (Das, 2022; Samartzis, 2015; Samartzis, 2016). Most of them are of neuroectodermal origin – more than 50% are astrocytomas and ependymomas (Villegas, 2004).

Intraspinal metastases typically occur in the sixth decade of life (Sung, 2013; Goyal, 2019; Kalayci, 2004; Mackel, 2020), usually 11.9-38 months after primary diagnosis (Lv, 2019; Rykken, 2013; Schiff, 1996; Sung, 2013; kalayci, 2004; Mackel, 2020), although it can happen even after 22 years predisposed by the presence of the ER+ hormone receptor, which delays the process (Rostami, 2013; Mackel, 2020).

MRI is the primary test to detect medulloblastoma (Basaran, 2014). The tumour on T1-dependent imaging is seen as an isodense lesion, while T2-weighted imaging shows a hyperintense mass with extensive oedema surrounding it (Figure 1, 2, 3). If hemorrhages occur they may be accompanied by heterogeneous image enhancement (Mechtler, 2013; Hsu, 2013; Rykken, 2013; Kalayci, 2004; Mackel, 2020).

There are 3 main treatment modalities for ISCM-radiotherapy, chemotherapy and microsurgical resection of the focal intramedullary tumour (Mechtler, 2013; Hsu, 2013). Radiotherapy remains the treatment of the first choice in radiation-sensitive metastases such as those from small-cell lung cancer, breast cancer or lymphoma. However, for rapidly progressive deficits or those lasting up to 48 hours, urgent radical resection of the ISCM should be the treatment of choice. Chemotherapy can be used in combination with radiotherapy or surgery in some chemotherapy-sensitive cancers, such as small cell carcinoma and haematological malignancies. Metastases from breast cancer have a good prognosis (Lee, 2007). In addition, metastases are extra-axial tumours, i.e., they grow expansively rather than infiltrate, so they are fairly well demarcated and can be relatively easily debrided and removed. The patient's case demonstrates the benefits of the surgical approach due to the improvement in neurological deficits and a significant reduction in pain.

To maximize the effectiveness of resection of intraspinal tumours, intraoperative electro-physiological monitoring by somatosensory and motor evoked potentials is helpful. MEP monitoring provides the most valuable information (Costa, 2007). It has been found that both preoperative MEP results and those obtained during surgery correlate strongly with the patient's clinical condition (Sala, 2007). When there is a significant decrease in MEP amplitude (less than 50% of the initial values), further manipulation should be discontinued (Sala, 2007).

The patient described here underwent tumour resection under MEP and TOF control due to reduced superficial and deep sensation of the left foot, paralysis in flexion of the right foot and also urinary retention. In addition, the patient was in stable condition and the intraspinal tumour was solid and did not occupy the meninges, making it easily accessible for surgical removal. The symptoms improved after surgery.

SHORT CONCLUSION

A myelopathy that arises during the malignancy course is often caused by compression of the spinal cord by metastatic tumour. The clinical manifestations of metastatic intramedullary spinal cord tumours are typically back pain, paraparesis, paresthesia, spasticity of lower limbs and autonomics dysfunctions. Close to 1/3 of patients with ISCM, neurologic deficits are the first symptoms of underlying systematic malignancy (Schiff, 1996; Chason, 1963). Intramedullary spinal cord metastasis can produce edema, distortion and compression of the spinal cord parenchyma, resulting in signs and symptoms that are similar to epidurial spinal cord compression. It is almost impossible to reliability distinguish these two conditions without radiographic imaging. However, asymmetric presentation of motor deficit or sensory disturbance in lower limbs pronounced more in favore of ISCM. Epidurial metastases tend to be more symmetrical. Some ISCM may also ocure in form of Brown-Sequard syndrome, defined as unilateral spasticity and weakness with contrateral loss of temperature and pain sensations. Moreover, primary tumorse in contrary to ISCM typically are slower in progression. The treatment options for ISCM are radiotherapy, chemotherapy and microsurgical resection of the

focal intramedullary tumour. The current standard of care is radiotherapy (especially among patients with established deficits). That is mainly due to surgeons' fear of surgical treatment of a patient with metastases. However, the method of choice for rapidly progressive deficits or those lasting up to 48 h should be urgent radical resection of the ISCM. Chemotherapy may be used in combination with radiotherapy or surgery in some chemotherapy-sensitive cancers such as small cell carcinoma and hematological malignancies. Metastases from breast cancer have a good prognosis. Moreover, metastases are tumours of the extra-axial type, i.e., they grow expansively, not infiltratively so that they are well-demarcated and can be dissected and removed relatively easily. The patient's case demonstrates the advantages of the surgical approach because of the improvement in neurological deficits and significant pain relief.

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Modern therapy of eye neoplasms

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ABSTRACT

Ocular neoplasms, despite their rarity, pose a significant problem in contemporary ophthalmic oncology. The diagnosis of a tumor in the organ of vision often causes the need to remove the eyeball. In recent years, however, the effectiveness of eye tumor treatment has markedly increased. Oncological therapy in ophthalmology is dynamically developing towards gene therapies, biotechnology and materials engineering. In addition to early detection of the disease, which plays a major role in the patient's survival, more and more attention is paid to reducing the systemic effects of therapy, preserving vision and improving the patient's quality of life. Among other things, this can be achieved through the use of nanoparticles, targeted therapy, immunotherapy as well as proton beam radiotherapy.

In this paper, we present an overview of new trends of ocular neoplasm therapies that have been researched over the last few years. On the examples of choroidal melanoma, conjunctival melanoma, retinoblastoma, primary retinovitreal lymphoma, we point out the proposed modern treatment methods dedicated to a given type of disease. Moreover, we indicate that the currently used methods of treating non-ophthalmic neoplasms, due to the similarity in oncogenesis to ocular neoplasms, may constitute a starting point for the development of new management in ophthalmic oncology. We discuss the difficulties related to the introduction of new therapies into clinical practice and justify the purposefulness of further research due to the promising results, identifying possible directions for their development.

INTRODUCTION

Oncology is one of the fastest developing fields of medicine. Currently, when planning oncological treatment, not only a given type of concoma is taken into account, but also the therapy is individually adapted to the patient, considering his age, health condition, prognosis and the characteristics of the disease itself. Advanced genetic and bioengineering technologies are developed very dynamically. Thanks to them, it is possible to determine the type of mutation precisely, its frequency and influence on the course of the disease and prognosis. Such a large amount of personalized data gives hope for the development of advanced therapies or increasing the effectiveness of those already used. Promising results of research on personalized vaccines, genetically modified T lymphocytes, interference in the genome, research on the role of the organism's microflora in the process of tumor formation are examples of the direction in which modern oncology is heading. Nowadays oncological treatment should not only be effective, but also the least burdensome and lowering the patient's quality of life.

OPHTHALMIC ONCOLOGY

Oncological therapy of ophthalmic patients is associated with many problems. The diagnosis of a maligancy of the eyesight often equals the necessity to remove the eyeball. Despite early diagnosis, the death rate is still high. However, the example of retinoblastoma shows that the effectiveness of the treatment of ocular neoplasms has increased in recent years. Currently, oncological therapy in ophthalmology is dynamically developing towards gene therapies, biotechnology, and materials engineering. In the near future, everyday clinical practice will be supplemented with new therapeutic possibilities. Traditional examination, combined with selecting high-risk groups, determining the prognosis for a given patient, and identifying specific genes responsible for neoplasms will allow for more effective diagnosis and treatment of neoplasms of the eye organ.

Ocular neoplasms are rare. They lead to significant impairment, loss of vision, and death of patients. The early detection of eyeball tumors is crucial. Their rarity results in significant difficulties in obtaining material for analysis. Nevertheless, extensive research is conducted to develop new, effective methods of treating them. Traditional radio- and chemotherapy do not always protect the patient from enucleation. The aspirations of scientists looking for new therapies are dictated by the desire to keep the

patient alive as long as possible, but also to preserve vision. The achievements of recent years give hope that eyeball tumors will no longer limit the ability to function independently, and even more so, they will cease to cause death of patients.

TUMORS OF THE EYEBALL

UVEAL MELANOMA

It makes up 80% of all melanomas of the eyeball (Krantz et al. 2017). It is derived from the melanocytes of the uveal membrane (iris, ciliary body and choroid). It is estimated that about 50% of patients metastasized when uveal melanoma was detected (Wang et al. 2020). About 30% of patients showed no symptoms. Almost 40% reported visual impairment (Damato, Damato 2012). According to the COMS study, 89% of the metastases were located in the liver. Mortality after detecting metastases reached 80% within the first year and 90% within 2 years. The survival time did not depend on the size of the primary tumor or the treatment of metastases (Diener-West et al. 2005), while the early detection and implementation of effective treatment of the primary tumor achieved a 90% survival rate (Wu et al. 2020), if metastasis did not occur.

Standard therapy, such as brachytherapy, radiotherapy and enucleation, is highly effective in the treatment of the primary tumor (Ramaiya 2007). Treatment of patients with metastatic form becomes problematic. Even if metastases were not developed at the time of detection, patients with uveal melanoma are particularly at risk (Kujala, Mäkitie, Kivelä 2003).

The DecisionDx-UMTM test using PCR (Greenhaw et al. 2020), available in the USA, is used for the prognostic evaluation of a tumor sample by analyzing 15 genes and, disregarding other clinical data, assigns patients to two risk groups – class 1 UM (uveal melanoma) associated with low risk of metastasis, and a class 2 UM with a high risk of metastasis. Thanks to this division, it is possible to adjust the intensity of therapy for a particular patient (Harbour, Chen 2013).

GENETIC ANALYSIS OF THE BASIS OF NEOPLASM

Genetic analysis of the basis of neoplasm has identified a number of mutations, oncogenes, that show potential as a target for antineoplastic drugs. Differentiation of the primary tumor mutation in relation to metastatic foci gives the theoretical possibility of developing targeted therapy and systemic action, both in the topical location and in the area of metastatic foci.

Using standard biomarkers, we are able to determine the expression of diseasespecific genes responsible for tumor growth and expansion and apply targeted therapy. Such typing requires the selection of neoplastic cells. Single Cell Technology (SCIT) can help. This method allows the isolation of homogeneous tumor cells from the collected biopsy material and the separation of neoplastic cells from infiltrating cells of the immune system and cells of healthy tissues. The cells separated in this way are multiplied and typed (Li et al. 2020). The method is more effective than flow cytometry and manual selection of neoplastic cells (Wang et al. 2021).

Examples of common biomarkers are:

BAP1 – is a suppressor gene regulating cell division (Field et al. 2019). The BAP1 mutation is more commonly associated with class 2 uveal melanoma (Harbour et al. 2010).

It is believed that mutations in the GNAQ and GNA11 genes (Van Raamsdonk et al. 2010) detected in 83% of uveal melanoma tumors are associated with an increased metastatic potential. GNAQ is more common in the primary tumor, and GNA11 in the metastatic focus (Onken et al. 2008).

A mutation in the IGF-1 gene causes an increased migration of tumor cells and an increased risk of metastases in the liver and other organs (Wilky et al. 2015).

The role of the c-KIT gene in the neoplastic process of choroidal melanoma has not been definitively established (Van Poppelen et al 2021). In healthy cells, it is responsible for normal growth, increasing the number of melanocytes and their homeostasis (Grichnik et al. 1998). Limited data on the presence of an activating mutation of the c-KIT gene in uveal melanoma suggest that the mutation is extremely rare (Wallander et al. 2011). Nevertheless, it was confirmed in 78% of uveal melanoma samples taken from the Archives of the McGill University Ocular Tissue Pathomorphology Laboratory (Pereira et al. 2005).

TARGETED THERAPY

The mechanism of action of drugs in targeted therapy is to inhibit specific signaling pathways leading to neoplasia.

It has been shown that drug-targeted therapy from the group of histone deacetylase inhibitors (HDAC) used in the case of a mutation of the BAP1 gene, based on the example of valproic acid, inhibits tumor growth in vitro and reduces the number of metastases (Landreville et al. 2012).

Cixutumumab – a monoclonal antibody inhibits the activity of IGF-1 and the migration of neoplastic cells. It has been proved in an animal model that the IGF-1R inhibitor picropodophyllin is well tolerated in vivo, inhibits migration and growth of tumor cells (Girnita et al. 2008) and reduces the level of vascular growth factor in tumor cells (Economou et al. 2008).

Studies on the effectiveness of tyrosine kinase inhibitors, such as imatinib, are ongoing but its effectiveness has not yet been established (Wu et al. 2020). The use of sunitinib (in adjuvant therapy) resulted in an increase in the average survival time of patients with the cKIT mutation in choroidal melanoma (Valsecchi et al. 2018).

Mutations in the GNAQ and GNA11 genes can be neutralized by inhibiting the PKC pathway (Sagoo et al. 2014). New inhibitors of the PKC pathway – such as enzastaurin or sotrastaurin – inhibit the PKC and MAPK signaling pathway, causing apoptosis of maligant cells. When combined with an antagonist of the MEK signaling pathway, greater efficacy was obtained by acting on two different pathways simultaneously. A study conducted on 101 patients showed that the PKC inhibitor selumetinib inhibits the MAPK pathway, increasing the effectiveness of traditional temozolamide and decarbazine therapy by 14% (Goh and Layton 2016).

Administration of cixutumumab with selumetinibab is well tolerated and gives initial positive therapeutic effects of IGF (Wilky et al. 2015).

IMMUNOTHERAPY

Immunotherapy is aimed at increasing the effectiveness of a passive and active immune response by providing monoclonal antibodies and anti-cancer vaccines.

Metastatic foci of skin melanoma and uveal melanoma were compared for PDL1 ligand expression. Significant differences in the expression of the PDL1 gene within the metastatic tumor of both neoplasms have been demonstrated. Low expression of this gene may be responsible for the failure of therapy with PDL1 inhibitors and results in suppression of the immune response of T lymphocytes (Granier et al. 2017). It was found that metastatic cells of uveal melanoma less frequently present the PDL1 antigen on their surface (Javed et al. 2017). The lower expression in the metastatic tumor may account for the lower efficacy of drugs in this form of choroidal melanoma. The effectiveness of pembrolizumab in the treatment of patients with metastatic form of uveal melanoma was assessed (Ny et al. 2021). At present, the therapy has not brought satisfactory results (Rossi et al. 2019).

Tebentafusp – a drug registered in the EU in February 2021, is a drug from the group known as bispecific fusion protein, consisting of a T-lymphocyte receptor recognizing the gp100 protein and a single-chain fragment of an anti-CD3 antibody (scFv) (Liddy et al. 2012). It locates the gp100 protein on the surface of neoplastic cells and activates T lymphocytes, inducing an immune response (Wessely et al. 2020). In the study, it extended the mean survival from 16 to 21.7 months (Marseglia et al. 2021). It is an interesting therapy for patients with metastatic form of uveal melanoma (Middleton et al. 2020).

CONJUNCTIVAL MELANOMA

It clinically manifests itself as a flat or raised pigmented lesion of the conjunctiva, located either in its nasal or in its temporal part. It tends to invade surrounding tissues, including invasion of the lymph nodes. One of the risk factors here, as in skin melanoma, is exposure to UV radiation (Cancer Genome Atlas 2015). The incidence of this neoplasm ranges from 0.2-0.8 cases per million (Spatola et al. 2020) and constitutes about 2-5% of eyeball neoplasms (Isager et al. 2006). The 10-year experience represents approximately 50% of patients (Abt et al. 2019). Radical excision of the lesion, marginal cryotherapy and brachytherapy give satisfactory results (Wong et al. 2014) but as much as 30-40% of local relapses are observed (Chauhan et al. 2014). Despite the fact that treatment regimens for the local form of this neoplasm have been developed, there is no agreed consensus for the management of metastases (Grimes et al. 2020).

ANALYSIS OF ONCOGENES

Mutations in the MAP signaling pathway – RAS, BRAF, MEK, ERK, PI3K / AKT / mTOR (McCubrey et al. 2007) and the TERT mutation associated with metastatic disease (Van Poppelen et al. 2021) were found in conjunctival melanoma cells. The most common mutation is BRAF, associated with a higher risk of metastasis and worse prognosis, followed by NRAS belonging to the family of RAS kinases activated by tyrosine kinase receptors (Wallander et al. 2011). The TERT mutation, occurring together with BRAF and NRAS, increases the metastatic potential of conjunctival melanoma (Van Poppelen et al 2021) and is associated with a much worse prognosis and shorter disease-free survival. The worst form of the disease is also associated with the TERT mutation (Gandini et al. 2021). Conjunctival melanoma is genetically similar to cutaneous melanoma and mucosal melanoma. It is believed that for this reason, targeted therapies effective in treating these diseases, such as BRAF I KIT inhibitors, may be used in the future in the treatment of conjunctival melanoma. MEK inhibitors are also effective.

CHECKPOINT INHIBITORS

The cellular response of the immune system to tumor cells is regulated by multiple checkpoints. The CTLA4 checkpoint is clinically relevant (Hodi et al. 2010). It can inhibit the developing immune response of T lymphocytes. The inclusion of drugs that inhibit its action gives positive results. The PD-1 inhibitors mentioned in the context of uveal melanoma, which have not yet been reliably tested in patients with conjunctival melanoma but are used in the treatment of skin melanoma or CTLA4 (e.g. ipilimumab), reduce the number of metastases and limit local invasion also in melanoma conjunctiva (Hodi et al. 2010). The combination of the above-mentioned drugs in one treatment regimen has brought positive results. The comparison of their effectiveness with the used nivolumab or decarbazine therapy gives hope for new therapeutic regimens.

RADIATION THERAPY WITH A PROTON BEAM

Proton beam radiotherapy (PBRT) is an alternative treatment for advanced conjunctival melanoma involving the eyelids and surrounding tissues. It allows for precise application of the radiation beam to the affected tissues, unlike brachytherapy, which delivers high doses of radiation also to adjacent tissues. Due to the Bragg Peak phenomenon (Lin et al. 2018), the spread of particles in tissues is inhibited by losing their velocity as they move through the tissue (Spatola et al. 2020). The technology is not new, it is an alternative to crippling surgical intervention and has positive results (Thariat et al. 2019). Currently, there are not many studies confirming the effectiveness of this therapy in conjunctival melanoma but there is evidence that it may be as effective as in the treatment of uveal melanoma (Gollrad et al. 2021).

RETINOBLASTOMA

Retinoblastoma is the most common eye tumor in children (Kivela 2009) and accounts for 3% of all childhood malignancies. It is usually diagnosed in patients under 5 years of age (Sun et al. 2020). The tumor is bilateral in 30-40% of patients. 6% of tumors are of family origin, 94% of tumors are sporadic (Dimaras, Corson 2019). The main symptoms are: visual impairment, strabismus and leukocoria (Abramson et al. 1998). The disease leads to vision loss and death. Diagnostics is based on ophthalmoscopic examination and imaging tests (ultrasonography, magnetic resonance imaging, computed tomography in older children). It is ineffective in detecting early changes.

THERAPEUTIC PROBLEMS

The initially used method of treatment was radiotherapy and enucleation (Kaewkhaw, Rojanaporn 2020). The young age of the patients, the need to remove the eyeball and the complications of radiotherapy motivated scientists to look for new methods of treatment. Systemic chemotherapy was introduced to reduce the tumor, followed by brachytherapy. Complications related to the use of radiotherapy and the fear of side effects in children have made chemotherapy the primary treatment effective in reducing tumor size, the risk of metastases and the degree of eye damage. However, aggressive treatment of a locally located tumor can lead to systemic complications affecting the developing child.

CURRENT THERAPEUTIC SCHEME

For several years, intra-arterial medications have been used to treat retinoblastoma. This therapy reduces systemic side effects and allows faster to achieve the therapeutic concentration of the drug in the tumor tissue without causing destructive systemic consequences.

Initially, they were administered into the internal carotid artery (Yamane, Kaneko, Mohri 2004), then the technique was improved and now many centers administer drugs directly into the ophthalmic artery (Abramson et al. 2008). A properly selected dose of carboplatin, melphalan, topocan (or a combination of these drugs) achieves cytostatic concentrations in the tumor, but does not suppress the immune response (Mostaghimi, Ahmadabad, Rezaei 2021). Even in the case of the so-called cavitary retinoblastoma, characterized by the presence of voids in the tumor mass (Rishi, Sharma, Sharma 2020) considered to be therapeutically resistant, spectacular successes were reported (in a small group of patients) (Zheng et al. 2021).

DIAGNOSTIC AND TREATMENT CHALLENGES IN RETINOBLASTOMA

Advances in diagnostics and treatment methods allow, in addition to saving lives, salvage the eyeball in the eye socket and often vision. Due to the fact that earlier detection is associated with a better prognosis (Sun et al. 2020), the time of appearance of symptoms until diagnosis is of a major importance (Kivela 2009). It is necessary to search for new, more sensitive and faster diagnostic methods.

The route of drug administration is problematic in the case of neoplasms of the eyeball. The water-insoluble drugs are particularly difficult to penetrate the eyeball. It should be taken into account that the application of local treatment encounters a number of anatomical barriers in the orbit and limits drug penetration into the tumor area. In addition, the administration of strong cytostatics to the eyeball area, to the orbital tissues, entails a number of complications, such as, for example, tissue necrosis in the orbit, orbital fat, atrophy of the optic nerve or impaired mobility of the eyeball (Murray et al. 1997). This has forced the development of methods for more efficient drug delivery to the tumor tissue. Considering the above, diagnostic and therapeutic methods using nanoparticles – nanotechnology are helpful (Sarwat et al. 2019).

NANOTECHNOLOGY IN THE TREATMENT OF RETINOBLASTOMA

Increasing the resolution of imaging eyeball tumors in magnetic resonance imaging (Gold NPs (nanoparticles) (Kozenkova et al. 2020), increasing the sensitivity of neo-plastic tissues to laser radiation (Silver NPs) (Park et al. 2020) or the use of nanoparticles to detect DNA methylation characteristic for retinoblastoma (Carbon nanomaterials) are examples of a new technology that shows promising results in the phase of research on in vivo models.

The challenge is to develop new ways and methods of drug administration. Modern methods of treatment using nanoparticles, such as: Nanocarrier, Melaphalan NPs, Galactose NPs, Hyaluronic acid NPs, Folic acid NPs, LipidNPs, SilverNPs, Gold NPs, are used for delivering drugs to the tumor tissue more effectively in the eyeball environment. The most commonly used are multi-functionalized NPs and lipid-based NPs, and metallic NPs.

Material bioengineering plays a significant role in obtaining the desired physicochemical properties of drugs, which, when administered to the inside of the eyeball, enable better penetration of drugs. An example is the coating of DNA molecules with hyaluronic acid which allows the complex to move more easily inside the vitreous body (Martens et al. 2017). The discovery of over-expression of lectin receptors on the surface of retinoblastoma tumor cells paved the way for research into new galactose-coated nanoparticles (Godse et al. 2021). This combination increases the affinity of the drug to neoplastic cells, saving healthy tissue. Lipid nanocomplexes formed from the combination of melphalan and miR-108 also allow the treatment to be concentrated in the tumor area (Su et al. 2015).

The biotechnological successes in the field of producing new drugs give hope for a wider application of the above-mentioned technologies in clinical practice. The use of selective therapy makes it possible to limit the effect of the drug to the tumor affected area, reduce the systemic toxicity of antineoplastic drugs and increase the effectiveness of the treatment.

TARGETED THERAPY

MLN4924 is an inhibitor of neddylation, the post-translational modification of a protein responsible for neoplasia. There are currently numerous studies on pevonedistat (clinical name MLN4924) in the treatment of malignant neoplasms. Intravitreal administration of MLN4924 was effective in animal studies in which the target was SKP2 oncogene found in retinoblastoma cells (Wang et al. 2010). Due to its low toxicity, this therapy shows promising results. In vitro studies showed that three-hour exposure to the drug resulted in a 50% reduction in tumor mass and extending this time had positive anti-tumor effects but increased toxicity to retinal cells. This gives hope for the development of therapeutic regimens for the use of intravitreal injections of MLN4924 (Aubry, Yu and Bremner 2020).

The protein kinase PLK1 plays the role of a cycle regulator in healthy cells (Bouhlal et al. 2016). Overexpression of the PLK1 protein kinase is observed in many malignancies such as melanoma, non-small cell lung cancer, esophageal cancer (Yim and Erikson 2014) and also in retinoblastoma (Singh et al. 2015). Rigosertib, and more specifically ON-01910.Na, is a PLK1 kinase inhibitor used in the treatment of lung cancer (Medema, Lin, Yang 2011). Tumor weight reductions have been reported in the eye with subretinal retinoblastoma in an animal model. The study is the starting point for the development of PLK1 targeted therapy in retinoblastoma (Ma et al. 2021).

PRIMARY VITREORETINAL LYMPHOMA

Primary vitreoretinal lymphoma – PVRL is a rare subtype of lymphoma and 20% coexists with central nervous system lymphoma – PCNSL. Initially, it involves the vitreous body, the retina, subretinal tissues, and the optic nerve with or without central nervous system involvement (Soussain, Malaise, Cassoux 2021). The ocular manifestation of this neoplasm precedes the symptoms of the central nervous system by an average of 29 months (Baron et al. 2020). Older people are more common to become ill. It may be initially confused with chronic uveitis due to the observed inflammatory cells in the anterior chamber and yellow subretinal infiltrates. The diagnosis is made on the basis of physical examination, imaging examinations (Yang et al. 2021) and the presence of lymphoma cells in the vitreous after biopsy (Wang et al. 2021). Research is ongoing into the possibility of diagnosing this disease through the analysis of the aqueous humour (Wang et al. 2011). Its inflammatory mediators, IL-10 / IL-6 (Shi et al. 2021), are to become a less invasive method of disease confirmation in the future (Wang et al. 2011).

CURRENT THERAPEUTIC REGIMENS

Two treatment regimens are available to clinicians. The first is high-dose methotrexate therapy with or without radiation therapy to the central nervous system. Another approach is topical treatment – radiotherapy, intravitreal injections of methotrexate or in combination, and systemic chemotherapy. Currently, there are studies on the effective treatment of lymphoma confined to the eyeball (Zhang et al. 2021).

In patients with newly diagnosed PVRL, the efficacy of intravitreal injections of methotrexate with rituximab (which is used to treat B-cell lymphoma and is effective in treating PVRL in ophthalmic monotherapy (Rishi et al. 2021)) and with lenalidomide has been studied. This treatment regimen was shown to be effective in 10 out of 11 patients. In one patient new lesions were found in the central nervous system during the course of therapy. This treatment has not been shown to be more effective than systemic chemotherapy. More research is needed on the efficacy of lenalidomide in PVRL therapy (Zhang et al. 2021).

Diffuse large B-cell lymphoma (DLBCL) is a subtype of vitreoretinal lymphoma (Miserocchi et al. 2019). Bruton's tyrosine kinase (BTK) plays a mediating role in the B-cell cycle (Vogel et al. 2021). A set of mutations characteristic for the above-mentioned lymphoma (Hiemcke-Jiwa et al. 2018) gave the direction to the study that showed that the BTK inhibitor ibrutinib has the ability to cross the blood-brain barrier and its use gives positive results in the treatment of DLBCL (Soussain et al. 2019).

Temozolomide (TMZ) is a well-tolerated second generation antineoplastic drug with good pene-

tration into the central nervous system and the cerebrospinal fluid. Its effectiveness in PCNSL has been confirmed in several small studies (Soussain, Malaise, Cassoux 2021). A retrospective study of the efficacy of this drug was conducted in patients with relapsed, refractory and ineligible for first-line treatment form of PVRL. Interestingly, the use of TMZ shows a good pricebenefit ratio compared to other therapies already used in the treatment of PVRL (Baron et al. 2020).

A therapeutic strategy for the treatment of this type of oncoma requires development. Presently, there is a lack of big and reliable studies providing knowledge about the effective treatment of isolated PVRL.

SUMMARY

Due to the large amount of research carried out, in the last two decades significant progress has been made in the diagnosis and treatment of neoplasms. Modern therapy of eye neoplasms presents researchers with a number of challenges, combining many branches of modern medicine. In uveal melanoma the DecisionDx-UMTM test using PCR enables to assess the risk of metastases and as a result to adjust the intensity of the therapy. Single Cell Technology helps to isolate neoplastic cells which are multiplied, typed and undergone targeted therapies. Furthermore, in metastatic form, new drug tebentafusp extends the survival by inducing immune response. In conjunctival melanoma, due to genetic similarity to cutaneous and mucosal melanomas, targeted therapies effective in treating these neoplasms, such as BRAF I KIT inhibitors, may be used in the future in the treatment of conjunctival melanoma. Checkpoint inhibitors, for example iplimumab, also give positive results. Moreover, proton beam therapy, thanks to its accurate application, may be a safer solution than brachytherapy. In retinoblastoma new techniques and ways of administration of the drugs are developed. Currently medications may be given directly to ophthalmic artery, increasing the concentration of the drug and reducing systemic side effects. What is more, the usage of nanoparticles enables better penetration of the drug in the inside of the eyeball. Targeted therapy, using PLK1 kinase inhibitor gives hope to be effectively used in the future. In primary vitreoretinal lymphoma there are studies on the treatment confined to the eyeball, limiting systemic side effects during chemotherapy or radiation to the central nervous system. Targeted therapy gives positive effects. A significant problem in the diagnosis and treatment of eye tumor is the relatively small number of affected patients. This results in limited access to data, so the effectiveness of the therapies described can be easily questioned. Nevertheless, the presented results give hope for the development of new therapeutic regimens and demonstration of their actual effectiveness. Hence the need for more studies on bigger number of patients. Another important problem is the high cost of the diagnosis and treatment. It is necessary to involve many highly specialized entities in the process of comprehensive diagnostics. Their coordinated operation gives positive results, but is a big organizational problem. These are relevant problems, the overcoming of which will result in faster, more accurate diagnosis and more effective treatment of oncological diseases in ophthalmology.

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Cribriform adenoid cystic carcinoma (ACC) in the upper medial part of the left orbit presenting with exophthalmos – a case report

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ABSTRACT

Introduction: Orbital tumours in adults are the most common cause of unilateral, painless, non-inflammatory exophthalmos. Localization of the tumour in the oculomotor muscle or infiltration of the optic nerve causes more disturbing symptoms, such as the appearance of double vision – diplopia and/or decreased visual acuity.

The most common cause of orbital tumours in adults is cancer metastasis (more often occupying the left orbit). Tumours can also spread to the orbit from surrounding tissues such as the sinuses, the nasal part of the throat or from the lacrimal gland.

Adenocarcinoma of the cystic gland (ACC) is a rare, slow-growing malignant tumour arising from glandular tissue, usually appearing around the age of 50. ACC usually involves the salivary glands but may involve other structures such as the nasopharynx, maxillary alveolar process, orbit, nasal cavity or lacrimal gland.

Case report: A 53-year-old man presented to the hospital with visual disturbances and exophthalmos of the left eyeball. Magnetic resonance imaging showed the presence of a well-demarcated solid mass measuring 37 x 20 x 36 mm, located in the upper medial part of the left orbit, without features of diffusion restriction, with intense contrast enhancement. The lesion involved the intraosseous part of the left orbital roof with thinning of the cortical layer of the inner lamina of the frontal bone. The lesion protruded into the posterior situs on the left side. The tumour compressed the levator palpebrae superioris muscle and the superior rectus muscle and the distal part of the intraorbital optic nerve. Small chronic vascular foci were observed subcortically and in the periventricular white matter. There were also inflammatory changes of the cuneiform sinus and the mastoid process of the left temporal bone with the presence of fluid collections and a left deviated nasal septum.

Histopathological examination identified adenocarcinoma type cribriform. Access was obtained through a pteroidal-anterior craniotomy. The tumour was infiltrating and passing through the orbital roof. The tumour was dissected and removed from the septum, situs and cuneiform sinus. The postoperative course was uncomplicated, there was an improvement in visual acuity.

Discussion: The prognosis of patients with ACC is unfavourable (Bhayani et al. 2012; Jang et al. 2017; Ko et al. 2007; Xu et al. 2017). Metastases may occur even after many years and high mortality is usually due to intracranial dissemination or distant metastases. The difficulty in achieving complete surgical resection is due to the complex orbital anatomy, which leads to frequent local recurrence. The histopathological type of tumour has also been shown to have prognostic significance. In most cases, ACC does not occur as one pure histological type and classification is based on the dominant form. There are three histopathological types of ACC: cribriform (the most common, moderately differentiated), tubular (well-differentiated and with the best prognosis) and solid (poorly differentiated).

INTRODUCTION

Adenoid cystic carcinoma (ACC) belongs to the group of malignant neoplasms typically originating from the salivary glands (Ammad Ud Din and Shaikh, 2022). In total, it constitutes 10% of all salivary gland tumours (Dillon et al., 2016a). It is typically slow-growing compared to other neoplasms and tends to invade perivascularly as well as haematogenously disseminate to distant organs and is most commonly seen in older populations (Chummun et al., 2001). This kind of lesion constitutes only around 1% of orbital tumours, thus its occurrence in this location is particularly rare (Font, 1998). The onset of the illness is typically characterised by the indolent and relatively sluggish growth without any symptoms of the patient (Dillon et al., 2016b). However, the tumour has a tendency for local infiltration as well as perivascular proliferation thus the first sights of illness may be caused by the infiltration of nerves or other structures located around the lesion. (Khan et al., 2001). The consequences of oculomotor

involvement and infiltration of the optic nerve are more disturbing symptoms such as the appearance of double vision – diplopia and/or decreased visual acuity (Chen et al., 2017; Najem and Margolin, 2022). The spread of the tumour toward structures with reduced resistance within the orbit leads to compression of venous vessels and displacement of the eyeball toward the from the tumour to the space of least resistance, the eyelid crevice (Bradley, 2017). It is also associated with a high risk of both local recurrence and intracranial proliferation (Moskaluk, 2013). Moreover, the correlation between the histological structure of the tumour and the prognosis appears. Presently, assessing the probability of late recurrences is still difficult (Jaso and Malhotra, 2011). The most significant methods of primary treatment are surgical resection and radiotherapy, but the worth of adjuvant therapies remains as a contentious issue (Ishida et al., 2020a; Kokemueller et al. 2004). During the course of illness, patients in many cases develop local recurrence and metastases, specifically in the lungs, bones and liver (Papaspyrou et al., 2011). The cause of the development of this kind of neoplasm seems to be impossible to indicate (Coca-Pelaz et al., 2015). Orbital tumours, despite the fact that they are a very rare condition and not a significantly epidemiological problem, are nevertheless the most common cause of unilateral, painless, non-inflammatory exophthalmos of the eyeball in adults. In the early stages of the disease, lesions that are mild and slow-growing such can be very subtle and often underestimated (Ishida et al., 2020b). Limited data are available on predisposing risk factors and the management of patients with advanced disease due to its rarity (Ouyang et al., 2017; Singaraju et al., 2022). Pathophysiology of ACC is a scarcely investigated area due to the rarity of the condition (Chae et al., 2015).

The most common cause of orbital tumours among adults is metastatic cancerous tumours. Primary tumours can occupy the breast (most commonly), lungs, urinary and genital tract (especially the prostate gland) (Lukšić et al., 2016). Moreover, tumours spreading to the orbit from the tissues surrounding, such as the sinuses of the nose (most often), the cranial cavity, and the eyelids. Other tumours of the orbit originate from vascular tissue, lymphoid tissue, nerve tissue and the lacrimal gland (Xiao et al., 2019). Stasis with swelling and vasodilation of the conjunctiva are also observed. Orbital tumours rarely provide the pain, except in the case of lesions that rapidly increase that may be the cause of the late diagnosis (Składzień J., 2000).

CASE REPORT

29th of January in 2018 year, 53-years old patient reported to the Department of the Ophthalmology in University Clinical Hospital in Zielona Góra because of the isolated exophthalmos of the left eyeball and visual acuity impairment. The patient reports that the complaints gradually increased over time until the patient's functioning became compromised. In the anamnesis the Diabetes Melitus and infected tooth decay. In addition, the patient reports severe pain in his lower extremities. He has recently been treated with metformin, methylprednisolone and amoxicillin. Due to the unilateral character of the symptoms and an absence of underlying disease the Magnetic Resonance Imaging has been ordered. The examination performed on 5th of January revealed the presence of a well-demarcated solid mass measuring 37 x 20 x 36 mm, located in the upper medial part of the left orbit, without features of diffusion restriction, with intense contrast enhancement. The lesion involves the medial portion of the ceiling of the left orbit with thinning of the cortical layer of the inner lamina of the frontal bone. The mass protrudes into the posterior situs on the left side. The tumour compresses the upper eyelid levator muscle, as well as the superior rectus muscle and the distal part of the intraorbital optic nerve. Small chronic vascular foci subcortical and in the periventricular white matter. Inflammatory lesions of the cuneiform sinus and the mastoid process of the mastoid process of the left temporal bone with the presence of fluid collections. Left convex curvature of the nasal septum. Trace of fluid in the alveolar lobe of the left maxillary sinus. A biopsy of the lesion was recommended, and histopathological examination of the retrieved material allowed a diagnosis of adenocarcinoma of the lacrimal gland type. The results were suspicious for adenocarcinoma of the lacrimal gland or from the mucosa of the paranasal sinuses; however, metastasis could not be entirely ruled out. Infiltration of nearby blood and lymphatic vessels was notable. The cribriform variant is the most common and consists of lobules with circular pools of mucin.

Staining for mucin (+/-) positive in the cytoplasm of some tumour cells. The final diagnosis was the adenocarcinoma, sieve type. It was decided to implement surgical treatment, a complete resection of the lesion along with a margin of healthy tissue. Operative access to the tumour was difficult, as the tumour infiltrated and passed through the roof of the orbit. Surgical treatment included a pteroidal craniotomy. At first, the tumour was separated from the septum, situs and afterwards the parts of the lesion were removed from the wedge sinus. The postoperative course was uncomplicated, moreover after the procedure the complaints of the patient disappeared and visual acuity was completely restored.

DISCUSSION

The role of the surgical treatment and postoperative radiotherapy seems to be crucial both in the process of restoring the patient's function and preventing or delaying tumour recurrence. However, strict follow-up after surgery should be implemented to assess for both local recurrence and radiation related complications (Esmaeli et al. 2006). In this case, due to the location of the lesion and the infiltration of the roof of the orbit, the resection was particularly difficult. Adenoma cystic carcinoma as the primary orbital tumours in the absence of lacrimal gland involvement is particularly rare. The absence of neoplastic cells in the lacrimal gland does not rule out the diagnosis of ACC in the assessment of an orbital tumour (Cantù, 2021). Given the aggressive nature of this neoplasm with a propensity for recurrence, intracranial dissemination and late distant metastasis, the diagnosis of adenoma cystic carcinoma should be considered in every case of the occurrence of the mass in the orbit (Venkitaraman et al. 2008).

CONCLUSION

The patient underwent the operation very well and the result was satisfactory. Bodily functions were restored and he regained his visual acuity. The above data seem to speak in favour of a timely surgery. Which can be, as shown by the case described by us, even at a very advanced stage. It should be remembered that tumours in this location are most often metastases and should be excluded first. Whenever possible, it is important to take surgical action which, together with rapid rehabilitation, allows the patient to regain his pre-disease condition and function. The role of surgical treatment and post-op radio-therapy appears to be crucial both in restoring the patient's function and in preventing or delaying tumour recurrence. However, close follow-up after surgery should be implemented to assess both local recurrence and radiation complications Despite the difficulty of the tumour location in the present case – infiltration of the orbital roof – the patient was successfully restored. This is an encouraging sign for neurosurgery in similar cases. However, it should be borne in mind that decisions should always be made on an individual basis with regard to the patient's personal predisposition. However, as suggested by (Venkitaraman et al., 2008) given the aggressive nature of ACC with its propensity for recurrence, intracranial spread and late distant metastasis, the diagnosis of adenoma cystic carcinoma should be considered in every case of an orbital mass and treated surgically (Ramakrishna et al., 2016; Vidović Juras et al., 2019).

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Thyroid cancer and Hashimoto thyroiditis

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ABSTRACT

Thyroid cancer is the most prevalent neoplasm that affects the endocrine system. Hashimoto's thyroiditis is the most common autoimmune thyroid disease and a major enemy of the thyroid gland. Some studies suggest a greater risk of thyroid cancer among patient with thyroid autoimmunity, while others, investigate its relationship with thyroid cancer etiology, progression and patient prognosis.

In this review, we have analyzed published data on the relation to the association between thyroid autoimmunity and thyroid cancer, addressing influence on thyroid cancer progression, diagnosis, and prognosis of the patients with thyroid autoimmunity (especially Hashimoto's thyroiditis) but not on pathogenesis.

MEDLINE database (PubMed) platform was used and keywords combination "thyroid cancer and Hashimoto thyroiditis" or "thyroid cancer and thyroid autoimmune disease".

Most studies show that thyroid autoimmunity is an independent risk factor for thyroid cancer.

Hashimoto's disease is associated with an increased risk of thyroid cancer, but patients with HT and PTC have a better prognosis

Keywords: thyroid cancer, Hashimoto thyroiditis, thyroid autoimmune disease

INTRODUCTION

In Hashimoto's disease, symptoms of subclinical hypothyroidism are observed in the initial stage, which, as the disease progresses and the thyroid is destroyed, turns into an overt hypothyroidism. Therefore, the symptoms of Hashimoto's disease are those of an underactive thyroid. In some patients, lymphocytic infiltrates, progressive fibrosis and, consequently, atrophy of the gland are observed. Although not in all patients, it is clearly marked (Ai, 2003). It is also suggested that Hashimoto's disease predisposes to the occurrence of neoplasms within the thyroid gland, in particular primary lymphoma and papillary carcinoma (Łęcka, 2011). The aim of this study is to verify the current know-ledge about the impact of Hashimoto's disease on the development of thyroid neoplasms.

MATERIAL AND METHODS

LITERATURE SEARCH

Relevant studies were identified by searching PubMed (NCBI). The search included studies published from the January, 1, 2020 up to March, 5, 2022. Keywords used in this search were "thyroid cancer and Hashimoto thyroiditis", "thyroid cancer and thyroid autoimmune disease". The searches were limited to studies in English.

INCLUSION AND EXCLUSION CRITERIA

The inclusion and exclusion criteria for studies are described in Table 1. The literature review only focused on articles linking the topic of Hashimoto's disease and thyroid cancer. Especially in the context of the risk of developing thyroid cancer in people with Hashimoto's disease. Studies with comorbidities other than Hashimoto disease have not been allowed. Potentially studies eligible for further review were selected by screening their abstracts and title.

Table 1. Inclusion and Exclusion Criteria as Based on the PICOS Elements

PICOS	Inclusion Criteria	Exclusion Criteria
Participants	Adult patients with Hashimoto disease with or without thyroid cancer	Other thyroid diseases and comorbidities, animals, single samples
Interventions	All stages of the disease, substitution treatment	

Comparators	Patients with Hashimoto disease
	Patient with Hashimoto disease and thyroid cancer
	Healthy subjects
Outcomes	The impact of Hashimoto's disease on the risk development of thyroid neoplasms
Study design	All types of research

PICOS = participants, interventions, comparators, outcomes, study design.

DATA EXTRACTION

Researcher reviewed all titles and abstracts individually, extracted related results and duplicate results were omitted. Table 2 summarizes the data extraction.

Table 2. Summary of the extraction criteria

Keywords / **Medical base – numer of results**	**thyroid cancer and Hashimoto thyroiditis**	**thyroid cancer and thyroid autoimmune disease**	**Elimination criteria**
Pubmed	1,741	3,716	more than 2 years old science article case study (single sample) books other than Hashimoto's disease comorbidities animal research
Qualified articles: 26			

RESULTS

4 articles from 2022, 8 from 2021 and 14 from 2020 were found. These are studies that referred to the impact of Hashimoto's disease on the risk development of thyroid neoplasms. Because there are also articles in Pubmed on the assessment of possible common pathophysiological features of both disease entities.

Table 3 summarized the most recent results (from 2020 and 2022 year) of the search for the association between the occurrence of Hashimoto's disease and thyroid cancer

Author /year	Population/ type of research	Type of cancer	Results/ Conclusions
2022			
[Klubo-Gwiezdzinska]	Review article	All types	HT is associated with 1.6 times higher risk of PTC and 60 times higher risk of thyroid lymphoma than in general population
[Lau]	521 patients with papillary thyroid cancer, two groups, with or without Hashimoto thyroiditis	PTC	Only one-fifth of patients with PTC have coexisting HT. These patients tend to have less-aggressive tumor features such as extrathyroidal extension

[Lynch]	266 adult patients with unilateral thyroid nodules demonstrating atypia	All types, malignancy	HT was not associated with malignancy on both univariate and multivariate analysis
[Wang]	444 patients diagnosed with PTC	PTC	The autoimmune response of HT seems to reduce the central lymph node metastasis of HT PTCs.
2021			
[Abbasgholizadeh]	Review article		It is significant role for HT in developing papillary TC, medullary thyroid cancer and lymphoma but not anaplastic thyroid cancer and follicular thyroid cancer
[Albano]	314 consecutive patients	All types	HT does not seem to have a prognostic role considering progression-free survival and overall survival
[Gan]	310 samples, including 42 PTC occurring with HT and 268 simple PTC samples	PTC	PTC concurrent with HT had a lower risk of recurrence versus non-HT groups
[Hamouri]	951 patients	PTC	A background of HT does not seem to reflect a more aggressive cancerous biologic behavior
[Liu]	756 patients with PTC coexistent with the HT than non-HT group	PTC	PTC combined with HT is more common in women, and TSH level in HT group is higher than that in patients with PTC alone.
[Machens]	852 (58.4%) patients with papillary thyroid cancer, 181 (12.4%) patients with follicular thyroid cancer, and 426 (29.2%) patients with sporadic medullary thyroid cancer	Papillary, follicular, and medullary thyroid cancer	HT may be associated with differentiated (papillary and follicular) thyroid cancer but not with medullary thyroid cancer
[Sakiz]	1409 patients with PTC, comprising 443 patients with pathology-proven PTC with CLT and 447 patients with PTC without CLT	PTC	The coexistence of PTC and CLT is very frequent. No positive effect of the CLT and PTC combination was detected on any clinicopathologic factor
[Xu]	9210 patients with papillary thyroid cancer, 19% had Hashimoto thyroiditis	PTC	Patients with coexistent HT had less aggressive characteristics at presentation and better outcomes of PTC than did patients without HT
2020			
[Dedivitis, 2020]	155 patients	PTC	There was no relationship between thyroiditis and multifocality in cases of PTC
[Dias Lopes, 2020]	Raview article	All types	The presence of autoimmune thyroid disease is a factor that increases the risk of thyroid cancer
[Feldt-Rasmussen, 2020]	Review article	PTC	Recent evidence indicates that (auto)immunity and inflammation may be strong risk factors for papillary thyroid cancer development
[Hussein]	644 patient with cancer without HT, 26 patient with cancer and HT	PTC	These observations suggest interaction between iodine supply, autoimmunity, and carcinogenesis
[Mochamed]	80 patiens, 80% were PTC without HT and 20% were PTC with HT.	PTC	HT represents a step in the process of autoimmune inflammatory disease ending by the evolution of PTC with better prognosi

[Lee]	2928 patiens with PTC, two groups: with chronic lymphocytic thyroiditis and without	PTC	The CLT patients with PTC had better behavior features and prognoses than did those with PTC alone despite frequent multifocality and extrathyroidal extension
[Osorio]	1136 patients, 1047 (92.2%) women and 89 (7.8%) men	PTC	There is a greater probability of diagnosing PTC in surgical specimens with confirmatory histological data for chronic lymphocytic thyroiditis; in addition, in males under 40 years old this probability increases
[Paparodis & Karvounis]	3909 subjects	PTC	The incidence of PTC was significantly higher in chronic autoimmune thyroiditis compared with multinodular goiter
Paparodis & Bantouna]	1357 subjects	PTC	TSH concentrations might play a role in thyroid cancer development and severity in patients with thyroid nodular disease in the absence of chronic thyroid autoimmunity
[Rotond]	510 patients with chronic autoimmune thyroiditis	All types	The presence of chronic autoimmune thyroiditis appears to be associated with a negligible risk of developing clinically overt differentiated thyroid cancer
[Ryu]	850 patients with PTC	PTC	CLT is associated with less aggressive tumor characteristics and lymph node metastasis
[Schiffman]	2787 patients with thyroid cancer and 2787 individuals without cancer	All types	Any kind of benign thyroid alteration is associated with an elevated risk of thyroid cancer, such as HT too
[Słowińska-Klencka]	557 patients	-	The presence of the "multiple, discrete marked hypoechoic areas" variant significantly increased the odds of obtaining a cytological outcome which would be an indication for surgical treatment
[Sulaieva, 2020)	30 patients with PTC and 30 patients with PTC and HT	PTC	HT coexistence could facilitate the activation of antitumor immunity and the promotion of a cancer immune cycle

HT – Hashimoto thyroidis, PCT – papillary thyroid cancer, CLT – chronic lymphocytic thyroiditis.

DISCUSSION

In recent years, the occurrence of thyroid cancer among adolescents has been steadily rising. Papillary thyroid carcinoma (PTC) accounts for at least 70% of thyroid malignancies (Vita, 2018). There are some known risk factors for developing thyroid cancer including exposure to ionizing radiation, gender, family history, obesity, substance abuse and exposure to flame retardants (Han, 2018; Hoffmann, 2017; Schmid, 2015). It has been shown that changes in the thyroid gland itself also contribute to the development of thyroid cancer (Brito, 2014; Staniforth, 2016; Yun, 2019; Schiffman, 2020). Thyroid cancer can coexist with Hashimoto's thyroiditis (HT), adenoma, and nodular goiter. Some study shows a 20-27.9% coexistence between PTC and CLT (Mohamed, 2020; Kim, 2018). The variation in the incidence between studies; may be attributed to the differences in pathological interpretation of HT.

HT, also named Hashimoto's disease or chronic lymphocytic thyroiditis, is the most common autoimmune disease, characterized by high serum thyroid autoantibody titers. Thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) are important clinical markers for the diagnosis of HT, and were positive in 75% and 90% of HT cases, respectively (Wen, 2019). HT results in the formation of a goiter and the development of hypothyroidism. HT occurs most frequently in middle-aged women (Lee, 2020).

Also the coexistence of thyroid cancer and HT has been increasing in recent years, and an increase in the risk of developing papillary cancer has been reported for HT patients (Lau, 2022, Zeng, 2018). Abbasgholizadeh et all. reported that HT is factor for developing papillary thyroid cancer, medullary thyroid cancer and lymphoma but not anaplastic thyroid cancer and

follicular thyroid cancer (Abbasgholizadeh, 2021). Klubo-Gwieździńska suggest, that HT is associated with 1.6 times higher risk of PTC and 60 times higher risk of thyroid lymphoma than in general population (Klubi-Gwieździńska, 2022). Three different mechanisms have been proposed to clarify the association between chronic lymphocytic thyroiditis and risk of development PTC: (i) TSH stimulation, (ii) chemokines and other molecules produced by the lymphocytic infiltrate, (iii) expression of certain proto-oncogenes (Vita, 2018).

Our recent literature review suggests that Hashimoto's disease is associated with an increased risk of thyroid cancer, what previous findings published also (Zeng, 2018; Schmid, 2015). However, in parallel there are studies showing that, there are no positive effect of the CLT and PTC combination was detected on any clinicopathologic factor (Sakiz, 2021).

Thyroid cancer prognosis and survival rate of about 97% when detected early, but the patients who develop lymph node metastasis tend to have disease recurrence, decreasing the survival rate (Dias Lopes, 2020). Some authors argue that HT patients with PTC did better behavioral characteristics and prognosis than those only with PTC despite frequent multifocals and extrathyroidal extension (Lee, 2020). Some of researches suggest that CLT is associated with less aggressive tumor characteristics and lymph node metastasis (Ryu, 2020). HT appears to have some potential protective effect against thyroid cancer, reducing the risk of malignancy (Lynch, 2022). Moreover, a less aggressive form of malignancy in PTC patients in the top of HT has been reported, though but this conclusion was associated with controversies in an endemic area of iodine deficiency goiter (Hussein, 2020). HT appears also to reduce the central lymph node metastasis, what is more significant in male sex with HT PTCs (Wang, 2022). Some potential positive effect of HT on PTC may be related to gender, tumor size and the size of thyroid peroxidase antibody level and more research is required to confirm (Wen, 2019).

COCNLUSIONS

In summary, HT is a risk factor for the occurrence of thyroid neoplasms, but comorbidity will play a protective role in the progression of cancer prognosis.

LIMITATIONS

Researchers focus only on English literature. The literature review concerned only the Pubmed platform.

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Ultrasound imaging of uterine leiomyomas and leiomyosarcomas – is there a reliable method to distinguish malignant and benign masses?

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ABSTRACT

Uterine myometrial tumors are predominantly benign conditions that affect one-third of women and represent the main indication for hysterectomy. Preoperative imaging is of utmost importance for characterization and for precise mapping of myometrial tumors to best guide therapeutic strategy. New minimally invasive therapeutic strategies including morcellation, myolysis, uterine artery embolization and image-guided radiofrequency or high-intensity focused ultrasound fibroid ablation have been developed for the treatment of women with symptomatic uterine leiomyomas. However, preoperative differentiation between atypical leiomyomas and leiomyosarcomas is critical on imaging as uterine sarcoma requires a specific surgical technique to prevent dissemination. A single, rapidly growing uterine tumor, associated with endometrial thickening and ascites, in post-menopausal women is suspicious of uterine endometrial stromal sarcoma and carcinosarcoma. Suggestive sonographic and MRI imaging features have been described, but overlap in imaging appearance between uterine leiomyosarcomas and cellular leiomyomas makes it challenging to ascertain the diagnosis. This review aims to illustrate the imaging features of atypical uterine fibroids, uterine sarcomas and their potential mimickers to make the reader more familiar with this serious gynecologic condition that needs special consideration.

Keywords: smooth muscle neoplasms, uterine fibroids, uterine sarcoma, ultrasound imaging, pattern recognition, STUMP, smooth muscle tumor of unknown malignant potential

INTRODUCTION

Leiomyomas (LM) are the most common estrogen-dependent uterine tumors that occur in 50–60% of women, rising to almost 70% by the age of 50 (Stewart, 2015; Wise, 2016). Even when asymptomatic, they may lead to infertility or they may present non-specific symptoms such as uterine bleeding, dysmenorrhea, dyspareunia and/or chronic pelvic pain (Freytag, 2021). These symptoms frequently reduce severely the life quality of affected women and their families. However, when patients with fibroids present with symptoms, it is not always possible to prove that they are actually caused by these particular type of uterine lesions (Donnez, 2016). On palpation and at surgery they frequently cause the uterus to appear bulky and may change the normal uterine contour (Fig. 1).

When symptomatic, these masses may represent indications for laparoscopic surgery and/or hysterectomy (Donnez, 2018). However, although vast proportion of all women in reproductive age may have uterine leiomyomas, only 10% of them has to be operated due to large tumor size or presenting symptoms. Some uterine fibroids have the capability to survive in the unfavorable conditions, having better adhesion ability, higher proliferation rate, and being more resistant to apoptosis (Raga, 2016). Intramural fibroids are usually well demarcated due to the formation of a pseudocapsule related to the compression of the surrounding myometrium. When the growth of these masses involves another outer or inner uterine myometrial layer, such fibroids are usually classified as subserous or submucous leiomyoma. Large uterine fibroids often degenerate as they outgrow their blood supply. The various types of degeneration include: (1) hyaline, (2) cystic, (3) myxoid, and (4) red degeneration. The most common, hyaline degeneration affects >60% of cases. In these masses tumor smooth muscle cells are replaced by proteinaceous tissue. Proliferation of myocytes and production of an extracellular collagenous matrix are two characteristic histological features found in

most leiomyomas. The collagenous matrix is often abundant in larger masses. In the areas in which the accumulating collagen is excessive, the myocytes are progressively separated from their blood supply, resulting in myocyte atrophy and eventually cell death. Hypocellular, hyalinized areas may be accompanied by cystic degeneration characterized by edematous and acellular tumor center while in hyaline degeneration (Flake, 2013). Two other rare types of degeneration are characterized by soft mucoid areas in myxoid type and tissue necrosis in red type fibroid. Rare leiomyomas manifestations and atypical site tumors include: metastasizing leiomyoma, peritoneal disseminated leiomyomatosis, intravenous leiomyomatosis, parasitic or retroperitoneal growth (Liu, 2021). Nevertheless, since the development of various types of uterine fibroids appears to be multifactorial with genetic and epigenetic factors controlling the progress of the disease, the etiology of these rare lesions remains unclear (Lagana, 2017; Ciebiera, 2020).

A large variation in fibroid growth rates has been described in the medical literature. Generally, these lesions may grow at very different rates and, conversely, they may even spontaneously regress (Li, 2021). The ability to predict the growth rate of fibroids with the use of various imaging techniques could help clinicians decide which their patients should be advised for treatment. For example, asymptomatic women with fibroids detected incidentally may require follow up if these lesions are likely to have a slow growth rate. Alternatively, surgical removal could be indicated in women with fast growing tumors. Vascularization type of fibroids is known to be important factor in tumor growth prediction. Abundant vascularity indicates growth potential and non-invasive treatments like e.g. high-intensity focused ultrasound (HIFU) or uterine arteries embolization are less effective in avascular fibroids (Łoziński, 2021; Pelage, 2005).

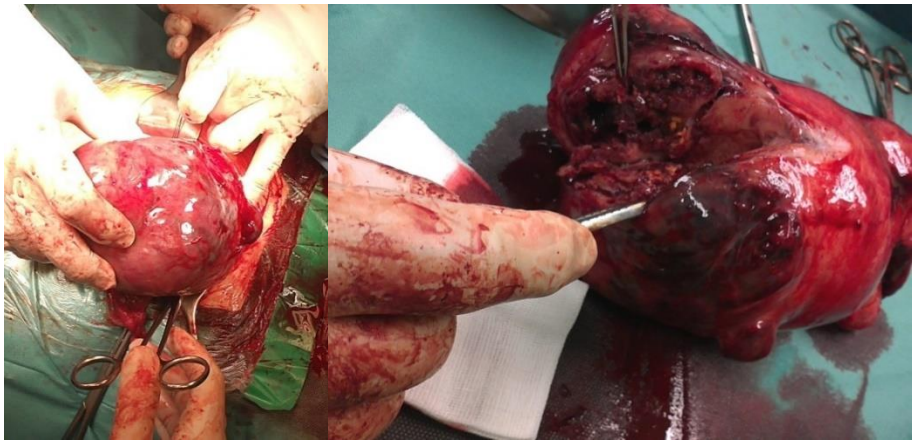

Figure 1. Typical macroscopic appearance of uterine leiomyoma at open surgery (A) and excised fibroid internal structure (B)

Rapid leiomyoma's growth, caused by its transformation into leiomyosarcoma (LMS) is rare and takes place in about 0.1-0.8% of all cases (Schwartz, 2006; Al Ansari, 2013; Bharambe, 2014). Preoperative identification of atypical uterine fibroids and sarcomas may be extremely difficult and time-consuming. In affected women a late diagnosis is a major problem and may contribute to disease progression and a worse response to surgical treatment. Currently most small and mid-sized uterine tumors can be removed with the use of minimally invasive laparoscopic surgery. Medical concerns indicated the increased longer-term morbidity associated with laparotomy and classical hysterectomy. When ovaries are removed there is an increased delayed pelvic bones fracture risk, cardiovascular disease, dementia, and pelvic floor prolapse. These possible complications have driven exploration of non-hysterectomy treatments for symptomatic uterine fibroids. In recent years several less invasive methods have gained an increasing role for this reason. These include fibroid morcellation at laparoscopic surgery, uterine artery embolization with polyvinyl alcohol derivatives, radiofrequency myolysis guided by transvaginal ultrasound, or HIFU under magnetic resonance imaging (MRI-HIFU)-guidance that destroys fibroid tissues (Donnez, 2016; Donnez, 2017; Laughlin-Tommaso, 2016). All these less invasive or non-invasive modalities are contraindicated in women with suspected malignant uterine lesions in order to avoid intra-abdominal tumor dissemination.

Uterine leiomyosarcoma accounts for 3-7% of all primary uterine malignancies with an incidence of 0.7 per 100,000 women (Rey Valzacchi, 2020). In a 10-years series of 921 hysterectomies or myomectomies for presumed myomas, Mühlenbrock et al. have found that the incidence of LMS was 1 in 460 (Muhlenbrock, 2021). In their group the incidence of any unexpected pathology in presumed myomas was 1 in 83 and included six atypical myomas, one leiomyoblastoma, one epithelioid myoma, two LMS, one mixed epithelial and mesenchymal tumor and one incidental cervical cancer. An important question can be asked here, if these malignancies could be suspected before surgery. Typically, solid uterine masses that at sonography demonstrate smooth and sharp margins, are homogeneous on gray-scale imaging and have peripheral concentric vascularity on color Doppler, in general are incompatible with the diagnosis of leiomyosarcoma. Since the risk of malignancy is low in these cases they are potentially suitable for minimally invasive treatments. On the other hand, some uterine leiomyomas may present atypical features that overlap with leiomyosarcomas, especially in younger females. Such "atypical" fibroids create the most difficulties in triaging patients to non-hysterectomy treatments. In clinical practice tumors derived from uterine smooth muscle cells present a broad spectrum ranging from leiomyosarcomas to leiomyomas, can be distinguished based on histopathological features including the degree of cytologic atypia, mitotic count activity (mitotic index per 10 high-power fields, HPFs), and presence of tumor cell necrosis.

However, in some of such lesions, these histopathological features may appear in an unusual combination which does not meet the diagnostic criteria of a leiomyoma or leiomyosarcoma. Such a heterogeneous group of lesions is characterized by histological and biological diversity that at histology cannot be certainly recognized as either a benign leiomyoma or a malignant leiomyosarcoma (Ip, 2009). These diagnostically challenging uterine solid masses are called "smooth muscle tumors of uncertain malignant potential" (STUMPs). Due to relative rarity of STUMPs their clinical behavior and prognosis have not been fully understood, yet, and the actual incidence of these tumors is still unknown. Moreover, even following detailed histological analysis a postoperative diagnosis of STUMP is also difficult due to the lack of uniform diagnostic criteria (Rizzo, 2020). Histologically, STUMPs are characterized by the proliferation of muscle cells in varying proportions and are classified into three categories according to the degree of differentiation: well-differentiated, intermediate-differentiated and undifferentiated. STUMPs are highly variable in size and may be as small as 2 cm and as large as 35 cm. The lesions are most often unilateral-98% of cases-solid or cystic-solid with smooth external surface. A capsular rupture is encountered in about 10% of cases, and ruptures are sometimes accompanied by ascites. Since the rate of extrauterine, intra-abdominal recurrence for atypical leiomyoma is low (<2%), the related risk for distant metastasis is a negligible (Rizzo, 2020). However, since the final histological diagnosis may be difficult, all women with confirmed STUMPs, especially when only myomectomy was performed should be informed of recurrence risk and monitored closely (Zhang, 2021).

In clinical setting, imaging techniques are crucial for the planning of medical or surgical treatment in women with gynecologic tumors. Pelvic ultrasound can be used both as primary or an adjunct modality to magnetic resonance imaging (MRI) of uterine lesions. Currently, computed tomography (CT) scan is not the investigation of choice for the characterization of pelvic masses. However, uterine fibroids are often seen incidentally on CT lower abdomen and pelvic scans performed for other reasons. The typical finding is a bulky, irregular uterus or a mass in continuity with the uterus. Ultrasound imaging in typical cases is capable to differentiate between LM and LMS and thus can help in planning treatment. However, there are also considerable limitations to the clinical application of selected ultrasound features that distinguish LM from LMS. Moreover, due to multiple differences in the ultrasound scanning techniques and parameters assessed by various studies and to the relative rarity of LMS at single institutions, there is continuing uncertainty regarding how to use and how to integrate various sonographic parameters with clinical and other imaging studies data to improve diagnostic accuracy. Typical problems with pelvic imaging of uterine smooth muscle tumors include:

1. the presence of multiple uterine masses in a single patient where

direct pathologic–imaging correlation may be difficult
2. variability of the imaging features of various fibroids in one patient that may lead to potential bias in reported results
3. assessement of echostructure within a hete-rogeneous mass, when this measure is non-standardized across various ultrasound systems
4. lack of blinded comparison of imaging characteristics and small numbers of fibroids and leiomyosarcoma cases and/or lack of measurement of interobserver agreement related to the imaging features that distinguish LM and LMS

This review aims to illustrate the ultrasound imaging features of typical and atypical uterine fibroids, sarcomas and other potential mimickers to make the sonographers more familiar with the preoperative differentiation between benign and malignant uterine smooth muscle cell tumors.

ULTRASOUND FEATURES OF LEIOMYOMAS

Two-dimensional (2D) gray-scale sonography is the primary imaging modality used to evaluate uterine fibroids. Preoperative ultrasound assessment of myometrial lesions is best performed by ultrasound experts, who compared with gynecologists, show a greater degree of agreement with histopathology and greater interobserver reproducibility of the imaging results. However, the experts in gynecological ultrasound are not always available and in clinical reality a standard sonographic examination is typically performed by non-expert examiners. In large uterine masses the difficulties of this imaging procedure may differ greatly due to the diverse clinical scenarios that include the echo distribution, placement depth, and number of fibroids found. The vast majority of uterine fibroids appear as oval or round isoechoic or hypoechoic, well-delineated single or multiple lesions located within the myometrium. However, various sonographic patterns have been described to date and the differences are thought to be due to the different forms of internal degeneration. Hypoechoic or anechoic spaces indicate the presence of areas of hemorrhagic and/or cystic degeneration or proteolytic liquefaction. A hyperechoic peripheral rim associated with posterior shadowing or a hyperechoic, internally speckled pattern is typical for a calcified uterine fibroid (Fig. 2.)

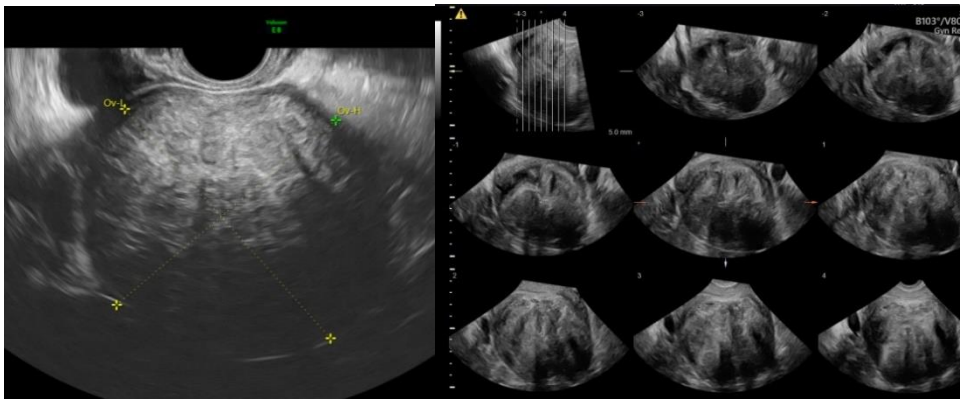

Figure 2. Transvaginal imaging of a typical, oval-shaped uterine leiomyoma with mixed echogenicity and posterior shadowing seen on 2D gray scale (A) and at tomographic three-dimensional ultrasound imaging (TUI)-image (B)

At ultrasound examination it may be clinically important to distinguish uterine fibroids and uterine adenomyosis. Adenomyosis usually appears enlarged, globular, with regular external contour, while fibroids not only cause the organ enlargement but also alter uterine contour (Cotrino, 2020). Typical sonographic features of adenomyosis include an inhomogeneous tissue with irregular and no defined borders that cause asymmetric thickening of the affected myometrium. The echostructure of adenomyosis is usually characterized by vascular spaces and radial stripes that, when moving the probe, may determine a visual effect called "rain in the forest sign" (Cotrino, 2020). Conversely, uterine fibroids appear as solid and well-defined lesions with a visible pseudocapsule and shadowing (Fig. 2A and 2B). Internal vascularity of typical uterine fibroids seen on color Doppler imaging is usually scant and typically peripheral (Fig. 3A and 3B).

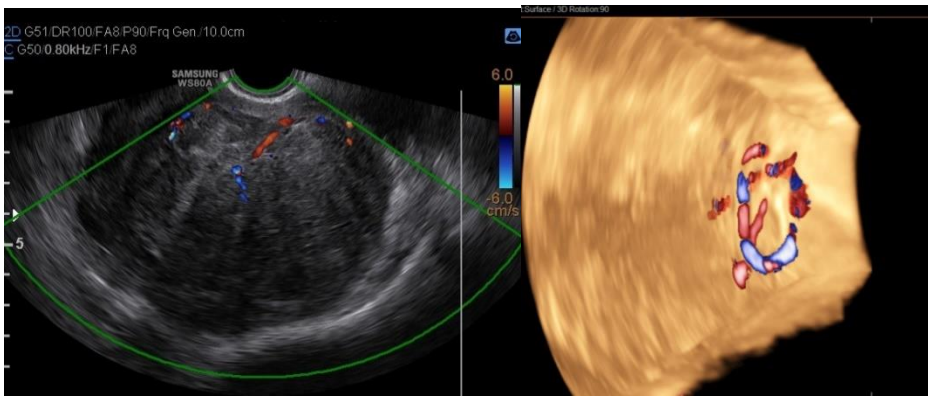

Figure 3. Transvaginal imaging of an oval-shaped uterine leiomyoma with mixed echogenicity and scant peripheral vascularity seen on color Doppler (A) and concentric blood vessels three-dimensional color Doppler image (B)

Tumor vascularity was traditionally thought of as a disease process intrinsic to the uterus, however, accumulating evidence suggests that fibroid growth may be linked with the systemic vasculature system (Kirschen, 2021). Moreover, fibroid vascularization correlates with absolute tumor volume change and also with fibroid growth rate per year (Seddon, 2011).

The standard clinical procedure for evaluation of fibroid vascularization is magnetic resonance imaging (MRI) with contrast. However, even very small vessels and blood flow in fibroids and their pseudocapsule can be also visualized with the use of color Doppler or power Doppler ultrasound. Volume and vascular-flow indices called VI, FI, VFI in uterine masses can also be calculated by 3D sonography using the manual contour tumor delineation (Perri, 2009; Testa, 2015). Nieuwenhuis et al. have found that in women with uterine fibroids without therapy, index of baseline vascularization (VI) measured with 3D power Doppler is correlated with absolute fibroid volume change at 12 months and with fibroid growth rate per year (Russo, 2022). The results of 3D sonographic vascularity assessment are highly dependent on image settings and experience of the operator and therefore may not be consistently reproducible. However, this imaging modality has been available for more than 20 years now and 3D ultrasound assessment of fibroid size and vascularity is much cheaper than MRI. Two examples of uterine fibroid vascularity on 3D sonographic imaging are presented below (Fig. 4A and B).

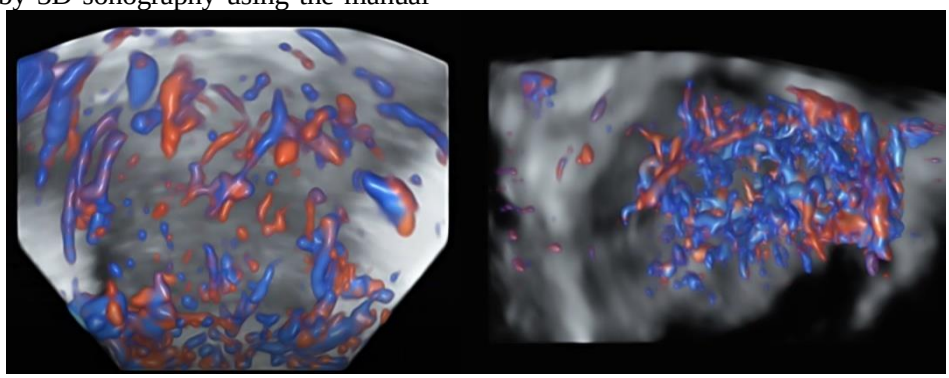

Figure 4. Transvaginal 3D imaging of a concentric vascularity on the periphery of uterine leiomyoma (A) and 3D image of abundant central vascularization within the oval-shaped uterine wall mass (B)

Although uterine fibroids are clonally derived from a single cell, despite being monoclonal, the cellular phenotypes that make up these lesions are heterogeneous consisting of predominantly smooth muscle cells (SMC) and fibroblasts (Ropacka-Lesiak, 2016). Depending of cell composition and the degree of internal degeneration fibroids may present complex echogenicity at ultrasound imaging. They may contain areas of solid parts adjacent to areas with fluid attenuation. When an acute necrosis occurs in a fast growing leiomyoma, at ultrasound examination more heterogeneous internal structures or internal sonolucent areas can be usually seen. When reviewing the ultrasonographic images in our database, we found that the features of these atypical uterine lesions could be classified into two main types: solid-

cystic and solid. Some rare benign smooth muscle cell derived masses like e.g. uterine fibromyolipoma display characteristic imaging findings that are due to the presence of internal fat. At pelvic sonography hyperechogencic and/or inhomogeneous echostructure is seen and resembles fat-containing dermoid cysts (Fig 5A). Another rare type, cellular leiomyoma is composed of compact smooth muscle cells with little or no collagen. Cellular leiomyomas are benign entity which may show imaging features of both degenerated leiomyoma and myometrial sarcoma. Typically at pelvic ultrasound, cellular leiomyoma is well defined without extra-myometrial invasion (Fig. 5B).

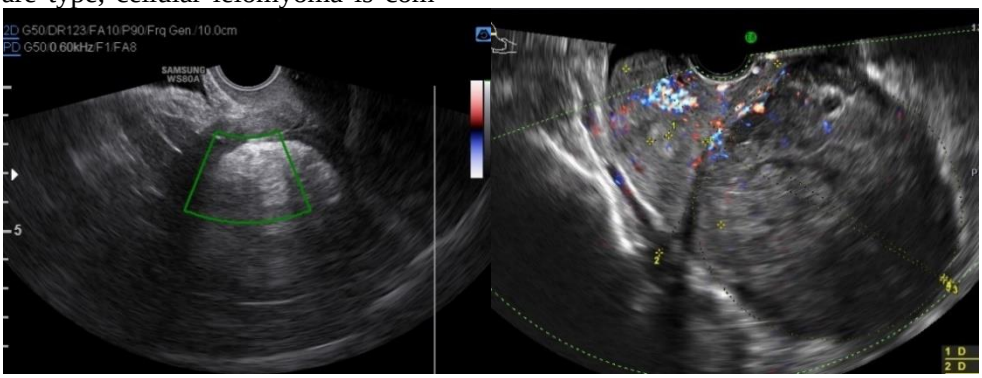

Figure 5. Transvaginal ultrasound images showing a hyperechogenic uterine lipoleiomyoma (A) and solid cellular leiomyoma (B). Transvaginal ultrasound shows in both cases uterine cervix (upper left corner) in a solid-cystic mass and solid lesion (B)

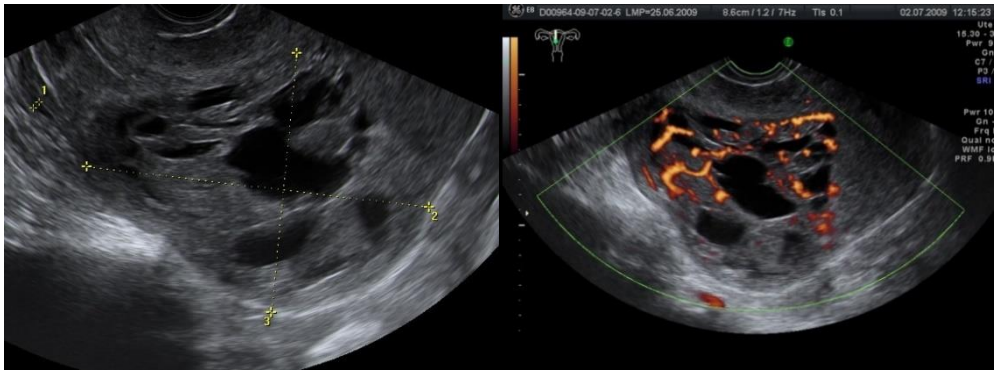

Figure 6. A case of degenerated cystic-solid leiomyoma (A) and cystic-solid, centrally vascularized angioleiomyoma (B)

In a vast majority of cases, transvaginal ultrasound combined with transabdominal scanning may clearly depict the uterine origin of fibroids. Nevertheless, some doubts may arise in cases of subserosal lesions that are pedunculated. These lesions may mimic other pelvic non-uterine masses. In particular, when uterine wall and cervix cannot be identified at pelvic sonography such atypical uterine lesions may be mistaken for multilocular adnexal cystic-solid tumors (Fig.7).

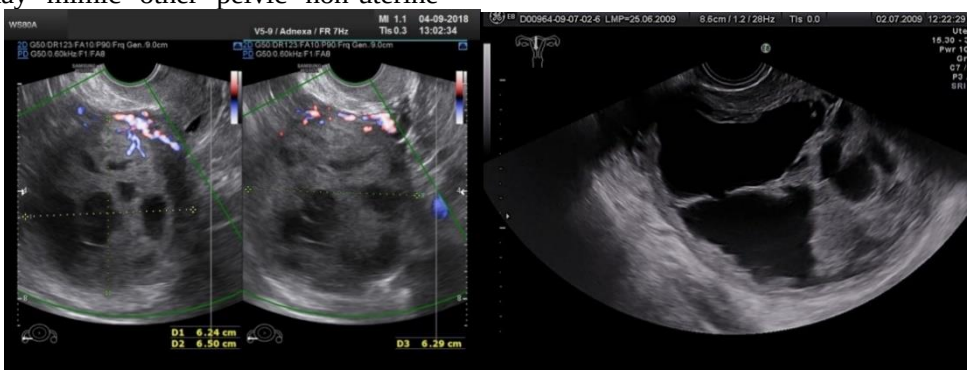

Figure 7. Two perpendicular images of atypical uterine fibroid with mixed internal echogenicity and multiple anechoic/fluid spaces (A) and a transvaginal gray-scale image of predominantly cystic multilocular mass with uneven internal margin's solid parts (B). No uterine clear structures were seen on pelvic sonography and both masses were mistakenly classified as probably malignant adnexal lesions

When sonographic assessment is difficult, such as in masses presented on Fig. 7, MRI is an extremely accurate tool for determining the anatomical origin of a pelvic mass. Particularly useful for this purpose are high-resolution T2-weighted images acquired orthogonal to the longest axis of the endometrium. In fact, the demonstration of conti-nuity of the pelvic mass with the adjacent myometrium enables the confirmation of its uterine origin, whereas the presence of a cleavage plane between the lesion and the adjacent myometrium helps exclude its uterine origin with certainty

ULTRASOUND FEATURES OF UTERINE SARCOMAS

Uterine sarcoma may occur spontaneously or, in rare cases, may be a result of malignant trans-formation of a pre-existing uterine leiomyoma. The specific preoperative diagnosis of uterine sarcomas is difficult and presents a real challen-ge for clinicians. Traditionally, it has been thought that a symptom indicating a high risk of sarcoma development is rapid growth of the "myoma". However, evidence from clinical studies suggests that the probability of uterine sarcoma in this clinical context is very low and does not exceed 0,1-0.23% [26]. The intro-duction of morcellation as a surgical technique in the laparoscopic removal of unexpected uterine sarcomas has made the clinical decisions even more difficult. Generally, the prognosis appears to be worse in women with latent uterine sarcomas that has been removed via laparoscopic morcellation (Perri, 2009).

Two-dimensional (2D) gray-scale sonography is currently the primary imaging modality used to evaluate presumably malignant uterine tumors. Color Doppler ultrasound may provide addi-tional information regarding the vascular pattern of the lesion. Testa et al. (Testa, 2015) have concluded that the detection of a large uterine myometrial tumor with inhomogeneous compact echogenicity, with irregular anechoic areas due to necrosis and absence of "radial stripy echogenicity" and with an irregular vasculari-zation could be suggestive of malignant myo-metrial lesions. Typical sonographic images of uterine sarcomas are presented in Fig. 8A and B.

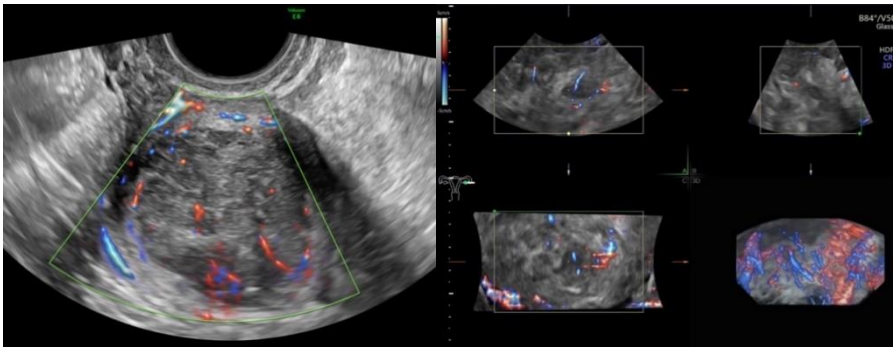

Figure 8. Typical ultrasound images of uterine leiomyosarcoma seen on 2D (A) and 3D (B) sonoangiography. Chaotic and central vessel arrangement within the mass can be better seen at three-dimensional blood flow imaging

Fig. 8 shows that at least in some cases several typical differences between LM's and LMSs like mixed echogenicity pattern and abnormal abundant tumor vascularity can be demonstrated on both 2D and three dimensional (3D) ultra-sound imaging. The additional use of 3D power Doppler blood flow and tumor vascularity assessment may provide additional information. The most recent analysis presented by Russo et al. (Russo, 2022) showed that ultrasound features of leiomyomas, such as circumferential and central lesion vascularity, cystic areas, and dimensions were all important parameters, especially when combined with the patient's age. These features were useful in the differen-tiation of typical uterine fibroids from malignant lesions in a pre-operative setting. However, our experience indicates that due to apparent overlap in imaging presentation between at least some atypical sarcomas and degenerated leiomyomas the ultrasound imaging may be misleading. Two examples of such difficult to differentiate uterine malignant tumors are presented on Fig. 9 and Fig. 10.

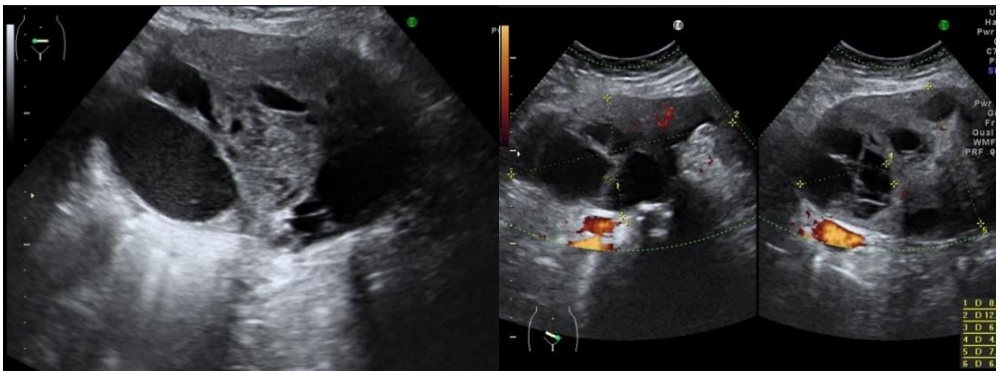

Figure 9. Atypical uterine cystic-solid leiomyosarcoma mimicking fibroid with mixed echostructure on gray-scale imaging (A) and at color Doppler blood flow mapping (B)

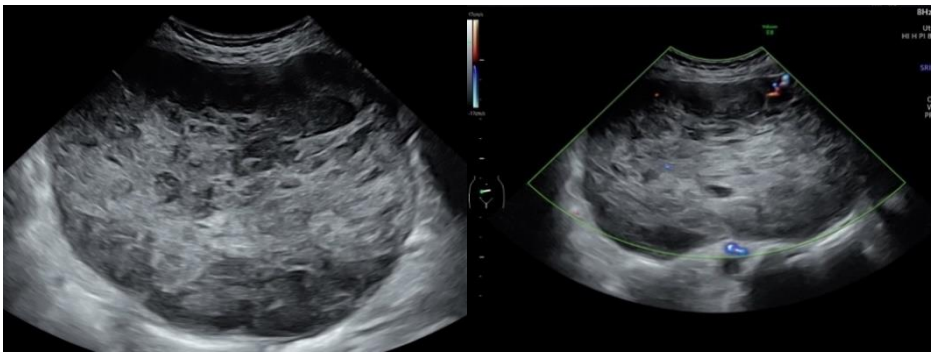

Figure 10. Atypical solid uterine leiomyosarcoma mimicking fibroid with mixed echostructure at gray-scale imaging (A) and at color Doppler where only scant peripheral vascularity could be seen (B)

SONOGRAPHIC IMAGING OF UTERINE SOFT TISSUE TUMORS OF UNKNOWN MALIGNANT POTENTIAL (STUMPS)

Atypical fibroids with unknown proliferation potential, called STUMPs comprise a group of relatively rare uterine lesion that do not have the characteristic clinical course. At imaging studies these tumors typically do not show malignancy features. However, because of their rarity and substantial variability of sonographic images, these masses should be differentiated with both leiomyomas and uterine sarcomas (Cotrino, 2022; Ropacka-Lesiak, 2016). As with the suspicion of sarcomas the final diagnosis should be only made after histopathological analysis. Fig. 11. presents a case of the histologically confirmed STUMP.

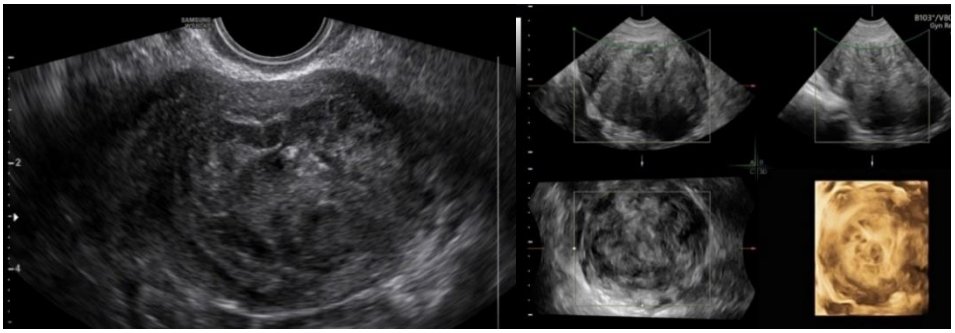

Figure 11. Transvaginal ultrasound image showing a tumor diagnosed finally as STUMP on gray–scale (A) and 3D imaging (B)

Mixed echostructure with internal shadowing, round, oval shape and scant vascularity suggested benign tumor. However, those ultrasonographic features have a low specificity and ultrasonography cannot be recommended as a reliable imaging modality to detect and characterize uterine STUMPS and atypical sarcomas. An open question remains if this lesion could be accurately predicted with the use of other imaging modalities. Apparently, when triaging these difficult cases of uterine tumors additional MRI imaging should be considered (Fujii, 2021; Aminzadeh, 2021). This observation is confirmed by the study of Amizandeh at al.

(Aminzadeh, 2021) who recently demonstrated that the marginal irregularity and/or ill-definition of lesion borders were highly reproducible observations for two independent, blinded observers reviewing a series of cases of LM, STUMPs and LMS. Marginal irregularity as well as DWI hyper/ADC hypointensity consistent with restricted diffusion was associated with 81% sensitivity and 78% specificity for LMS/STUMP.

SUMMARY

Uterine fibroids at ultrasound imaging present typically as well-defined, solid oval shaped masses. The lesions with a whorled appearance may resemble the echogenicity of the myometrium, but sometimes may be hypoechoic. Even non-calcified fibroids often show a degree of posterior acoustic shadowing. Although most cases have predictable sonographic features, for each histological entity there are some cases that do not exhibit typical features. The examples may include absence of vessels in a tumor solid parts seen on high resolution color Doppler, a relatively large solid vascularized part with no malignancy or smooth tumor margins in a malignant sarcoma. The appearance of non-typical morphology may also be due to physical limitations like e.g. the absence of Doppler signals when the distance between the ultrasound probe and the uterus is large. The difficulties may also be associated with abnormal uterus position over the symphysis pubis after cesarean section, histological characteristics, for example, presence of endometrial cysts in myometrium or other true outliers. The diagnostic accuracy of ultrasonography in differentiating between benign and malignant uterine masses has been shown to be dependent on the expertise of the sonographer.

The difficulties with the differentiation of atypical tumors at the time of the female pelvic structures imaging could result in misdiagnosis that in turn may lead to unwanted follow-up and treatment anxiety. Therefore, consultation with experienced centers should be the first step in the management of uterine masses with non-typical sonographic appearance. Because of apparent overlap in imaging features between degenerated leiomyoma and sarcoma, it is now suggested to consider collection of small tumor tissue sample from suspicious leiomyoma detected on pelvic and/or abdominal imaging. Biopsy samples are obtained transabdominally using "true-cut" method or using transcervical ultrasound-guided biopsy Following such biopsies histopathological and immunohistological analysis can be performed to improve diagnostic accuracy. Although time-consuming and costs incurred by biopsy it should be kept in mind that at least some of misdiagnosed uterine tumors may be fatal, and malignancy recurrence following conservative surgery is likely to happen. These women should also be closely monitored for possible complications that may happen during follow-up.

Finally, we conclude that although several tumor features on ultrasonography, CT and/or MRI can raise suspicion of a uterine malignant tumor, none of these modalities could provide a definitive diagnosis. Sonographic imaging and differentiation of uterine tumors presumed to be leiomyomas should always include a possible presence of other entities that could be atypical degenerated fibroids, adenomyosis, solid adnexal masses, focal myometrial contractions, and/or uterine leiomyosarcomas. "True-cut" or transvaginal ultrasound guided biopsy samples for immunohistochemistry should be considered before surgery in women with difficult to characterize solid or solid-cystic uterine lesions. Apart from MRI, newly designed studies based upon 3D ultrasound technologies will certainly be important in the precise evaluation of the future growth of typical and atypical fibroids and their potential response to medical and surgical treatments.

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The main mechanisms of blood vessels formation in ovarian cancer

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ABSTRACT

Introduction: Ovarian cancer (OC) is often detected (70%) in an advanced stage of development, which results in poor treatment outcomes and poor prognosis. The characteristic of this disease is the low survival rate: 20-25% for stage III tumours (according to FIGO) and 5% for stage IV tumours. Despite numerous studies, the pathogenesis of OC is not fully understood. The study aimed to review and analyse the literature on the mechanisms of blood vessel formation in OC.

Material and methods: In order to search for scientific articles, the PubMed database was used with the following keywords: ovarian cancer, tumour angiogenesis, vasculogenic mimicry, antiangiogenic therapy, VEGF, and VEGFR.

Results: In the pathogenesis of OC, the formation of blood vessels determines rapid tumour growth, tumour spread, and metastasis. The most common mechanism of the formation of new blood vessels in a tumour is sprouting angiogenesis. It is a complex and multi-step process involving: the production of pro-angiogenic growth factor by neoplastic cells as a result of hypoxia, activation, proliferation, and migration of host vascular endothelial cells, formation of new vessel sprouts and their elongation, formation of lumen and maturation of new vessels. Another angiogenesis-independent mechanism of tumour vascularization is the vascular mimicry in which neoplastic cells participate. In OC therapy, drugs from the group of angiogenesis inhibitors are used. In cases of developing resistance to anti-angiogenic drugs, treatment aimed at inhibiting the formation of vessels in the mechanism of vasculogenic mimicry opens up the possibility of an effective OC therapy.

Summary: Angiogenesis and vasculogenic mimicry play a key role in the development and progression of OC. The knowledge of the factors influencing these processes may contribute to increasing the effectiveness of OC therapy.

INTRODUCTION

Ovarian cancer (OC) is often (around 70%) detected in advanced stages (III and IV AJCC stages), which are characterized by a low 5-year survival rate (41% for stage III and 20% for stage IV), with an overall survival – 47% (Torre, 2018). Despite many studies pathogenesis of the OC is not fully understood. It is known that the formation of new blood vessels is involved in the pathogenesis of OC and it determines the rapid growth of the tumour, tumour spread, and metastasis. There are several mechanisms for the new blood vessels formation in OC, such as vasculogenesis, sprouting angiogenesis, intussusceptive angiogenesis, vascular cooption, and vasculogenic mimicry (Cao, 2013; Viallard, 2017). Vasculogenesis is the formation de novo of new blood vessels from endothelial progenitor cells. It occurs mainly in embryonic and foetal life, and after birth this process is at a low level. In sprouting angiogenesis blood vessels are created from the existing vasculature. Intussusceptive angiogenesis relies on the intravascular splitting of the vessels. Vessel cooption is formed by the migration of tumour cells along existing blood vessels and incorporation into the tumor. Vasculogenic mimicry (VM) is an angiogenesis-independent mechanism, in which cancer cells differentiate into endothelium-like phenotypes to create structures acting as blood vessels (Cao, 2013; Viallard, 2017 , Luo, 2020). Among the above-described mechanisms, angiogenesis and VM play a key role in the pathomechanism and development of OC (Cortez, 2018).

In this review, we discuss the key mechanisms of new blood vessels formation in OC, namely sprouting angiogenesis and vasculogenic mimicry, along with potential targets for antineoplastic therapy in OC.

SEARCH STRATEGY ANF SELECTION CRITERIA

The aim of the work was to collect data about angiogenesis mechanisms in OC, determine the importance of vasculogenic mimicry in OC, and show new possible treatment options. The authors review information's from original articles published since 2002. The articles were searched in the PubMed database, using the following keyword: ovarian cancer, tumour angiogenesis, vasculogenic mimicry, antiangiogenic therapy, VEGF, and VEGFR. Manually selected materials related to the topic were added.

ANGIOGENESIS

The most common mechanism of new blood vessels formation in a neoplastic tissue is sprouting angiogenesis, which is the formation of new blood vessels from pre-existing vasculature (Liu, 2021). Sprouting angiogenesis is a complex and multi-stage process usually caused by hypoxia (Viallard, 2017). Hypoxia in neoplastic cells produces and stabilizes the hypoxia-inducible factor-1 (HIF), which is composed of α and β subunits. The HIF-1α subunit is known to be sensitive to hypoxia which contributes to its stabilization. The active HIF is a transcription factor that induces the expression of pro-angiogenic genes, e.g., vascular endothelial growth factor (VEGF) and its receptor (VEGFR2) as well as other proangiogenic factors (Gupta, 2016; Zimna, 2015).

VEGF is the master stimulator of both physiological and pathological angiogenesis and lymphangiogenesis and occurs in four isoforms: VEGF-A, -B, -C, -D. Isoforms VEGF-A, -B, stimulate endothelial cell proliferation, regulate the formation of blood vessels from pre-existing vessels at a later stage, and increase vascular permeability and chemotaxis of vascular endothelial cells (Ferrara, 2005; Benedito, 2012). Isoforms VEGF-C, -D, regulate lymphangiogenesis. VEGF interacts with three subtypes of VEGF receptors occurring on the cellular membrane known as VEGFR-1, VEGFR-2, and VEGFR-3. All these receptor types possess their own intracellular tyrosine kinase activity. The VEGFR-1 and VEGFR-2 regulate angiogenesis and vascular permeability, and the VEGFR-3 mainly regulates lymphangiogenesis (Alitalo, 2002). Interaction of VEGF with particular subtypes of receptors activates signalling pathways, e.g. PI3K/Akt, Ras/Raf- MEK/Erk, eNOS/NO, and IP3/Ca^{2+} (Shibuya, 2011). These participate in the generation of specific biological responses including proliferation, migration, increasing vascular permeability, or promoting endothelial cell survival.

The solid tumour, including OC, grows up to 2-3 mm without blood vessels. At this stage, the tumour tissue contains a huge number of cancer cells. The cells placed in the centre are hypoxic and malnourished because nutrients and gases enter them only by diffusion leading to hypoxia condition and consequently to the production and secretion of many pro-angiogenic molecules, including VEGF. These molecules migrate in the tumour environment reaching the host's blood vessel and binds to its receptors localized on the endothelial cells (EC) (Garrido, 2019). Activated endothelial cells secrete metalloproteinases (MMPs) that break down the basal membranes and the matrix around the host vessel. Fibroblasts, smooth muscle cells, and leukocytes can also participate in this process (Bellon, 2004). Increased concentration of VEGF under hypoxic conditions leads to the activation of plasminogen and, as a consequence of its activity, plasmin is formed. Like MMPs plasmin belongs to proteolytic enzymes that is also involved in the breakdown of basement membranes and components of the extracellular matrix. This process is very important as it determines the proper course of angiogenesis. Too low a degree of matrix digestion causes insufficient angiogenesis while too high degree of digestion also disturbs angiogenesis (Quintero-Fabián, 2019). The next step of angioge-nesis is the proliferation and migration of endothelial cells. The activated ECs begin to migrate in response to proangiogenic cytokines and consequently form a bud (sprout) of a new vessel (Saman, 2020). Characteristic of this process is the structural and functional heterogeneity of endothelial cells. There are tip and stalk cells in the forming vessel. The tip cells are located at the top of the budding vessel. They have a receptor for VEGFR-2 on their surface and characteristic filopodia, enabling them to migrate in the VEGF gradient. The stalk cells stand out of high proliferative potential and have VEGFR-1 receptor. They participate in the formation of the new vessel lumen and are also involved in the formation of intercellular connections as well as the synthesis of the components of the basement membrane in the new vessel. The differentiation of both these cell types is mainly controlled by the VEGFA and Notch signalling pathways (Liu, 2021). Integrins, transmembrane proteins, participate in the migration process and influence EC differentiation, proliferation, and survival. Two integrins are particularly important for angiogenesis: αvβ3 and αvβ5 (Zhu, 2010). Afterwards, endothelial cells still proliferate and migrate, which elongates the tubes of new vessels. Subsequently, the vessel lumen is formed and finally, new blood vessel matures thanks to the recruitment of pericytes and smooth myocytes (Zhu, 2010; Saman, 2020).

ANTI-ANGIOGENIC THERAPY

Standard treatment of patients with ovarian cancer, regardless of the clinical stage, relies on surgical resection of neoplastic lesions and implementation of chemotherapy based on platinum derivatives (carboplatin) and toxoids (paclitaxel). Such treatment allows obtaining of complete responses in approximately 75% of patients. However, in 3/4 of them, the disease recurrence is observed. Ultimately, as was mentioned above, the 5-year survival rate is low (41% for stage III and 20% for stage IV) (Cortez, 2018). In addition to chemotherapy, therapy that inhibits neovascularization is increasingly used in OC patients. Antiangiogenic treatment includes drugs that block angiogenic growth factors, especially VEGF, as well as inhibitors of angiogenic growth factors receptors (Chelariu-Raicu, 2019).

Nowadays, the standard first-line treatment for advanced OC patients remains a combination of paclitaxel and carboplatin with or without bevacizumab (Liu, 2021). Bevacizumab (Avastin), a recombinant, humanized monoclonal anti-VEGF A antibody is the most common anti-angiogenic treatment in OC patients and it used to treat advanced and recurrent ovarian cancer. It inhibits the formation of new blood vessels in the tumour and destroys existing blood vessels (Lim, 2020; Reinthaller, 2016; Markowska, 2017) leading to delays in tumour progression. Unfortunately, therapy by bevacizumab prolongs progression-free life only by 2-4 months (Cortez, 2018). Its synergic action with immune checkpoint inhibitors is currently being explored (Garcia Garcia, 2020).

Tyrosine kinase inhibitors, which act as inhibitors of angiogenic growth factors receptors, constitute a large group of antiangiogenic drugs (table 1). Cediranib is a VEGF 1-3 tyrosine kinase inhibitor that has been shown to improve progression-free survival (Ledermann, 2016). Pazopanib, a multi-kinase inhibitor, inhibits VEGFR, PDGFR, c-KIT, c-Fms, and FGFR. Good treatment results of this drug were observed in platinum-resistant and platinum-sensitive ovarian cancer treatment regimens (du Bois, 2014; Floquet, 2015). Nintedanib, a multi-kinase inhibitor inhibits both receptor tyrosine kinases, such as VEGFR, PDGFR, FLT3 FGFR, and non-receptor tyrosine kinases, such as Lyn tyrosine kinase, lymphocyte-specific tyrosine kinase (Lck) and proto-oncogenic Src kinase. Phase III studies have shown that nintedanib used in combination with carboplatin and paclitaxel gives very good therapeutic effects (du Bois, 2016; Chelariu-Raicu,2019). Unfortunately, other investigators reported little benefit of these drugs in OC clinical trials (Yang, 2020 Kurnit, 2021) (Table 1, Figure 1).

Other signaling pathways that are targeted in OC therapy include the action of PDGF, FGF, and angiopoietins activating the Tie 2 receptor (Saharinen, 2017). Trebananib is an example of a VEGF-independent inhibitor, that binds to angiopoietin 1 and 2 and inhibits angiogenesis. Angiopoietins are involved in the final stage of angiogenesis. Good effects of these therapeutic agents have been noted in patients treated with paclitaxel in recurrent ovarian cancer (Monk, 2014) (Table 1, Figure 1).

Table 1. Drugs targeting angiogenesis in OC therapy

Drug name	Regulated pathway/molecule	Type of drug
bevacizumab	VEGF A	Humanized monoclonal antibody
cediranib	VEGF 1-3	Tyrosine kinase inhibitor
pazopanib	VEGFR, PDGFR, c-KIT, c-Fms, and FGFR	Tyrosine kinase inhibitor
ninentanib	VEGFR, PDGFR, FLT3, FGFR, Lyn tyrosine kinase, lymphocyte-specific tyrosine kinase (Lck), proto-oncogenic Src kinase	Tyrosine kinase inhibitor
trebananib	angiopoietin 1 and 2	Peptibody

Anti-angiogenic drugs are currently an important element in the treatment of ovarian cancer (Cortez, 2018). However, these types of drugs are not completely effective because they cannot effectively stop tumour neovascularization. The reason is, among others, antiangiogenic treatment-induced hypoxia, which can induce VM formation and reduce the effect of cancer treatment. Xu et.al. reported in animal model studies that short-term treatment with bevacizumab in OC increases metastases and VM structures formation (Xu, 2012). This fact points

to a likely mechanism of resistance development to anti-VEGF therapy. It can therefore be suspected that substances targeting VM could be a chance for effective treatment of OC. So it is essential to know the pathways and molecules that regulate the VM.

VASCULOGENIC MIMICRY

VM is a tumour microcirculation that does not depend on endothelial cells and can provide sufficient blood supply for tumour growth. VM is responsible for creating over 40% of new vessels in ovarian cancer (Cao, 2013). The mechanism of VM formation include the epithelial-mesenchymal transition, particularly its subtype called epithelial-endothelial transition (Wei, 2021). Mimetic vessels of VM are tubes lined with cancer cells resting on a discontinuous basement membrane-like structure (Valdivia, 2019), they do not have the pericytes characteristic of blood vessels. Among the glycoproteins of this membrane are type I and IV collagens, as well as Laminin5γ2 and its split products 5γ2x and 5γ2 ' (Wechman, 2020). Clinically, VM is identified by positive and negative staining methods; using periodic Schiff acid (PAS) to stain glycoproteins and using antibody-based labelling to identify vessels containing endothelial cells using CD31. Histologically, vessel-like structures PAS-positive a CD31/34-negative are consi-dered signs of VM (Wechman, 2020).VM has two distinct types: tubular and patterned matrix type (Luo, 2020). VM of tubular type are lined by EC-like tumour cells and covered by secretory glycoprotein, and the patterned matrix type is covered by the PAS-positive matrix (Cao, 2013; Viallard, 2017; Luo, 2020).

VM SIGNALLING PATHWAYS

Multiple extracellular factors as well as tumour hypoxia and autophagy are involved in VM. The intracellular regulators of VM follow three major signalling pathways: VE-Cadherin, Notch, and the HIF family of transcription factors (Wechman, 2020). VE-cadherin (CD144) / EphA2 / FAK / ERK1 / 2 / MMP2 / laminin5γ2 is one of the main signalling pathways. VE-Cadherin modulates the phosphorylation of EphA2 kinase associated with its ligand, ephrin-A1. PI3K mediates the phosphorylation of EphA2 and VE-cadherin, which increases the activity of MMP-14 and MMP-2. MMPs are known to cleave laminin5γ2 into γ2 ′ and γ2 fragments, leading to VM. VEGF-A was reported to increase the expression of EphA2, MMP-2, MMP-9, and VE-cadherin (Zhang, 2019). Another important signalling pathway is Nodal / Notch / Smad2 / 3 and Twist 1 which enhances the expression of VE-Cadherin. Wei described the p-STAT3 / HIF-1α and HIF-2α signalling pathway inducing tumour shoots and the expression of numerous cytokines and transcription factors, such as VEGF, Twist, Snail, Zinc Finger E-Box Binding Homeobox 1 (ZEB2), transforming growth factor beta-3 (TGF-β3), Lysyl Oxidase (LOX), and MMP-14, MMP-9, MMP2 (Wei, 2021). Colorectal cancer 1 (MACC1) metastases are also known to trigger HGF / c-Met signalling and induce epithelial mesenchymal transition (EMT) in VM. Qi reported the contribution of the Wnt / PKCα / PI3K / Snail, a non-canonical (β-catenin independent) pathway, in the VM. Wnt activates phospholipase C via frizzled receptor. Frizzled is a family of atypical G protein-coupled receptors that serve as receptors in the Wnt signaling pathway and other signaling pathways. This activation leads to increased plasma calcium levels, which activates PKC. Wnt can also upregulate PI3K and Snail expression. This increases the motility and invasiveness of OC cells and enhances EMT which leads to VM (Qi, 2014). Ayala-Domínguez presented that VM can be stimulated by a migration-inducing protein (Mig-7) that is induced by EGFR activated by Ln5γ2 (Ayala-Domínguez, 2019). The effect of TGF-β on VM has been also elucidated. TGF-β binds to type I and type II receptors, leading to phosphorylation of the transcription factor Smad-3 and contributing to EMT and then to VM (Sicard, 2021).

Cancer stem cells (markered with CD44 and ALDH1 expression) are also considered to play a role in VM. Their presence provides a poorer prognosis (Wechman, 2020). The marker of cancer stem cells is CD133 which is associated with VM, resistance to chemotherapy, and shorter survival (Liang, 2016). VM correlates also with the expression of the CD177 gene encoding NB1 protein (Jiang, 2020). *In vitro* study shows that SEMA4D and VEGF have a synergic effect on promoting VM (Chen, 2018). VEGF-A/EphA2/ MMP9/2 pathway play also an important role in VM development (Lim, 2020) (Figure 1).

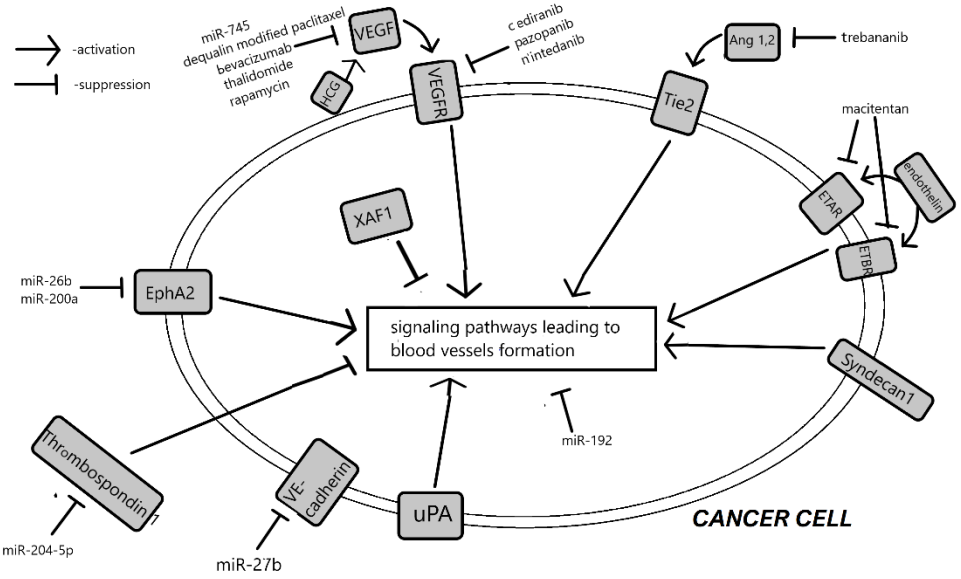

Figure 1. Molecules modulating signaling pathways involved in the formation of new blood vessels formation by angiogenesis and vascular mimicry in ovarian cancer

Ang 1, 2 – angiopoietin-1 and -2; EphA2 – ephrin type-A receptor 2; ETAB, ETBR – endothelin-1 and endothelin B type receptor; HCG – human chorionic gonadotropin; miR – microRNA; Tie2 – angiopoietin-1 receptor; uPA – urokinase-type plasminogen activator; VE-cadherin – vascular endothelial cadherin; VEGF – vascular endothelial growth factor; VEGFR – vascular endothelial growth factor receptor; XAF1 – X-linked inhibitor of apoptosis (XIAP)-associated factor 1

THERAPEUTIC TARGETING OF VM

Many anti-angiogenic drugs, such as those mentioned above, are currently used to treat a variety of cancers, including OC. However, they are not fully effective, as their use leads to hypoxia that can induce the formation of VM channels. Therefore, a therapeutic approach that targets both angiogenesis and VM is currently being promoted. It is believed that this approach will ensure a more effective treatment of aggressive cancers, such as OC (Chen, 2014).

There are several anti-VM therapies with agents (Xie, 2019; Li, 2018) (Table 2, Figure 1). One of which is dequalin (DQA) modified paclitaxel plus several other drugs such as ligustrazine micelles, thalidomide, trastuzumab, tapamycin, and resveratrol which inhibit VM by targeting VEGF (Chen, 2014). Both thalidomide and rapamycin are known to target VEGF to inhibit tumour VM formation (Su, 2008; Zhang, 2008). The in vitro studies showed that macitentan, an antagonist of both ETAR / ETBR endothelin receptors, was able to inhibit VM by blocking endothelin-1-induced activation of Akt and MAPK signalling pathways (Sestito, 2016). Urokinase plasminogen activator (uPA) has the ability to degrade the extracellular matrix (ECM), which is an important step in VM. Tang reported that uPA downregulating molecules such as arginine-glycine-aspar-tate cyclic motif (cRGD) can inhibit VM (Tang, 2016). It was also shown that over-expression of the X-linked inhibitor of apoptosis-related factor 1 (XAF1) is associated with lower VEGF expression and fewer VM structures (Wang, 2017). In vivo studies showed that human chorionic gonadotropin (HCG) upregulates endothelial markers CD31, VEGF, and factor VIII and induces VM. Therefore, it is possible to speculate that the use of anti-HCG therapeutic targeting may provide a novel opportunity to circumvent tumours that express HCG, such as ovarian cancer (Gao S, 2016).

Moreover, an important role in VM plays also syndecan-1 (SDC1). In ovarian cancer models, the anti-SDC1 46F2SIP antibody, in combination with L19-IL2, a B-fibronectin specific immunocytokine modulates EMT markers, stemness and alleviates hypoxia, and may be effective in suppressing VM (Orecchia, 2019).

Various miR molecules are among the VM negatively regulating molecules (table 2). Of such molecules is miR-765 suppressing VEGFA/AKT1/SRC-α axis. MiR-745 was described by Salinas-Vera YM to target VEGFR/ AKT1/SRC-α pathway. It suppresses VM formation by decreasing the levels of VEGFA, AKT1, and SRC-α transducers and exerts

a negative regulation of VEGFA by specific binding to its 3′-untranslated region (3'UTR) (Salinas-Vera, 2019). miR-27b targeting VE-cadherin was shown to inhibit ovarian cancer cell migration and VM via binding to the 3′UTR of VE-cadherin mRNA (Liu, 2017). The target of miR-200a, which was studied on ovarian cancer, and miR-26b is ephrin A2 (EphA2). As authors have shown it inhibits EphA2 expression thus suppressing VM formation (Sun, 2014). Wu et al. have shown that miR-192 inhibits many genes associated with angiogenesis in many orthotopic mouse models of ovarian and kidney cancer (Wu, 2016). Lower levels of miR-192 in tumours are associated with high angiogenesis and low overall survival in patients with OC or clear cell carcinoma kidneys. Chen et al. proved that miR-204-5p can promote angiogenesis in ovarian tumours via Thrombospondin 1 (THBS1) (Chen, 2019) (Table 2, Figure1).

To effectively inhibit angiogenesis, multiple angiogenic/VM pathways need to be blocked simultaneously. Therefore, miRNAs may be an ideal therapeutic approach in this context.

Table 2. Molecules targeting VM in ovarian cancer

Molecule	Regulated pathway/molecule	Type of impact
dequalin (DQA) modified paclitaxel	VEGF	suppression
thalidomide	VEGF	suppression
rapamycin	VEGF	suppression
macitentan	ETAR / ETBR endothelin receptors	suppression
arginine-glycine-aspartate cyclic motif (cRGD)	Urokinase plasminogen activator (uPA)	suppression
X-linked inhibitor of apoptosis-related factor 1 (XAF1)	VEGF	suppression
human chorionic gonadotropin (HCG)	CD31, VEGF, factor VIII	induction
L19-IL2 Immunocytokine with the Anti-Syndecan-1 46F2SIP Antibody	syndecan-1 (SDC1)	suppression
miR-745	VEGFA/AKT1/SRC-α	suppression
miR-27b	VE-cadherin	suppression
miR-26b	EphA2	suppression
miR-200a	EphA2	suppression
miR-192	many genes associated with angiogenesis	suppression
miR-204-5p	Thrombospondin 1 (THBS1)	induction

CONCLUSION

Angiogenesis and vasculogenic mimicry play a key role in the development and progression of OC. The knowledge of the factors influencing these processes may contribute to increasing the effectiveness of OC therapy. Due to the participation of both angiogenesis and VM in cancer development, both angiogenesis inhibitors and VM inhibitors should be considered in the treatment of OC. In cases of developing resistance to anti-angiogenic drugs, treatment aimed at inhibiting the formation of vessels in the mechanism of vasculogenic mimicry opens up the possibility of an effective OC therapy.

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Review and Research on Cancer Treatment
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Contemporary techniques and technologies used in orthopedics and in particular in the treatment of cancer

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ABSTRACT

The aim of the chapter is to discuss the issues related to cancer of the musculoskeletal system. Contemporary techniques and technologies used in orthopedics and in particular in the treatment of cancer. The most common cancers of the musculoskeletal system and current treatment options in Orthopaedics were analyzed. The division of tumors by primary and secondary origin and the degree of cell atypy (benign and malignant) and dependent treatments used in Orthopedics. In our work we will focus on contemporary surgical techniques used in Orthopaedics. We will Focus In our work on contemporary surgical techniques used in Ortho-paedics. We will focus on presenting the most common cancers occurring in adults and children and the difficulties of treatment and cure of the disease and at the same time maintaining the best possible function of the patient. In particular, the types of prostheses and techniques of supplying individual areas of the body will be analyzed, depending on the issues related to the patient's age. The article reviews domestic and foreign professions, the article reviews domestic and foreign professional scientific publications on modern methods of orthopedic treatment in oncology. In addition to the classic analysis of literature, photos based on literature will be used. The work will be illustrative Conclusions. Taking into account the type of cancer, the degree of malignancy and the prognosis depending on it, appropriate treatment methods are used that are not always associated with curing the patient of cancer, but may bring benefits in the form of a longer survival period and improvement of the quality of life.

Hypothesis: Do modern methods of cancer treatment in orthopedics have valuable applications in compre-hensive therapy of cancer of the musculoskeletal system?

INTRODUCTION

According to the American Cancer Society, more than 40% of primary skeletal cancers in adults are chondrosarcomas. This is followed by osteosarcomas (28%), chordoma (10%), Ewing sarcomas (8%) and histiocytic sarcomas/fibro-sarcoma (4%). The remaining number of cases includes several types of rare bone cancers. In children and adolescents (< 20 years of age), osteosarcomas account for 56%, Ewing sarcomas – 34%, and chondrosarcomas – only 6% (American Cancer Society, 2018).

Bone tumors are classified as metastatic tumors and orthotypic tumors. Osteosarcoma is the third most common cancer among children and adolescents and the most common orthotopic bone cancer (Simpson E., 2018). Bone is the site of metastasis of hematopoietic tumors, such as prostate, breast or lung cancer. Every year in the United States, more than 600,000 cases of patients with bone metastases are diagnosed in the elderly (>40 years) (Krzeszinski J.Y., 2015). Therefore, early diagnosis of the disease and treatment based on the individual variability of the patient is needed (Rubin E.H., 2014).

Therapy of tumors of the musculoskeletal system requires the help of doctors of various specialties; oncologist, orthopedic surgeon, radiologist, pathomorphologist, radiotherapist, vascular surgeon, thoracosurgeon sometimes also plastic surgeon and long-term recovery time combined with rehabilitation. The dilemma between limb rescue and amputation should be based on the individual needs of the patient and his family.

When determining the process of surgical treatment sparing the limb, especially in cases of tumors localized in the skeletal system and pelvis, the age of the patient and the possibilities of his rehabilitation should be taken into account. Surgical procedures, due to the high risk of complications, require considerable commitment on the part of the patient, doctors and physiotherapists in the postoperative period. At the moment, the standard in surgical treatment is treatment that saves the limb, which allows to reduce the patient's disability and improves its

functioning. Among the methods most often used in limb-sparing treatment are; modular oncological endoprostheses, growing endoprostheses used in children, auto- or bone allotransactions, rotational plastics, arthrodesis of large joints, and in some locations (shoulder, pelvis) only radical bone resections (Goryń T., 2018).

Tumors of the musculoskeletal system are a wide group of tumors, from insignificant, benign lesions to very malignant sarcomas that are life-threatening. In Poland, 200-250 new cases of malignant tumors of the skeletal system are detected annually (Marku-szewski, 2019).

SEARCH STRATEGY AND SELECTION CRITIERIA

In the fifth edition of the WHO classification of soft tissue and bone tumors, which was published in April 2020, there is a similar division as in the fourth edition describing the same organization from the following group.

1. Chondrogenic tumors
2. Osteogenic tumors
3. Fibrous tumors
4. Vascular tumors
5. Osteoclast bones, Giant cell-rich tumors
6. Dorso-string tumors
7. Other mesenchymal bone tumors
8. Cancers of the hematopoietic system of the bone

There is also a new chapter as "undifferentiated" small round-cell sarcomas of bones and soft tissues

The fifth edition of the WHO classification includes important histological changes and molecular division associated with bone cancers. There are several new units and subtypes of tumors. The WHO classification is a key standard with respect to the diagnosis and differentiation of bone tumors. Providing international resources to people caring for patients with bone cancer or cancer, e.g. oncologists, pathologists, surgeons. Thanks to new molecular, histological and genetic changes in unclassified bone lesions. It is advisable to continue the study to understand the pathogenesis of bone tumors

Soft tissue and bone tumors as a heterogeneous group of tumors included in more than 100 different types, and histological subtypes are diagnosed and counted through the criteria for classification of tumors (WHO). Diagnosis of soft tissue and bone tumors is very difficult because it has histological diversity. Over the past three decades, the classification of bone tumors along with soft tissues has changed with progress in mind and understanding the pathogenetic basis of the rarity of these tumors. Characteristic molecular changes in most types of cancer (i.e. mutations, gene fusions) have led to unified diagnostic criteria, and to the development of useful diagnostic tests for soft tissues and pathologies of bone tumors (Creytens D., 2021).

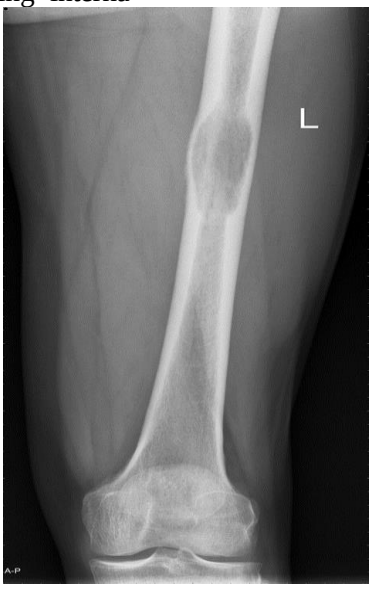


Photo: Metastasis of kidney cancer

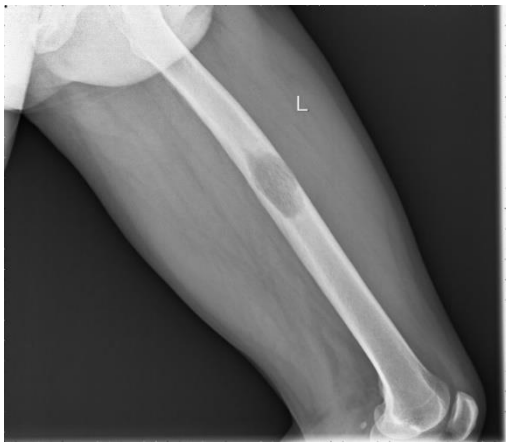


Photo: Metastasis of kidney cancer

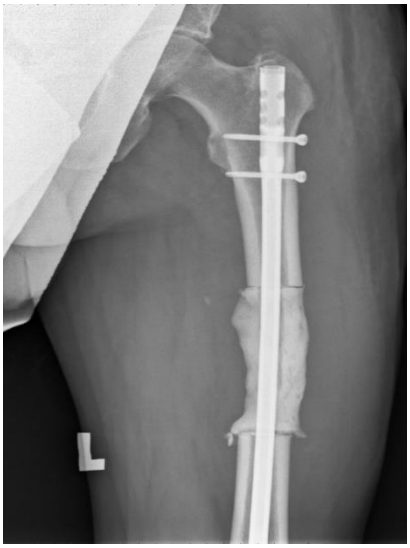


Photo: After treatment of metastatic kidney cancer

Diagnostic evaluation of musculoskeletal disorders (Canale 1, Kusz 2, 2013)

1. Differential diagnosis of lesions located in the bone shaft.
2. Ewing's sarcoma.

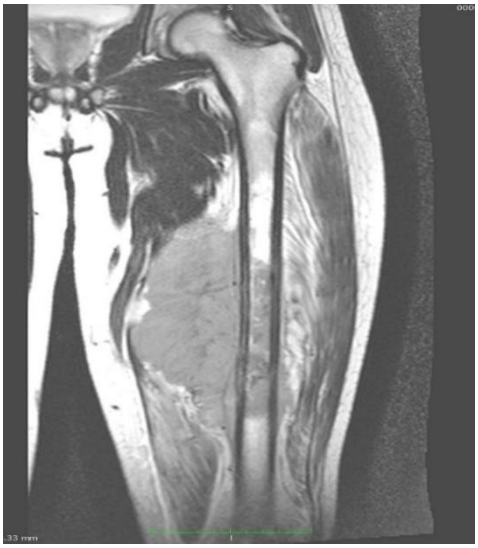


Photo: Ewing's sarcoma in a 23-year-old man

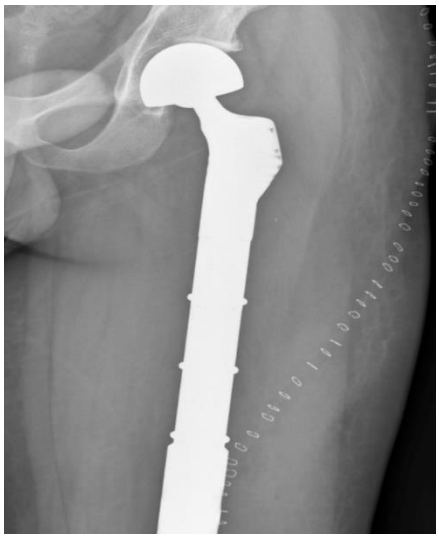


Photo: After treatment of Ewing's sarcoma

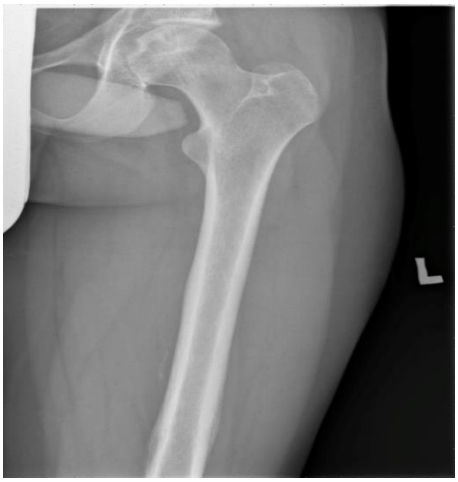


Photo: Ewing's sarcoma in a 23-year-old man. Biopsy performed, erroneously from the front. The need to remove the scar from the biopsy during the final operation

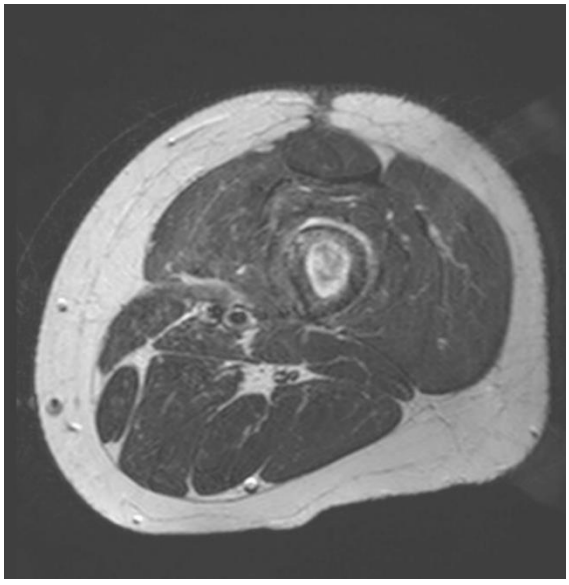


Photo: Ewing's sarcoma in a 23-year-old man. BAmeloblastoma

3. Differential diagnosis of lesions located at the base of the bone
4. Giant cell tumor.

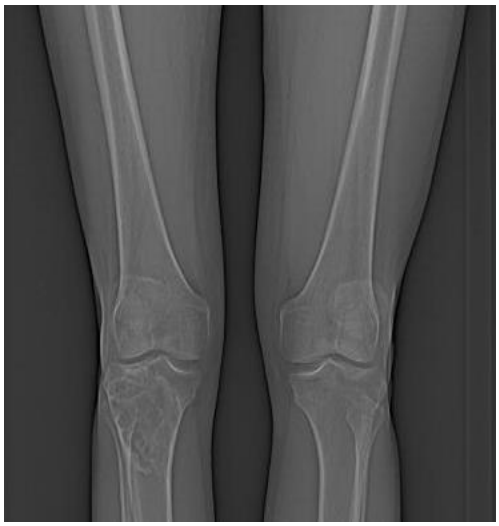
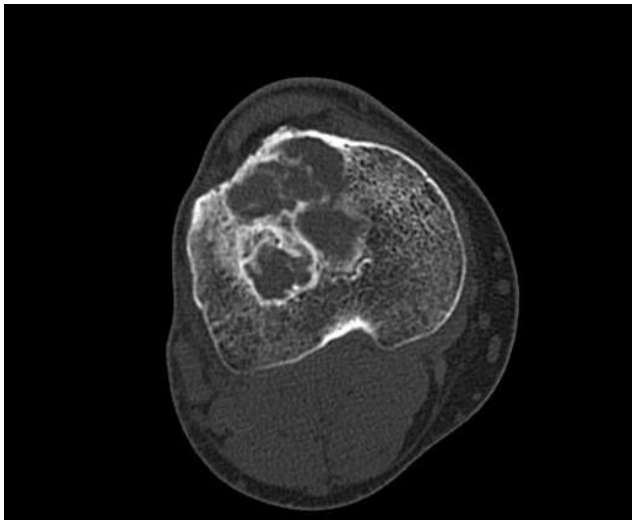


Photo: Giant cell tumor



Photos: Giant cell tumor

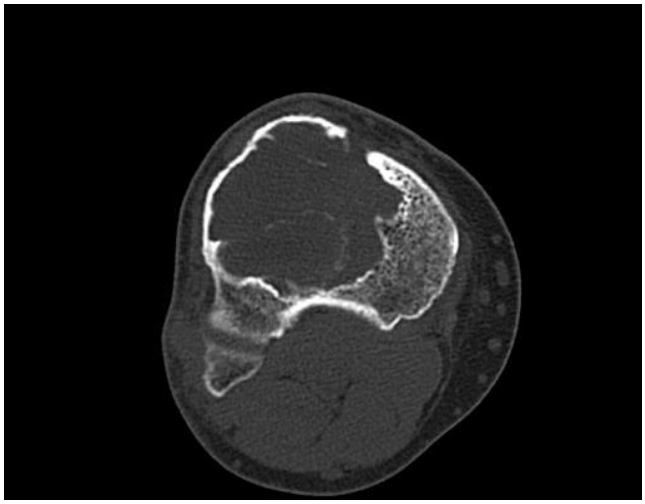


Photo: Giant cell tumor

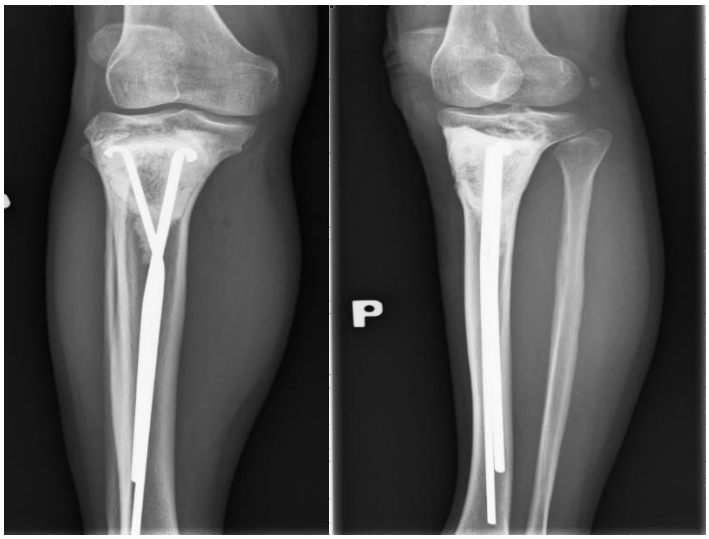


Photo: Giant cell tumor, after treatment with Denosumab, in order to preserve the articular surface was not resectioned, stabilization with grafts, cement and Rusch rods

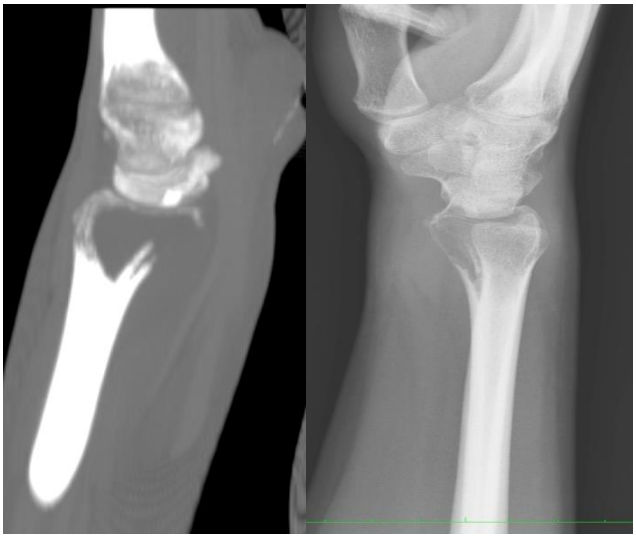


Photo: Giant cell tumor

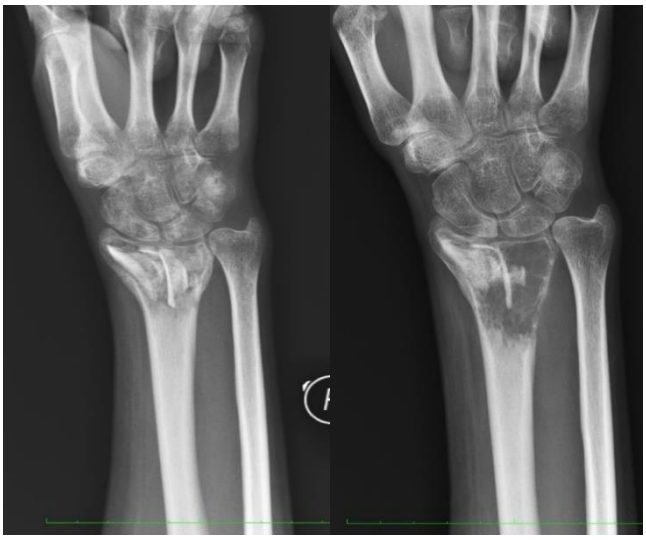
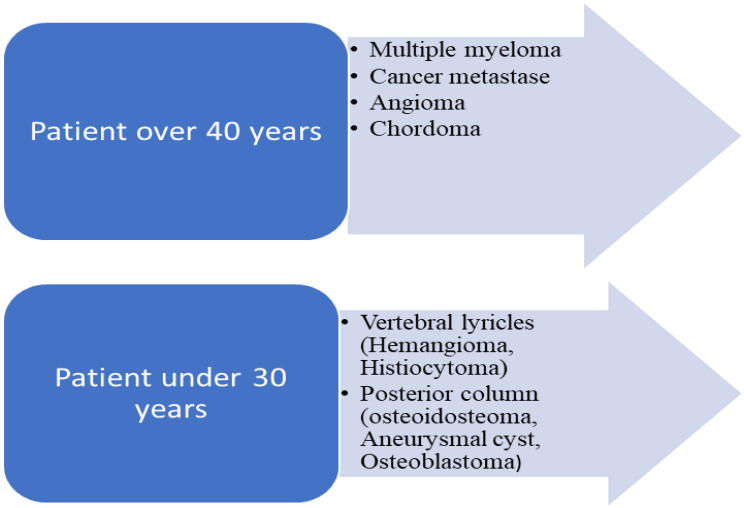


Photo: Giant cell tumor

5. Chondroblastoma.
6. Chondrosarcoma.

Table 3. Differential diagnosis of lesions in the spine (Canale, Kusz, 2013)



7. Differential diagnosis of disseminated lesions (Canale, Kusz, 2013)
8. Chondrosarcoma.

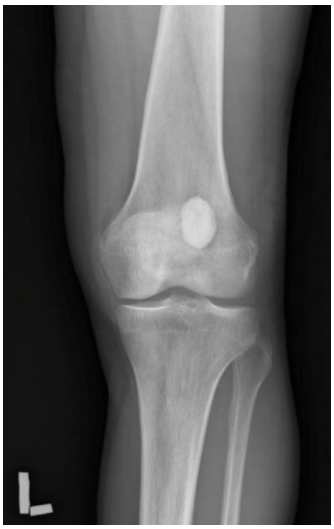
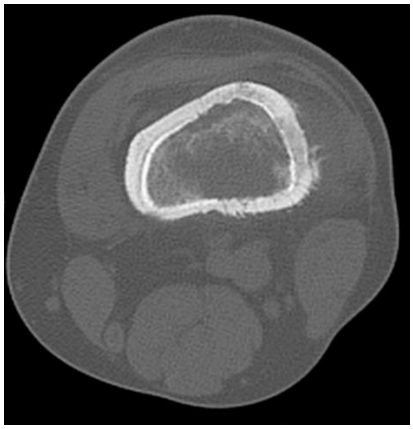


Photo: Atypical cartilage in the peripheral asphyxia of the femur, the lesion was cut out and the cavity was filled with cement. After 2 years without ailments, gradual layering of periosteum, suspicion of osteosarcoma, a biopsy was performed, cartilaginous cartilage was found. Resection performed, a resection prosthesis was put on



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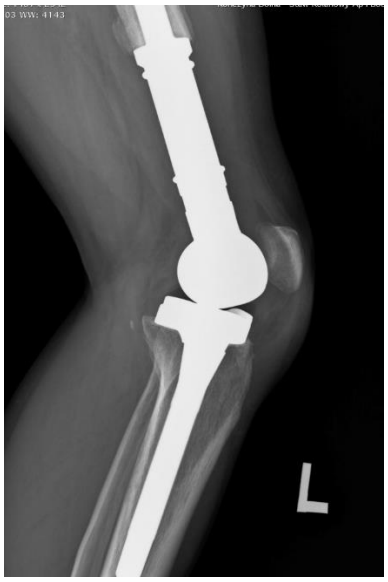

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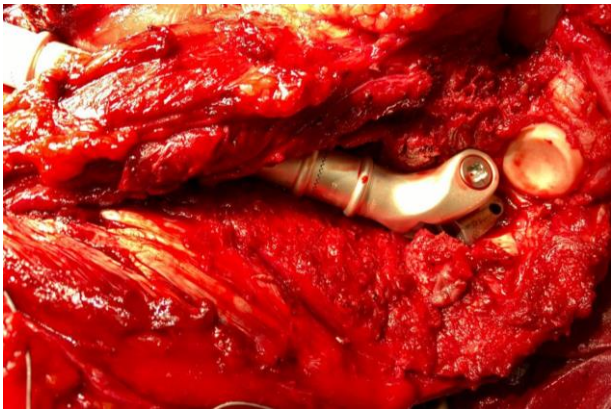


Photo: Cartilage of the entire humeral bone, Total prosthesis of the humeral bone

9. Osteosarcoma.

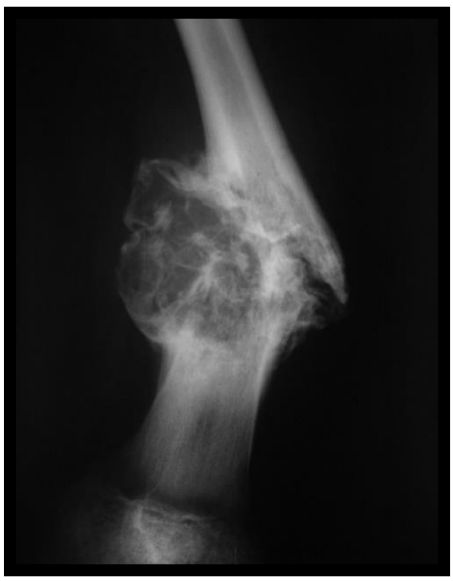


Photo : Osteosarcoma

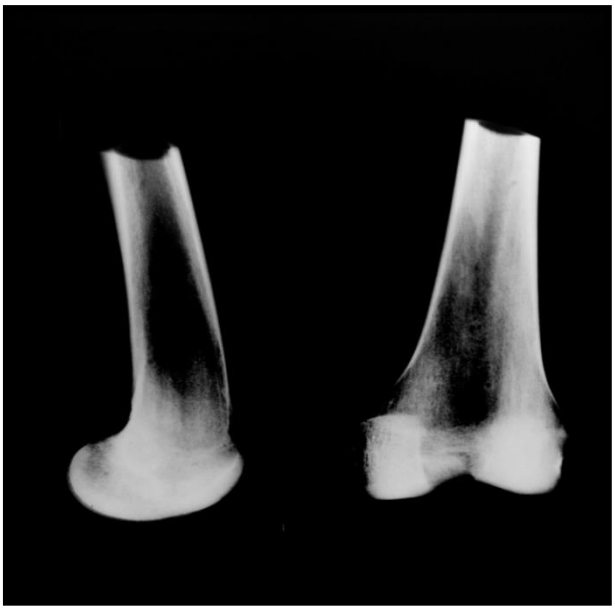


Photo : Osteosarcoma

10. Histiocytoma.
11. Multiple myeloma.
12. Fibrous dysplasia.
13. Bone metastases.

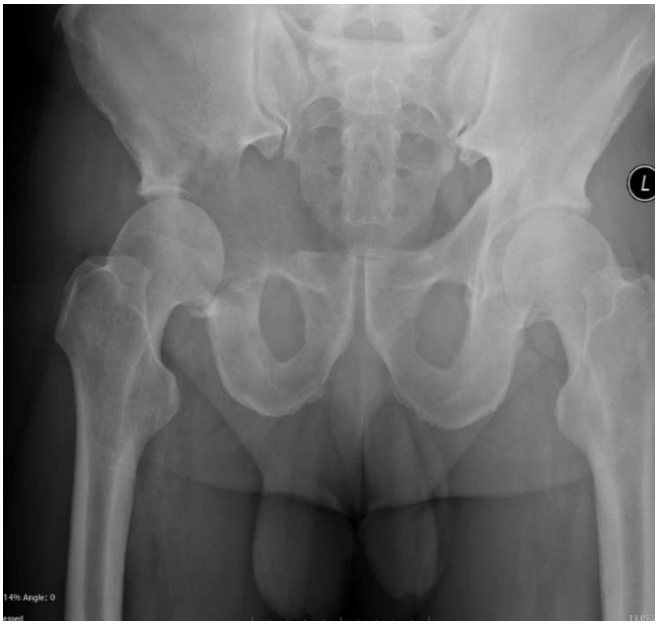


Photo: Metastasis of cancer to the kidneys

14. Infection.
15. Hemangioma.
16. Hyperparathyroidism.

Diagnosis for cancer usually consists of several elements:

1. Medical record and clinical examination.
2. Diagnostic imaging.
3. Biochemical research.
4. Collection of material, histopathological examination.

In the diagnosis of a patient with a tumor of the musculoskeletal system, we start by collecting an anamnesis and conducting a physical examination. Further diagnostics based on tests are also needed:

1. X-ray examination.
2. Three-phase bone scintigraphy.
3. COMPUTED Tomography.
4. MRI PET (positron emission tomography).
5. Laboratory tests.

REVIEW

Preoperative imaging techniques, early diagnosis and effective chemotherapy comprehensively act on many tumors arising in the epiphyseal-epiphyseal areas of the long bones and can be excised segmentally with joint preservation (Zekry KM, 2017).

Modern surgical techniques Currently, resection of a tumor with a fragment of unchanged bone along with obtaining the right margin of healthy tissues (R0 resection) is used as the primary method of treatment. The goal of local treatment should be radical resections.

During the inability to obtain a proper margin and R0 resection, limb-sparing treatment should be abandoned or treatment should be abandoned (Goryń, 2018) R2 resections (non-radical macroscopic) weaken the patient's prognosis and most often lead to significant disability, so they should not be performed. During radical resection, a wide, at least 2 cm, margin of healthy bone must be used. Equally important as R0 resection is to achieve a functional effect related to the treatment carried out. A functional limb is treated as a limb enabling proper support or grasping functions, the functional effect includes the preservation of deep and superficial sensation, the operation of the muscular system enabling the proper range of motion of the limb and adequate coverage of the diseased fragment with soft tissues (Goryń, 2018). Currently, modular oncological endoprostheses (megaprostheses), growing endoprostheses used in children, bone auto- or allo-transhvers, rotational plastics, arthrodesis of large joints, and in some locations (shoulder, pelvis) only radical bone resections are often used in sparing treatment. Thanks to modern techniques of manufacturing endoprostheses, it is possible to use implants developed for a specific patient 3D printing (so-called custom made). In terms of technology, it is currently possible to reconstruct most cavities and joints after removing the primary tumor. Unfortunately, the technical possibilities associated with the production of implants also have their negative sides. Erroneous qualifications related to the use of custom-made implants are possible. The basic principle in oncological surgery, which speaks of radical resection as the most important prognostic factor for the patient's fate, is forgotten – the secondary goal is to preserve the functionality of the limb. Tumors located in the pelvis require a special approach when it comes to planning surgical treatment. The main indicator is the age of the patient and the possibilities of his rehabilitation. Pelvic resections are associated with a high risk of complications, require the involvement of the patient as well as medical staff, physiotherapists. For surgeons performing extensive tumor resections, reconstructions of bone and joint defects are a challenge. The most common causes of revision are periprosthetic infections, aseptic or septic loosening of the endoprosthesis, mechanical damage to parts of the endoprosthesis, and reoperations associated with local recurrence or distant metastases.

Titanium as a reconstructive material and the use of hydroxyapatite that enables faster healing of the implant and innovative modifications of the implant surface in the form of positive silver ions that reduce the risk of infection in the postoperative period (416 Oncology in Clinical Practice – education 2018, volume 4, No. 6) (Chillag, 2016, Stanmore Implants Issue, 2015 edition). Non-invasive growing prosthesis the growing endoprosthesis in children is an innovative implant, its elongation along with the maturity of the child does not require reoperations. In 2006, at the Warsaw Institute of Mother and Child, the first operation to implant a growing endoprosthesis took place in a 14-year-old boy, it was implanted by Prof. Wojciech Wożniak. As the first child in Poland, 14-year-old Michał has a special endoprosthesis. In the case of children in whom the skeletal system is almost mature, the reconstructed lower limb can be extended by 1cm.

As the authors have proven (Masrouha, 2021), the Repiphysis prosthesis, in addition to the benefits of limb preservation, is also characterized by a high rate of mechanical damage along with the need for revision. The authors recommend revealing potential short- and long-term complications and also point to other treatments if their use is considered (Masrouha, 2021).

According to Grimer RJ. Removal of growth cartilage during extensive tumor resection can lead to significant leg length discrepancies (LLD), in children with an immature skeletal system. This situation happens in the diagnosis of bone sarcoma, which often involves the paraphysis of the knee joint (Grimer RJ., 2005). Reconstruction by inserting an endoprosthesis mostly interferes with the adjacent growth

cartilage of the same joint, so the divergent length of the LLD limbs will inevitably appear, as the opposite limb will grow normally. The medium-term result showed that non-invasive retractable endoprostheses in children with bone cancer present precise limb elongation with reduced mortality in the medium term and very good functional results, despite complications (Picardo NE., 2012). Before non-invasive retractable dentures were available world-wide, home retractable dentures played a vital role in saving the limb of pediatric patients with a bone tumor in China that could be extended with minimal incision (Changye Zou, 2020).

Photo: growing prosthesis used in children

Surgical techniques: Resection of the acetabulum of the hip Joint In the case of lesions located in the middle or anterior half of the pelvis, resection of the acetabulum of the hip joint is recommended with sparing the limb. A detailed assessment of the clinical sophistication is needed.

Cancerous lesions in the periacele area may occur in different areas of the acetabulum and may be of different sizes. Of the available treatment techniques, there are many types of reconstruction. The authors conducted a systematic review and presented the most comprehensive review of acetabulum reconstruction after resection of tumor lesions (Brown, 2018). The authors found that most of the perimenal lesions came from metastases (41%), chondrosarcoma (29%), osteosarcoma (10%), and Ewing's sarcoma (7%). The mean age of the patients, which was 49 years, was less than that of most patients undergoing THA (total hip arthroplasty), the median age of 69 years (Brown, 2018).

Reconstruction of the acetabulum of the hip joint after resection of cancerous lesions within the acetabulum is technically difficult and many techniques are used with varying success. The authors found a high percentage of complications and high mortality after oncological resections and reconstructive procedures of around aceteral lesions. Recent prostheses, including custom-made dentures and porous implants and tantalum augments, have shown positive early radiological and functional results (Brown, 2018). There are many reconstruction methods available, each with its own risks and benefits. The authors found that the complication rate is high, but newer technologies and improved reconstruction techniques improve implant life (Brown, 2018).

Resection of the pubic and sciatic bones In case of infection or cancerous tumor, partial or complete resection of the sciatic or pubic bone may be indicated.

6. Pelvic bone resection (internal hemipelvectomy).

Photo: pelvic prosthesis Lumic (Implantcast)

It is important in this method to leave a sufficient margin of surgical resection for patients who want to rehabilitate intensively.

According to the authors, better surgical results of removing a pelvic tumor with infe-rence on the sacrum are brought by the use of a new classification of surgical accesses in the pelvis. This classification includes: 3 pelvic-sacral degrees (PS): I, II and III, divided into Ps A (pelvic osteotomy through the hip) and Ps B (resection of the iliac acetabulum with acetabular and sciatic osteotomy / pubic symphysis). The authors suggest that the resection technique should be adapted to the type of tumor (Zhang, 2018). Treatment of malignant neoplasms of the pelvis is one of the most difficult problems of oncology of the musculoskeletal system.

7. Sacroiliac joint resection.

Malignant tumors of the pelvis have a poor prognosis. Particular difficulty is the reconstruction of bone defects with extensive tumor occupancy within the pelvis. The most problematic are tumors of the acetabulum of the hip joint or sacroiliac joint. Priority is the operation to save the limb and the choice of the appropriate surgical technique.

An innovative operating system was created using pelvic hemiple endoprosthesis and sparing the sacrum, because it is attached to the l5 and l4 lumbar vertebrae. The authors found this technique very promising (Wang, 2019).

8. Sacral resection.

Combined antero-posterior (ventro-sacral) access is the best technique for removing a giant cell tumor or chordoma. Primary tumors from the sacrum or retroperitoneal region are rare and most of them are benign in nature, e.g. chondrosarcoma and neuroblastoma (York, 99, Kayani, 2014).

Robot-assisted minimally invasive surgery (using the Da Vinci Surgical System) of the sacral region can provide precise tissue dissecision under perfect view. This is a technically feasible procedure that involves minimal blood loss, fewer injuries, and short hospitalization. It is especially suitable for pre-sacral benign tumors (Yin, 2018).

Sacrum tumors make up about 1–7% of all spinal tumors (Kim KR., 2021).

9. Resection of the vertebral body.

Multiple myeloma and other lymphoproliferative neoplasms are the most common primary malignant bone tumors (Patnaik, 2016).

The authors concluded that chronic, permanent back pain should be diagnosed using magnetic resonance imaging or computed tomography because they are important for planning chondrosarcoma resection (Fukuda, 2019).

10. Resection of the scapula.

If there are infections or benign and malignant neoplastic lesions, various fragments of the scapula are removed. Depending on the occupied surface of the scapula, smaller fragments or the entire scapula are removed. The cut is made along the subscapular muscle. This muscle is a protective barrier against tumor inking (Canale, Kusz, 2013).

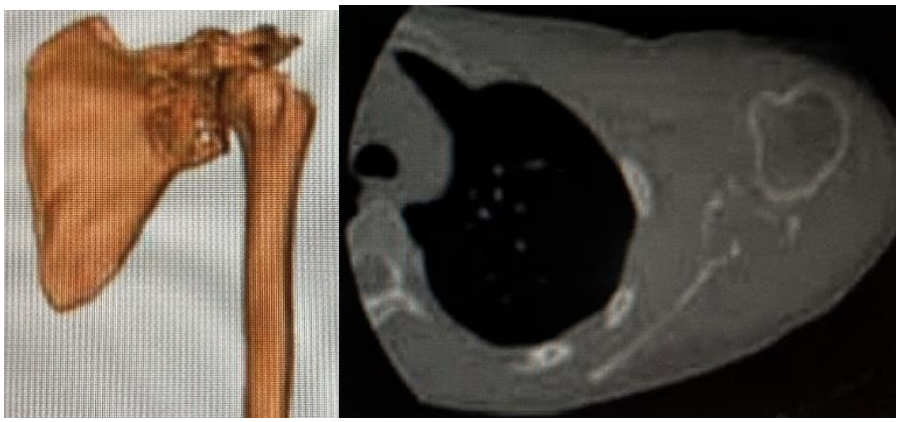
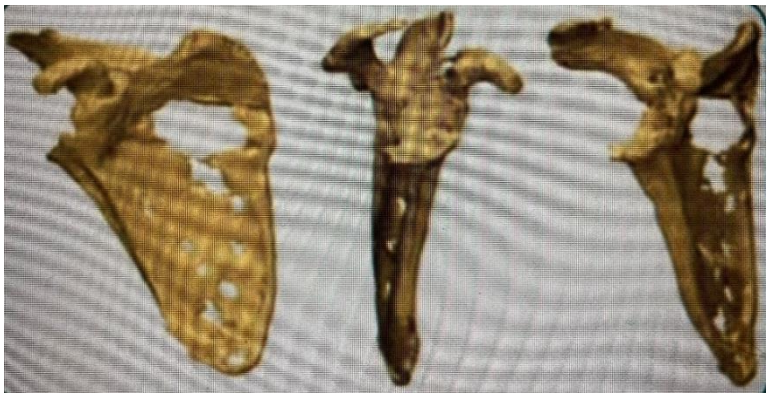


Photo: showing a tumor of the left scapula reaching to the articular acetabulum (preoperative sutuation)



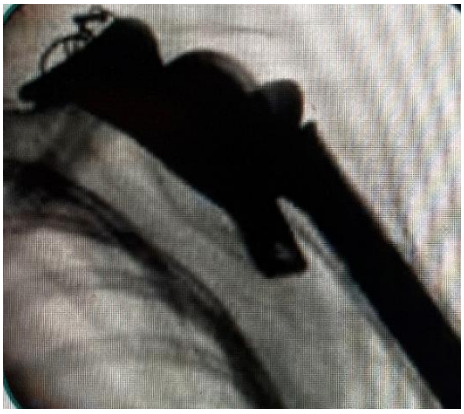


Photo: after implant insertion

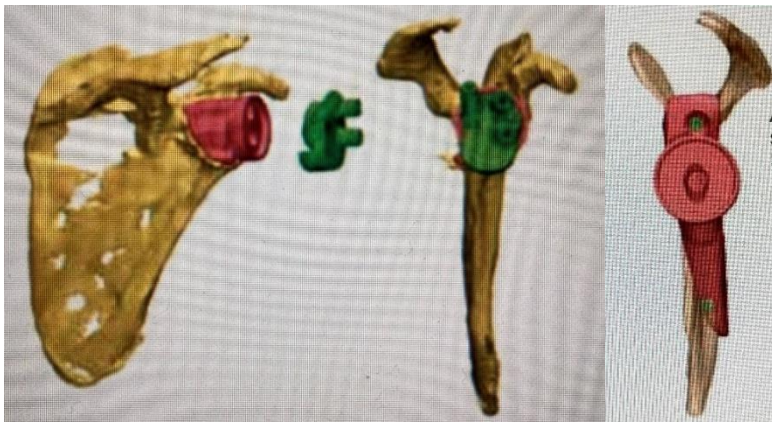


Photo: scapula acetabulum implant

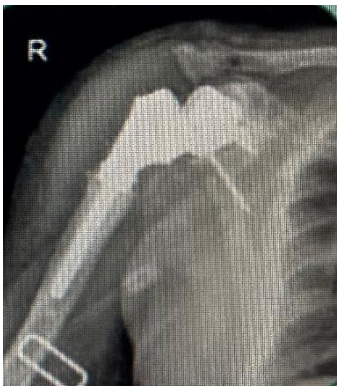


Photo: after implant insertion

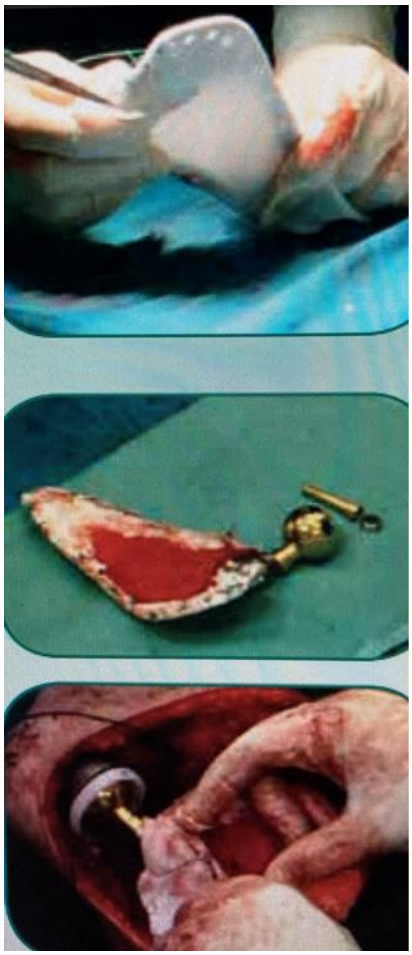


Photo: scapula implant

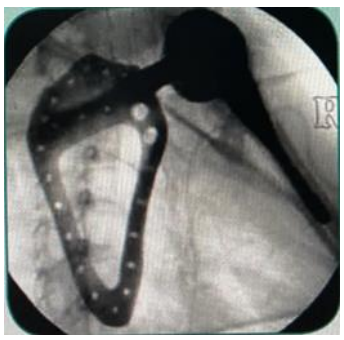


Photo: X-ray after implant surgery

11. Resection of the shoulder girdle.

Often cancerous tumors of the scapula infiltrate the shoulder joint, lead to segmental and extra-articular need to cut out the head of the humeral bone with the scapula. LGHBT (head long biceps) is a route of infiltration of the tumor into the shoulder joint. Resection involves partial resection of the scapula (Canale, Kush, 2013).

Jianxiong LI in 2020 conducted a study of 17 patients with scapular tumors treated with the method of complete resection of the scapula combined with artificial replacement of the scapula. The authors found that surgery could provide better appearance and function of the shoulder joint, but it was a retrospective study (Jianxiong Li, 2020).

12. Resection of the proximal part of the humeral bone.

During the biopsy of the proximal part of the humerus, care must be taken to ensure that cancerous changes do not get into the deltoid-thoracic furrow, because it is at risk of spreading cancer cells. This resection is a frequently used surgical method of sarcomas of the proximal part of the humeral bone (Canale, Kush, 2013).

Photo: humeral bone prostheses

13. Resection of the dictal part of the humeral bone.

Sarcomas located within the elbow joint, rarely can be excised with a limb-sparing technique.

14. The technique of resection of the humeral shaft with the preservation of the elbow and humeral joint of the patient is used to treat cancerous tumors of the humeral shaft. Using an allograft, a prosthetic humeric shaft or an autogenous graft, the limb can be preserved.
15. Resection of the proximal part of the ulna.

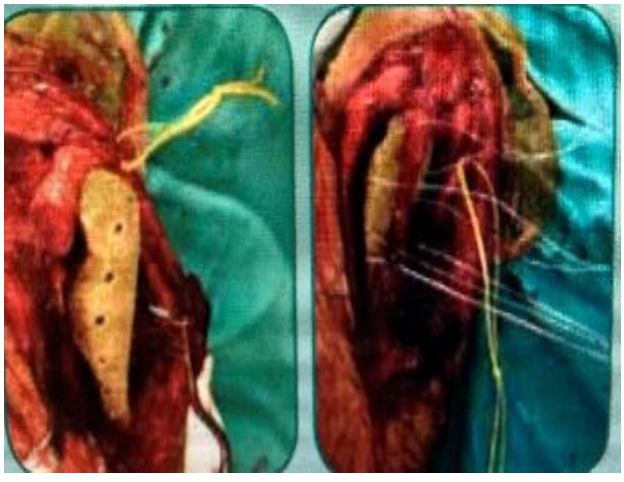


Photo: surgical procedure for insertion of the proximal part of the ulna

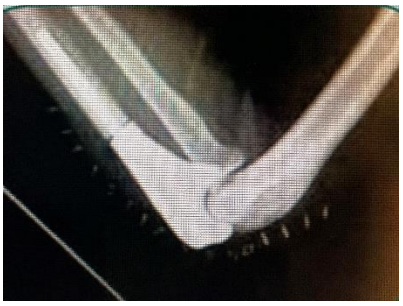


Photo: after the procedure of insertion of the proximal part of the ulna

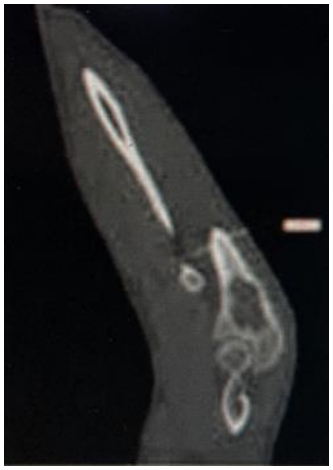


Photo: chondrosarkoma of the proximal part of the ulna

16. Resection of the proximal part of the radial bone.

Larger fragments of the proximal part of the radial bone can be resectioned without reconstruction (Canale, Kusz, 2013).

17. Resection of the distal part of the radial bone.

In patients with a giant cell tumor, resection of the distal part of the radial bone is particularly practiced. It is performed by alloplasty or arthrodesis using allo- or autogenic bone graft.

18. Resection of the distal part of the ulna

Excision of the distal part of the ulna in a giant cell tumor without the use of a graft is similar to Darrach surgery, along with the tumor the periosteum is excised.

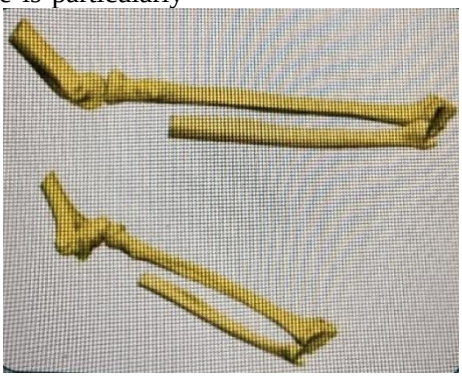


Photo: illustrates the resection of the proximal part of the ulna

19. Resection of the entire femur.

Using hip and knee joint endoprostheses, the technique of removing the entire femur using a modular prosthesis along with reconstruction was described by Lewis.

20. Resection of the proximal part of the femur.

Most tumors of the proximal femur area allow resection to be performed with a margin of healthy tissues and allows reconstructive surgery and better limb function than enucleation in the joint. Indications for amputation are local recurrence, fracture with displacement, complications after biopsy. In some centers, a post-resection prosthesis is originally used (Canale, Kush, 2013).

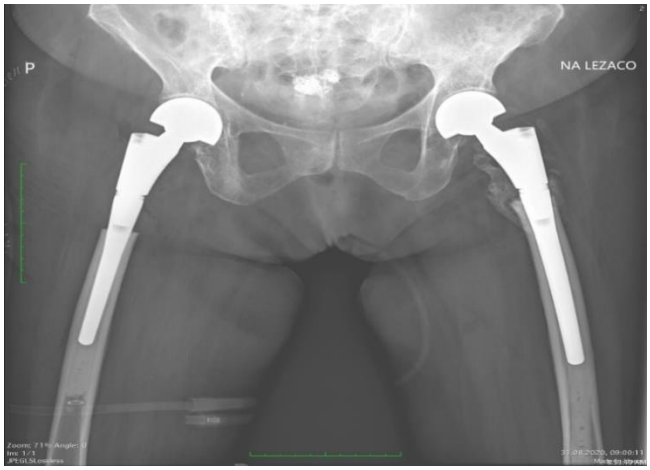
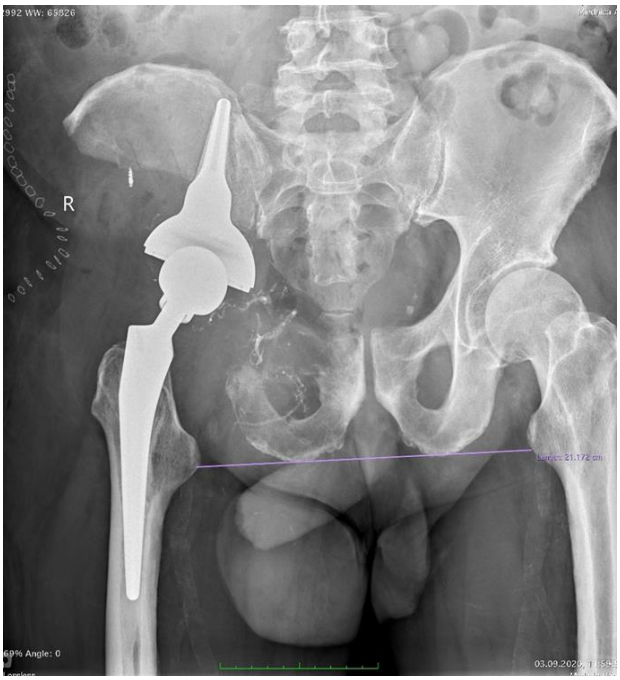


Photo: Metastatic breast cancer put on a resection endoprosthesis of the hip joints first left then right, visible ossification of the left femur after distant surgery



21. Resection of the dictal part of the femur

The most common localization of primary malignant neoplasms of the bone is the distal part of the femur, rarely occupying the joint and neuroscular structures. Arthrodesis, osteocartilaginous graft, prosthesis should be included in the methods of supply. If the tumor infiltrate the joint, the treatment is amputation.

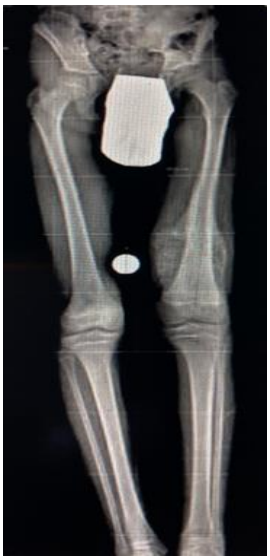


Photo: Osteosarcoma of the distal part of the femur

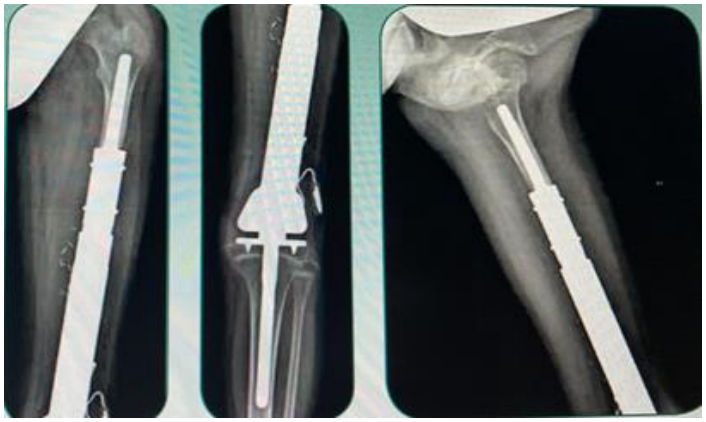


Photo:implant of the distal part of the femur

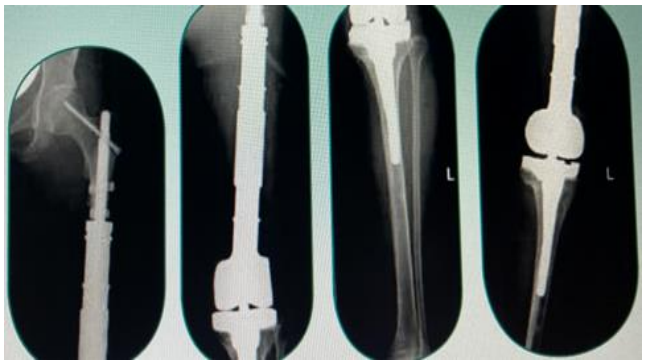


Photo: prosthesis of the distal part of the femur

22. Intraarticular resection of the distal part of the femur with reconstruction using an endoprosthesis.

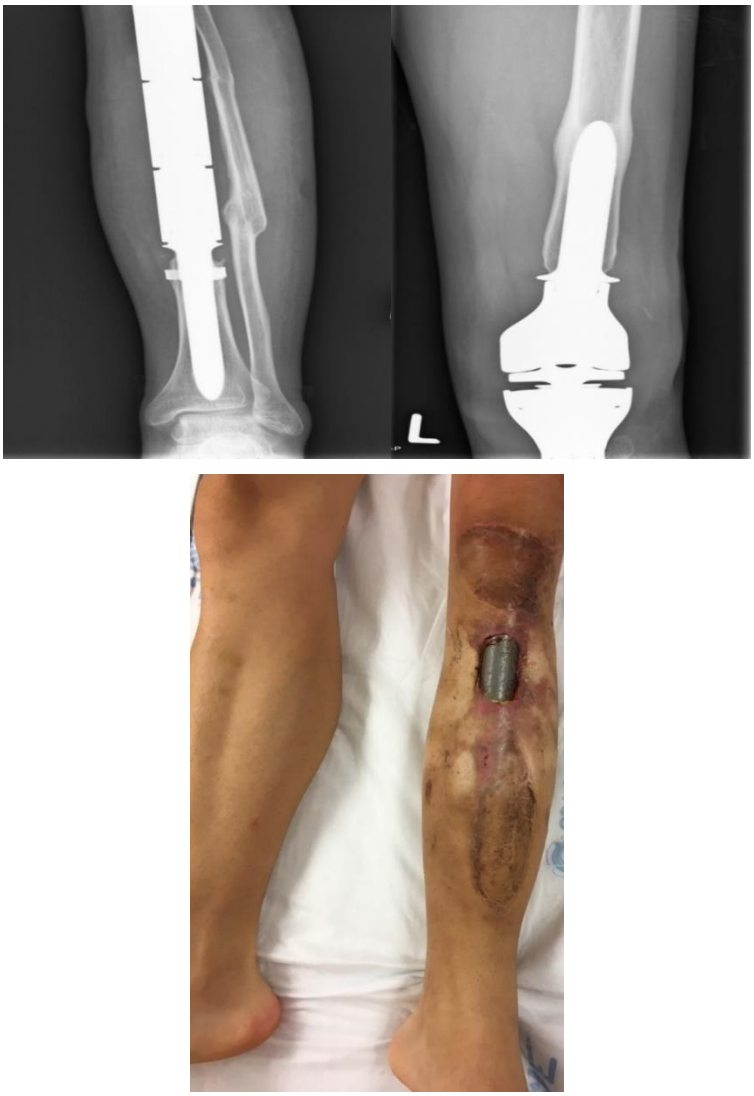
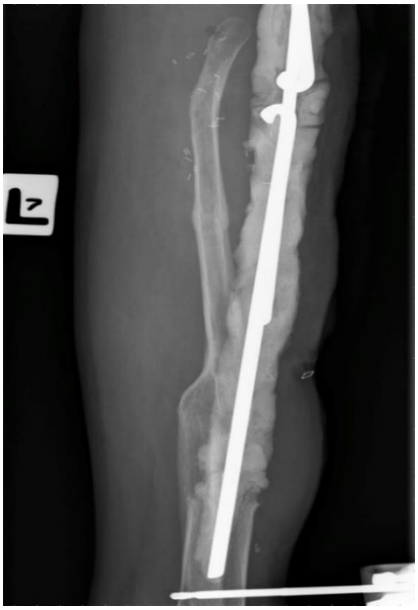
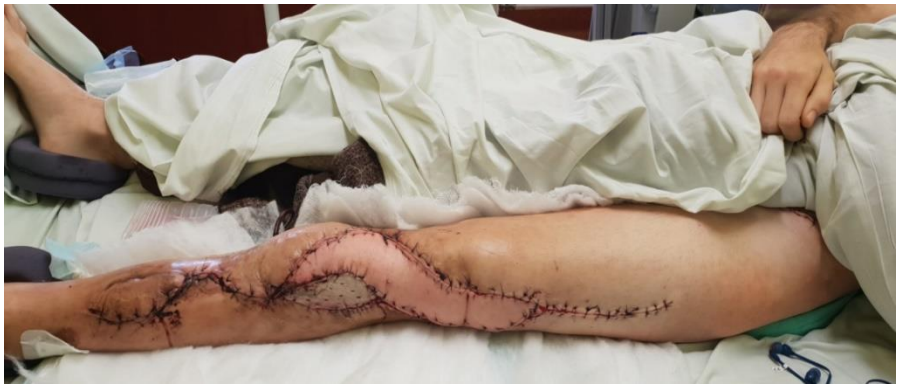


Photo: Osteosacoma of the tibia in an 18-year-old





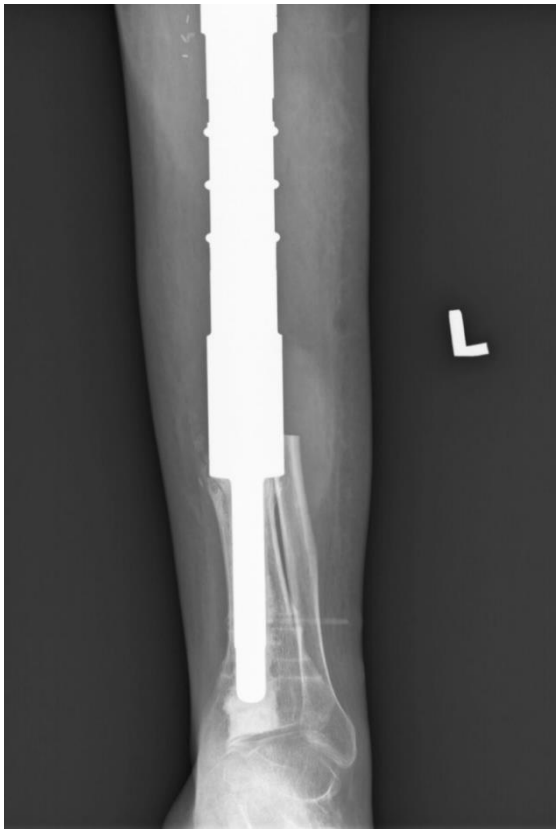


Photo: After operation

23. Resection of the proximal part of the tibia. In the proximal part of the tibia, the primary bone tumor is localized. This is the second most common location.

Resection of the distal part of the femur or the proximal part of the tibia and arthrodesis of the knee joint reserved for strong and young patients who should undergo intensive rehabilitation.

24. Resection of the distal femur or the proximal tibia using a bone allograft with arthrodesis.

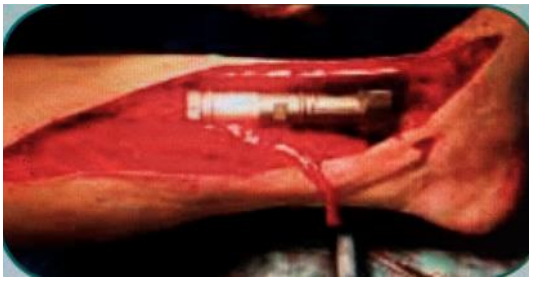


Photo: distal tibia implant

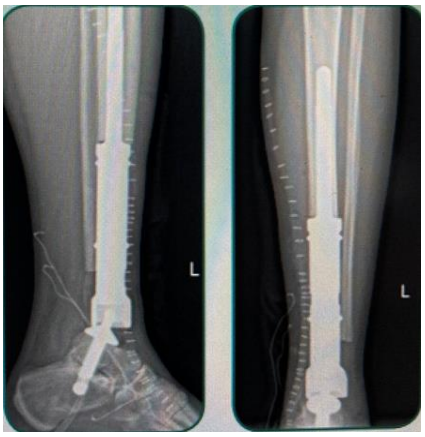


Photo: after the procedure of insertion of the implant of the distal part of the tibia

25. Resection of the distal part of the fibula.
26. Resection and arthrodesis of the ankle joint.

Better results in the treatment of tumors of the distal end of the tibia are brought by post-knee amputation with secondary prosthesis than sparing treatment.

ROTATIONAL PLASTIC

Rotational plastic surgery is a method of reconstructive surgery of the lower leg performed instead of a complete amputation of the limb. The method consists in filling the knee joint with an ankle joint. Rotational plastic surgery can allow patients to save part of their leg and engage in physical activity.

Winkelmann specified in rotational plastics 5 groups (Winkelmann WW., 2000).

1 Group AI – The distal part of the femur, the knee joint and the proximal part of the tibia are removed and the lower leg is twisted 180 degrees and then the femur connects to the tibia.

2 Group AII – The distal part of the femur, the knee joint and the proximal part of the tibia are removed. Successively, the further part of the femur rotates with the distal part of the tibia.

Group BI – the hip joint and the proximal part of the femur are removed, the limb rotated by 180 degrees. Then the pelvis is connected to the distal part of the femur. Then the knee joint function is replaced by the hip joint and the ankle joint is replaced by the knee joint.

Group BII – The lower part of the pelvic bone, the hip joint and the proximal part are excised, the limb rotates 180 degrees. Then the function of the knee joint is replaced by the function of the hip joint and the ankle joint is replaced by the knee joint.

Group BIII – there is a resection of the entire femur, and the pelvis with the tibia is connected with an endoprosthesis.

The program to improve the patient after rotational plastic surgery should include preoperative, postoperative treatment (Kowalczyk, 2021).

When inserting a rotational prosthesis, it is necessary to increase the range of motion of the plantar flexion, because the ankle joint imitates the knee joint.

SHORT COCLUSIONS

It is still difficult to accurately locate and diagnose skeletal cancers. (Karamzade-Ziarati N., 2019). Doctors, however, prefer ordinary radiography to diagnose malignant bone tumors, but a clearly positive radiographic indicator of bone tumor malignancy may favor subsequent examinations, usually causing significant bone damage (Ferguson J.L., 2018). In the initial colonization of tumor, cancer cells and the bone marrow microenvironment synergistically regulate tumor growth, mainly including osteoclast activation and slightly dissolving hydroxyapatite (Pang Y., 2020). When a bone-targeted probe was used as a diagnostic method, small changes in bone density could be clearly visualized, providing valuable information for early diagnosis (Slooter M.D., 2015). (Baljer B.C., 2020) also present the indistinguishable boundaries of bone tumors which force doctors to find a balance between reducing the percentage of positive margins and maintaining bone function (Baljer B.C., 2020). Currently, bone cancer is a big problem. Thanks to the progress of technology, it is possible to treat a large part of cancers of the skeletal system. The topic we have taken up describes the treatent options for individual cancers of the skeletal system. According to Simon, the choice between limb rescue and amputation should be chosen based on the individual needs of the patient and his family.

1. Will the chosen method of treatment make the patient survive?
2. The impact of short- and long-term mortality in both cases?
3. The impact of the function of a limb with a prosthesis or a spared limb?
4. Are there psychosocial consequences of these surgeries? (Canale, Kush, 2013)

PRINT 3D

Printing biological materials and manufacturing with materials such as ceramics or plastic, even if these technologies seem to be completely different, but they have many related applications in these technologies. No other technology will adapt and adapt the structure to the complexity of the patient's body, 3D – bio-printing covers the three main factors of treatment in oncology and the finding of new methods of oncological treatment: it helps in the diagnosis, in modeling and delivery and testing of drugs. The creation of an oncological model is a priority for an individual oncological treatment strategy and the discovery of new methods of fighting cancer. 3D bioprinting using human cells is much more popular compared to traditional 2D and 3D cell cultures produced using other tissue engineering methods.

Tissue engineering involves growing cells, seeding them on biocompatable carriers, and enabling the growth and maturation of specific tissues (Gao G., 2016). 3D bioprinting is used for precise cell stratification, biological scaffolding and biological agents. Compared with traditional tissue engineering methods, the technologies used by the 3D bioprinting scheme allow for greater precision in the spatial relations between individual fragments of the desired tissue. 3D bioprinting is very promising in the applications of regenerative medicine used in oncology and beyond.

Adheal applications of 3D bioprinting give a chance to replace tissues. The most important feature of bioprinting compared to traditional tissue engineering strategies is the ability to influence the differentiation of stem cells at different stages of the creation of this process (Irvine S.A., 2016). In oncological orthopedics, 3D bioprinted implants have found great application (Wong K., 2015; Imanishi J., 2015). Wong and others they described a patient with cartilaginous cartilage in the front of the pelvis who was treated with a custom-made titanium monoblock pelvic implant. Imanishi and Choong (2015) described the case of a patient with stage 2 calcaneal cartilage who underwent calcaneal bone replacement surgery with a titanium implant produced in 3D. Dong and others (2018) examined a patient who was treated using a 3D printed polyetherether-ether-concrete total scapula prosthesis with a diagnosis of a benign fibrous scapula tumor.

The author, (Jong Hoon P., 2021) described the case of a woman who had been experiencing shoulder pain for 3 months, which intensified during shoulder activation. On physical examination, there was no limited mobility in the shoulder joint, there was only pain during the external rotation of the shoulder joint in the 90° visiting position. X-rays showed an irregular shadow with bone lesion on the scapula, in the S1 region according to the Malawer classification (Malawer MM., 91), computed tomography and magnetic resonance imaging showed about 8.9 × 7.9 × 4.2 cm, heterogeneous, strengthening mass with internal calcifications in the left subscapular muscle with co-existing damage to the scapula. No abnormalities were observed with the humerus, ribs and thoracic vertebra. Positron emission tomography-CT showed a concentration of radioactivity in the left shoulder blade with abnormal mineral metabolism in the bones and the absence of distant metastases. As a result of the biopsy, the following were diagnosed: cartilage scapular cartilage, Malawer S1, Enniking II B, cartilage scabbard II degree. The doctor performed a wide resection of the localized cartilaginous cartilage within the subscapular lesion and resectioned the muscles around the scapula. A 3D printed segmented scapula prosthesis was inserted. The researchers found a significant improvement in shoulder function after surgery and 6 months after surgery using a 3D printed segmental prosthesis.

Another example is pelvic surgery, which is complicated by its complex anatomy and the location of many neuroscular and visceral structures. The pelvis has a high contrast compared to the surrounding soft tissue on computed tomography scans, so it can be easily converted into 3D models for virtual surgical planning using computer-aided design (CAD) and computer-aided manufacturing techniques (Fang Ch., 2019). Surgical applications of three-dimensional printing in the pelvis and acetabulum: from models and tools to implants

3D printing presents virtual 3D planning, allowing surgeons to have a tangible sense of models, real sizes (Boudissa M., 2018), (Cromenns BP., 2017) Hung CC., (2019), conducted a retrospective comparative study of 30 patients using the above method and noted a reduction in surgery time of 70 minutes, a reduction in blood loss of 270 ml, fewer complications, and better radiological outcomes compared to conventional planning using CT images. A study conducted by Zhang (Zhang YD, 2018) of nine case-control studies involving 638 patients found that 3D printed bone models for planning surgical pelvic and acetabulum fracture resulted in a significant reduction in surgery time, blood loss compared to traditional imaging-based planning techniques. Other authors have also studied other cases of people with little difference in techniques and have shown positive benefits (Hung C.C., 2018; Shon H.C., 2018; Chen X., 2015) Chen X., (2017) explored a minimalist, positive, and negative 3D printed bone surface template. This is an intuitive approach to contouring a plate with implants located between two templates. The negative template has designed holes to guide the trajectory of the screws. In this study, 14 corpses, 64 plates and 339 screws were placed without penetration of the hip joint. The described method is beneficial in minimizing the time and material costs devoted to 3D printing.

The author (Kim JW., 2017) presented a technique in which each larger fracture shard is printed separately, and the reduction is evaluated manually using tools to reduce the bones and glue them together. Landmarks and entry trajectories for interfracture screws are located using a simulated operation under fluoroscopy. Similarly, the researcher (Zeng C., 2016) presented 10 patients in whom fracture fragments are digitally reconstructed in software. Similarly, Hongging Z., in 2020, described a procedure to implant 3D printed vertebral bodies using robotic stereotactic radiotherapy in 14 patients.

ROBOT DA VINCI

Surgical procedures using the da Vinci robot are important in many medical fields. An important advantage of the da Vinci robot is its accuracy and precision, as well as the limitation of actions that are undesirable during the procedure. Natomast an unfavorable feature is the high price of the procedure. The first operation using the da Vinci robot took place in 2010 at the Provincial Specialist Hospital in Wrocław. Using surgical robots, the time of the procedure is shortened and a faster recovery of the patient is possible. An example of the surgery performed described according to the researchers, (Junqiang Yin., 2018), examined patients with benign sacral or presacral tumors who underwent transperitoneal resection using the da

Vinci Si HD robotic surgical system. Robot-assisted minimally invasive cross surgery can provide precise tissue dissecision under perfect view. This method is associated with minimal blood loss, fewer injuries and short hospitalization. It is especially suitable for precross benign tumors. Resear-chers found that it is possible to use the da Vinci surgical system in the treatment of cross tumors, especially precillary benign tumors Robotics techniques have beneficial and promising applications in orthopedic surgery, is a complex and demanding method that is involved in research, from design to clinical application. In recent years, robotics has gradually improved and spread, and more surgical robots have received approval from the Food and Drug Administration for use in clinical practice (D'Souza M., 2019) Some studies have shown that the robotic method is more accurate in placing orthopedic implants compared to traditional techniques. The benefit is less intraoperative radiation exposure, as well as postoperative bleeding and pain, and has a better prognosis (Bargar WL., 2018; Song EK., 2011)

The surge in surgical robotics in orthopedics occurred after 2014, particularly in the countries of the United States, China, and the United Kingdom (Cheng Li., 2021). Reducing the incidence of surgical complications and striving for better and better surgical results has become a major focus of interest and much research in the field of robotics and postoperative imaging. The principles of minimally invasive surgery (MIS) – that is, achieving better surgical results with reduced morbidity – have found recognition among doctors and patients. The main advantages of the robot – precision, repeatability of repetitive tasks, durability and lack of fatigue – make robotics an attractive choice (Zamorano L., 2004)

Robotics has found application in the practice of various subspecializations of ortho-pedists – starting with the use of ROBODOC® (Integrated Surgical Systems, CA) in cement-free total hip alloplasty (THA) (Paul H.A., 92). As shown in clinical trials, robotic surgery improves: implant placement, frontal plane alignment, accurate tibial inclination in total knee arthroplasty (TKA) or single-compartment knee arthroplasty (UKA) is designed to improve the fit of the femoral component, discrepancies in limb length and valgus-valgus of axis orientation in THA (Lonner J.H., 2010) Robotic surgery has also been studied through experimental studies and studies of corpses in other orthopedic subspecifics, such as orthopedic trauma, hip arthroscopy, and shoulder arthroscopy (Oszwald M., 2010).

MINIMAL INVASIVE SURGICAL STRATEGIES FOR SPINAL TUMORS

Surgical techniques and minimally invasive equipment have a major impact on spine surgery. Initially, they were popular only in degenerative surgery of spinal disease and injuries, but these methods were also used in tumor surgery. In the case of patients with benign bone tumors, by minimizing damage to muscles and skeletal system elements, it can reduce the risk of chronic pain and avoid iatrogenic instability. In contrast, patients with malignant tumors of the Spine, through the lack of delays in systemic therapy and radiotherapy, may cause a greater role in accelerating the return home and continuing cancer treatment. Minimal invasive surgical strategies have an impact on reducing the ripping of soft tkeneks, which affects faster healing and creates the possibility of a faster return to postoperative therapy.

The main indications for surgery in patients with spinal cancers are tumor control, decompression of the spinal cord and restoration of the mechanical stability of the spine segment. Minimally invasive surgery in spinal tumors involves minimal access through percutaneous instrumentation (tubular and expandable retractors) introduced by muscle access and a neuroscience technique. Oncological surgery through robot-assisted endoscopy gives hope to patients for a faster recovery after treatment (Barzilai O., 2020).

ADJUVANT THERAPY

It is a type of treatment, complementary to the basic treatment, which is most often resection. The basic form of treatment is the use of chemotherapy, followed by hormone therapy and radiation therapy (PWN, 2013). The surgeon performs the elimination of microchases, the elimination of local resumption and the observation of distant metastases. Thanks to the comprehensively conducted therapy, the chance of recovery in the patient increases. After removal of the tumor, favorable conditions for the action of chemotherapy appear (Vincent T., 2008). In a study conducted by the investigator (Rolf D., 2018), which included

329 eligible patients with localized high-risk soft tissue sarcoma, survival in patients was significantly improved by adding regional hyperthermia to neoadjuvant chemotherapy with an absolute difference at 5 years and at 10 years compared with neoadjuvant chemotherapy alone.

Neoadjuvant therapy is a systemic treatment of tumors preceding primary treatment. In neoadjuvant therapy, preoperative chemotherapy, hormone therapy are used, but less often radiotherapy. Therapy involves the elimination of microchases that worsen further treatment (PWN, 2013). Neodjuvant treatment, by reducing tumor size and infiltration on structures, may reduce the qualification of advanced cancer and indicate changes in the TNM classification (Vincent T., 2008). After the use of adjuvant chemotherapy, tumors of significant size, tumors with a significant degree of malignancy and tumors located in the limb are features of the tumor that, to some extent, are beneficial for overall survival. The most important prognostic factors in retroperitoneal space sarcomas are gender, stage, histology, and the extent of surgical resection (Anaya DA., 2009) despite advances in surgical resection, neoadjuvant or adjuvant radiotherapy and adjuvant chemotherapy. Over the past 20 years, the overall prognosis for soft tissue sarcomas has not changed, and the 5-year overall survival for stage III soft tissue sarcomas is still ~50% (Weitz J., 2008). To improve this result, new strategies or techniques are needed. One possible methodology is the use of neoadjuvant chemotherapy. The benefit of this therapy is multifaceted. First, it can help shrink the tumor and improve limb rescue rates after primary surgical resection, in addition, neoadjuvant therapy leads to a s Another benefit of neoadjuvant therapy is to improve the rate of realization of negative margins of surgical resection (Oszwald M., 2010).

CONCLUSIONS

The presented methods of cancer treatment are based on classic surgical procedures based on tumor resection in the margin of healthy tissues. Over time, prosthesis is modified, supplying the treated parts of the musculoskeletal system. The chapter presents original photos of prosthetic parts of the skeletal system and includes modern solutions for supplying cancer of specific joints. The article attempts to consolidate innovative methods such as m.in. 3D print, treatment using the DaVinci robot, minimal invasive strategies for the treatment of spinal cancer.

Thank you to Implancast for sharing the photos.

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If subarachnoid haemorrhage occurs, is it worth to look further to rule out cancer? A Case Report of a young man for whom neurosurgery saved vitality, behaviour and abilities

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ABSTRACT

A 26-year-old patient with suspected SAH was admitted to hospital. A CT scan was performed to exclude haemorrhage. This allowed subarachnoid haemorrhage to be ruled out, and nodular changes from the oedematous zone and the effect of compression of the mass were visualised. An additional imaging study – MRI with contrast – was performed to establish the diagnosis. The examination visualised a tumour measuring 45 x 45 x 32 mm, part of which was located in the nasal cavity and rhinorrhea on the right side with stenosis at the level of the rhinorrheal lamina. The tumour had a heterogeneous structure with cystic spaces, posthemorrhagic foci and an abundant network of pathological vessels. There was oedema, wedging under the brain sickle of approximately 14 mm and compression of the right lateral ventricle. 2 weeks later the patient was admitted to hospital for a seizure, COVID-19 positive. On admission GSC:14. During his stay in the Hospital Emergency Department multiple episodes of convulsions were observed. A CT scan of the head was performed and showed a focal lesion in the anterior cranial fossa located mainly on the right side measuring 63 mm x 50 mm x 53 mm with secondary destruction of bony structures. The tumour caused a mass effect with displacement of brain structures to the left side for a distance of approximately 10 mm with extensive white matter swelling. The patient was qualified for urgent surgical treatment. A bipartite craniotomy was performed, achieving removal of the tumour and plasty of the anterior cranial fossa. Histopathological examination led to the diagnosis of a low-differentiated tumour probably olfactory neuroblastoma with Ki67 expression in more than 90% of the cell nuclei. Olfactory neuroblastoma is a difficult tumour to diagnose, occurring more frequently in young adults and less frequently in people in their 40s and 50s. Olfactory neuroblastoma is an extremely rare malignant neuroectodermal tumour arising in the nasal cavity. It accounts for approximately 2% to 3% of all intranasal tumours, with an incidence of approximately 0.4 cases per million. These tumours arise almost exclusively from the highly specialised sensory olfactory neuroepithelium, which is normally found within the upper nasal vault, including the upper nasal concha, upper septum, nasal roof and sacral plate of the ethmoid. The patient we described, after neurosurgery, was actively and systematically rehabilitated and attended psychotherapy. He has now returned to his previous physical and psychological function and has not been found to have any deficits in lower limb motor function. He has not reported any other complaints and denies any impairment. He reports that his state of health is satisfactory and that his quality of life has improved significantly compared to the period before the surgery. He remains under an ambulatory outpatient follow-up, with no local recurrence or enhancement of treatment.

INTRODUCTION

Neuroendocrine carcinoma (NEC) of the head and neck can be subdivided into well-differentiated NEC (carcinoid), moderately differentiated NEC (atypical carcinoid) and poorly differentiated NEC, the later being subdivided further into small cell and large cell neuroendocrine carcinoma (Sarradin et al., 2018; Mills, 2002). Neuroendocrine carcinoma (NEC) rarely presents primarily in the head and neck. This neoplasm is malignant in nature and associated with a poor prognosis (azevedo). Diagnosis is only possible through the assessment of patholomorphologists and the best treatment method has not been established yet. Small-cell neuroendocrine carcinoma (SmNEC) is a distinct malignancy, arising most commonly in the lungs. Due to the extremely rare occurrence of this neoplasm in the head and neck region, no standard of care has yet been defined (Bellahammou et al., 2017). Diagnosis of this tumour is not easy due to its morphological characteristics and the size of the biopsy, which does not always distinguish NEC from other tumour types. Immunohistochemical staining plays a significant role in confirming the epithelial and neuroendocrine nature of this type of tumour, which secretes specific cytokeratins such as CAM 5.2 and neuroendocrine markers such as synaptophysin, neuron-specific enolase, chromogranin or CD56 (Montone, 2015). The histopathological examination of the patient identified a low-grade tumour, where the differential diagnosis should include neuroendocrine carcinoma. A diagnosis of grade IV olfactory neuroblastoma is less likely. In addition, expression of calretinin and NSE, and a negative response to p63 were observed. Immunohistochemical results established CK (AE1/AE3)+,

CD 56+, SYN +/-, EMA+/-, CD 117, S100 and p53 -/+, expression of the proliferative antigen Ki67 in more than 90% of cell nuclei. The expression of cytokeratins and neuroendocrine markers can vary from case to case. As described in the literature, most cases showed expression of chromogranin, synaptophysin and CD56, with only one expressing enolase (Aguiar et al., 2015; Bellahammou et al., 2017; Lee et al., 2011; Lin et al., 2007).

Small cell neuroendocrine carcinomas of the nasopharynx are highly malignant tumours and therefore carry a poor prognosis. Therapeutic options for these tumours are variable: chemo-radiotherapy, radiotherapy, surgery (and their combinations). However, the treatment of choice is still undefined, as few cases of such patients have been described in the literature so far. Of these, only one patient described so far has been treated surgically and survived 11 months after surgery (Deviprasad et al., 2008).

Very similar immunohistochemistry results were obtained in another publication by Bhardwaj et al. They describe at the time of the first biopsy positive pancytokeratin (CK) and negative

leukocyte common antigen (LCA), chromogranin and synaptophysin. Due to the destruction of the slide, it was decided to re-biopsy, which revealed SmNEC. This finding was based on immunopositivity for CD56, CK, and chromogranin (focal); synaptophysin and p40 were negative. The Ki-67 labelling index was high (90%) and almost identical to that described in our patient (Ki-67> 90%) (Bhardwaj et al., 2018). No universal principles have led individual centres to develop their own, often controversial, management recommendations. The most specialised centres adopt surgery and complementary radiotherapy as the 'gold standard' of management (Ow et al., 2014). The significance of neoadjuvant or adjuvant chemotherapy in more advanced cases remains unknown, and the indications for regional lymph node resection or radiation coverage are debatable (Fukushima et al., 2012). Olfactory neuroblastoma (esthesioneuroblastoma) is a neoplasm originating in the sinuses of the nose and nasal cavity, with specific clinical and pathological features and a varied presentation and natural history. The tumour characteristics are remarkably heterogeneous.

The exact location and cell type from which the neoplasm originates have not yet been determined, and in recent decades the same type of neoplasm has been referred to by different names, such as olfactory neuroblastoma, neuroendocrine carcinoma, esthesion-euroepithelioma or esthesioneurocytoma. Nevertheless, the common origin was defined as neural crest/immature olfactory neurons, as suggested by the presence of typical neuronal filaments in the tumour cells and the results of molecular analyses (Su et al., 2014) Commonly accepted name remains (Sampath et al., 2006) is a rare malignant neoplasm of the nasal passages and sinuses, first described by Berger and Richard in 1924 (Hassoun et al., 1981). Tumours of the nasal cavity and nasal sinuses are a relatively rare, diverse and heterogeneous group of malignancies. Olfactory neuroma accounts for only 3% of all nasal cavity and sinus tumours (Broich et al., n.d.). Tumours involving the frontal lobes affect the behavioural, complex and directed activities of humans. Forntal lobes are the site of arbitrary and conscious actions, the highest organised area of the cerebral cortex, controlling our behaviour, cognitive functions and emotional states. Traditionally, this area is referred to as the 'silent area' because no obvious neurological symptoms are found as a result of its damage. Despite the absence of neuropsychological deficits such as perceptual disorders (agnosias), motor disorders (apraxias and paresias) or speech disorders of the aphasia type, behavioural and personality changes characteristic of prefrontal area pathology do occur. These changes significantly interfere with the social functioning of patients (*Cognitive impairments in the examination of a patient after surgical treatment of anterior cranial base meningioma – case study*, 2010). Following the surgical intervention, favourable changes in personality and a significant improvement in the patient's social life were observed. The patient has been under outpatient control since then, he reports no somatic complaints and his standard of living is satisfactory. Without recurrence or metastasis, he did not require intensification of treatment.

CASE REPORT

Patient, 26-year-old male admitted to the Hospital Emergency Department. A computer tomography (CT) was performed to exclude subarachnoid haemorrhage (SAH), as indicated by the referral. It showed the presence of a tumour-like lesion surrounded by a zone of

palpable oedema and showing a mass effect. It was recommended to extend the diagnosis with contrast-enhanced magnetic resonance imaging (MRI). An MRI visualised a 'dumbbell' shaped tumour, part of which was located in the nasal cavity and situs on the right side with a constriction at the level of the situs lamina. The tumour had a heterogeneous structure with cystic spaces, posthemorrhagic foci and an abundant network of pathological vessels. Its dimensions were 45 mm x 45 mm x 32 mm. Oedema, wedging under the brain sickle of approximately 14 mm and compression of the right lateral ventricle were also evident. 2 weeks later the patient was admitted to hospital due to a seizure, COVID-19 positive. On admission GSC:14. During the residence in the Hospital Emergency Department, multiple episodes of convulsions. A CT scan of the head was performed and showed a focal lesion in the anterior cranial fossa located mainly on the right side measuring 63 mm x 50 mm x 53 mm with secondary destruction of bony structures. The tumour caused a mass effect with displacement of the brain structures to the left side for a distance of approximately 10 mm with extensive white matter swelling. A CT scan of the chest was also performed and showed a single focal parenchymal lesion in the left lung area. The patient was qualified for urgent surgical treatment. A bifrontal craniotomy resulting in tumour removal and anterior cranial fossa plasty was performed. Patient was systematically rehabilitated after surgery and no deficits in lower limb motor function were observed. Discharged home with a healed postoperative wound. Oncology and psychiatric consultations were also recommended. Histopathological examination led to the diagnosis of a low-differentiated tumour probably of olfactory neuroblastoma character with Ki67 expression in more than 90% of cell nuclei.

DISCUSSION

Olfactory neuroblastoma (ONB) is an extremely rare malignant neuroectodermal tumour arising within the nasal cavity. It has incidence is about 2% to 3% of all intranasal tumours with an incidence of approximately 0.4 cases per million. These tumors arise almost exclusively from the highly specialized sensory olfactory neuro-epithelium nor-mally encountered within the superior nasal vault, including the superior nasal concha, superior septum, roof of nose, and the cribriform plate of ethmoid (Thompson, 2009). It can manifest at any period of life, although it predominates in young people. A second peak of incidence prevails later in adult life. There are two peaks of increased incidence of ONB – the first in the second decade of life and the second in the sixth decade of life (Al-Osaimi et al., 2021). There is no definitive gender or racial predilection. To date, the etiological basis and risk factors are unknown. There is also no link to occupational exposure (Faragalla & Weinreb, 2009). Typically, these are slow growing tumors with long-standing symptomology, often resulting in delayed biopsy and definitive diagnosis. Implementation of treatment each time should be preceded by confirmation of the histological subtype of the lesion and exclusion of similar neuroendocrine tumours in the differential diagnosis. Other non-ONB neuroendocrine tumours have a high percentage of systemic failure and require the initiation of systemic management. In comparison, ONB is linked to excellent outcomes with locoregional-only therapy. Non-specific initial symptoms characteristic of this neoplasm, such as nasal obstruction and recurrent epistaxis, make a correct diagnosis much more difficult and delay the implementation of treatment. The initial diagnostic studies, besides Computer Tomography, can include MRI or PET CT to more clearly define the local extent of the malignancy. Local recurrence that may occur many years after the surgical excision of the lesion or distant progression remains a major problem in the medical treatment of ONB. Salvage therapy involves operation, surgery and postoperative radiotherapy, radiotherapy itself, palliative chemotherapy or supportive care according to the nature of the recurrence and the initial treatment of the patient. New strategies involving combined CT and/or escalation of dose made possible by sophisticated irradiation techniques such as IMRT or proton therapy ought to be explored potentially (Ozsahin et al., 2010). The relapsing remitting disease is frequently very treatable, with prolonged survival and success, so extended follow-up is indicated for detection and suitable medical treatment (Rimmer et al., 2014).

CONCLUSION

In summary, neuroblastoma has a difficult diagnosis. Histological diagnosis should always be complemented by immunohistochemistry. Surgical resection with adequate margins is the first treatment for resectable lesions. Olfactory neuroblastoma demands advanced aggressive surgical resection and radiation therapy. The patients should be carefully supervised in the awareness that Iocoregional recurrences are frequent and can appear some years after treatment. The long-term survival prognosis is bad.

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The effect of plant extracts from *Scutellaria baicalensis, Stevia rebaudiana, Eleutherococcus senticosus, Schisandra chinensis* and *Boswellia serrata* on human fibroblasts and *Borrelia burgdorferi spirocheates* – in vitro study

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ABSTRACT

Lyme disease caused by *Borrelia burgdorferi* is a multisystemic disease affecting numerous tissues and organs of the human body. Plant extracts with antimicrobial properties can be used to support the treatment of *Borrelia burgdorferi* infections. It was decided to evaluate the toxic effects of extracts from *Scutellaria baicalensis*, *Stevia rebaudiana*, *Eleutherococcus senticosus*, *Schisandra chinensis* and *Boswellia serrata* on human cells and to evaluate the MIC (Minimal Inhibitory Concentration) on *Borrelia burgorferi* spirochetes. The extracts from these plants present scientifically proven antimicrobial activity. The plant extracts were obtained with 80% methanol and then the content of flavonoids, phenolic acids, tannins, flavonoids were determined. The antioxidant potential of plant extracts was also evaluated. Cytotoxicity tests were performed on human dermal fibroblasts exposed to the concentration of 0.05 to 1 mg/ml of the plant extracts because fibroblasts have been widely used in cell culture as an *in vitro* model to tests of cell viability and toxicity of many compounds. There was also determined MIC for *Borrelia burgdorferi*. In the case of human cells, *Boswellia serrata* extract shows no cytotoxicity. The remaining ones are characterized by toxicity above 50/100 micrograms/ml. The highest ability to inhibit the growth of *Borrelia burgdorferi* was demonstrated by *Stevia rebaudiana, Scutellaria baicalensis* and *Eleutherococcus senticosus* (1.0 mg/ml). The weakest antibacterial properties were demonstrated by extract of *Schisandra chinensis* and *Boswellia serrata* (2.0 mg/ml). *Boswelia serrata* extract may be of interest in the context of application in Lyme disease therapy due to the lack of cytotoxic activity against human cells.

Keywords: *Borrelia burgdorferi*, MIC, NHDF, *Scutellaria baicalensis, Stevia rebaudiana, Eleutherococcus senticosus, Schisandra chinensis, Boswellia serrata*

INTRODUCTION

The bacteria *Borrelia burgdorferi sensu lato* belongs to the family of spirochetes (*spirochetae*). It is a Gram-negative bacterium with a highly twisted elongated cell. Borreliosis (Lyme disease) caused by *Borrelia burgdorferi* is a multisystemic disease affecting numerous tissues and organs of the human body. The main problems are the life strategy of *Borrelia burgdorferi*, the complex immune response and the inadequacies of diagnostic methods. Among the problems complicating the treatment of Lyme borreliosis are the high efficiency of the spirochete in the initial colonization of tissues, its rapid dissemination and rapid penetration of the central nervous system. This is compounded by the ability to infect almost all tissues, to evade immune response by penetrating cells (e.g. fibroblasts) (Fikrig, 2006). Bacterial insensitivity to commonly used antibiotics is becoming increasingly common (Lantos, 2015).

Plant extracts with antimicrobial properties can be used to support the treatment of *Borrelia burgdorferi* infections. Plant extracts containing active substances with proven antibacterial, anti-inflammatory and immune system stimulating properties can significantly contribute to the cure of borreliosis (Feng, 2015; Zhao, 2019).

Baikal skullcap (*Scutellaria baicalensis*) is a plant that comes from the family *Lamiaceae*. The homeland of Baikal skullcap is eastern Siberia, the Zabaikal Mountains, the Maritime Country, northern China, Mongolia and Japan. The pharmaceutical raw material, which is used for medicinal purposes, is the root of the *Scutellaria baicalensis*. It is a small (25-60 cm high) perennial plant. It develops simple stems with not large lanceolate leaves, at the top of which not too large blue or blue-violet labial flowers grow (Zhao, 2019). The main chemicals that can be found in *Scutellaria baicalensis* root are mainly flavonoids: baicalin, wogonoside, baicalein, oroxylin A, norwogonin, wogonin, chrysin as well as terpenes and tannins (Wang 2018). Due to its rich composition, Baikal skullcap has multidirectional therapeutic effects. One of its properties is anti-inflammatory

action. Products made from the *Scutellaria baicalensis* can be used not only in acute inflammatory conditions, but they are also highly effective against chronic inflammation (Kim, 2009). Moreover, after their use there is also a reduction of pain and swelling in arthritis, among others (Yang, 2013). *Scutellaria baicalensis* exhibits also antiviral activity (e.g. against HIV, HCV, HBV, EBV, and influenza viruses (Błach-Olszewska, 2008), anti-bacterial (e.g. against *Staphylococcus aureus*) (Qian, 2015) and antifungal (e.g., against *Candida albicans*) (Wong, 2010).

Stevia rebaudiana is a perennial plant belonging to the *Asteraceae* family, native to the northeastern region of Paraguay and the border region of Brazil. It contains compounds known as steviol glycosides (e.g. Stevioside, Rubusoside A-F, Dulcoside A). Although they are 300 to 400 times sweeter than sugar, they do not contribute any calories to our diet because they are not absorbed in the human digestive tract (Leszczyńska, 2011). Apart from glycosides, *Stevia* also contains polyphenols e.g. Caffeic acid, Cinnamic acid, Syringic acid due to stevia extracts may have the following effects: antioxidant, antidiabetic, anti-inflammatory, and anticancer (Myint, 2020).

Siberian ginseng (*Eleutherococcus senticosus*, syn. *Acanthopanax*) belongs to *the Araliaceae* family. The area of occurrence of this species covers mainly north-eastern Asia: China, Korea, Japan, Manchuria, Siberia. *Eleutherococcus senticosus* is a shrub growing up to two meters tall, occasionally reaching four meters, very strongly branched. The stems are covered with light gray bark, from which numerous thin spines grow (Goulet, 2020). Seven compounds were isolated and classified into a new group of glycosides called eleuterosides. Each compound was assigned a classification symbol in the form of a letter and possibly a number indicating the subgroup. The isolated compounds were named eleuterosides: A, B (syringin), C, D, E (acanthoside D), F and G. Besides them, the composition of the root includes, among others: caffeic acid, chlorogenic acid, ferulic acid, vanillin, flavones, resistin, polysaccharide complexes, thymidine, campesterol, stigmasterol, β-carotene, pectins, macro- and microelements, vitamins, glycoproteins, sessiloside and tauroside H1 (Załuski, 2008). *Eleutherococcus senticosus* is a medicinal plant known for 4000 years, used in Chinese medicine to increase human vitality. Studies on species of the *Araliaceae* family indicate that rhizome extracts of *Eleutherococcus senticosus* have biological activity similar to that of root extracts. The broad spectrum of activities of *Eleutherococcus senticosus* extracts include anticancer, antioxidant, immunostimulatory, immunomodulatory and antidepressant properties. Immunostimulatory properties are revealed by increasing the proliferation and differentiation of T lymphocytes and by increasing cytokine production by macrophages. The similar mechanism of activation of these cells is based on the interaction between the toll-like receptor (TLR) located on their surface and the polysaccharide complex in the extract (Załuski, 2008; Lee, 2015). Antimicrobial activity was studied on *Pseudomonas aeruginosa*, *Streptococcus aureus*, *Salmonella*, *Escherichia coli*, *Bacillus cereus*, *Bacillus subtilis* and *Micrococcus luteus* (Chen, 2021). Anti-inflammatory activity associated with modulation of pro-inflammatory cytokines (TNF-α and IL-6) has been demonstrated in animal model experiments using mice (Takahashi, 2014). Studies using oligonucleotide microarrays in animal models have shown that the extracts may have neuroprotective effects (Li, 2016).

Schisandra chinensis is a dioecious climber belonging to the family *Schisandraceae*, growing up to 8-15 meters long. Its natural habitat is in northeastern China, Korea, Japan, the eastern part of Russia, the Kuril Islands and Sakhalin. The most important part of the plant from a medicinal point of view is its fruit – small red berries with a lemony taste grouped in clusters (Szopa, 2012). The most important components of the fruit are lignans, of which more than 40 have been identified to date: e.g. schisandrin, deoxyschisandrin, schisandrin B, schisandrin C, gomisin A, schisanthenol, and schisantherin A (Sowndhararajan, 2018). There are also triterpene compounds (schintrilactone A i B, wuweizidilactone C–F), fhytosterols (stigmasterol and β-sitosterol), vitamins (C and E), organic acids (citric, fumaric, malic, malonic and tartaric), poly- and monosaccharides (glucose, fructose, arabinose and galactose) and numerous bioelements (Ca, Mg, Fe, Mn, B, Zn, Cr, Ni, Cu and Co). The plant is characterized by neuroprotective, immunomodulatory, antioxidant, antitumor, hepatoprotective, antimicrobial (mainly on *Staphylococcus aureus* and *Bacillus subtilis*) (Sowndhararajan, 2018; Zhang, 2020; Li, 2018; Yuan, 2018; Mocan, 2014).

Boswellia serrata (*Burseraceae*) is a deciduous tree reaching four-five meters in height. It grows throughout India. It is a species of tree that grows mainly in dry and mountainous areas of North Africa, India and the Middle East. The resin extract from the frankincense tree has been used for thousands of years in Hindu folk medicine to treat various ailments. The oleoresin is harvested by incising the bark of at least five-year-old plants. A viscous substance slowly oozes from the wounded areas and hardens in the air. Fresh guggul is golden in color, semi-solid in consistency and highly viscous. It darkens to a yellow-brown color after hardening (Sharma 2009). *Boswellia serrata* extract contains many active ingredients such as mono-, di-, tri, tetracyclic triterpene acids and pentacyclic triterpene acids such as β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic-acid oraz 3-acetyl-11-keto-β-boswellic-acid (AKBA) (Roy, 2019). *In vitro* and *in vivo* studies using animal models have shown that boswellic acids exhibit anti-inflammatory and anti-arthritic effects. They have been shown to inhibit TNF-α, IL-1β, IL-6, and MMPs, decrease nitric oxide (NO) levels, and as a result, reduce swelling in rats with induced arthritis (Yu, 2020, Umar. 2014). AKBA has also shown promise as an antimicrobial agent against all Gram-positive and Gram-negative bacteria tested, e.g. *Staphylococcus aureus*, *Enterobacter aerogenes* and antifungal for *Candida albicans* and *Malassezia furfur* (Ismail, 2014; Raja, 2011; Stefano, 2020).

In light of above information, it was decided to evaluate the toxic effects of these extracts with scientifically proven antimicrobial properties on human cells and to evaluate the MIC (Minimal Inhibitory Concentration) on spirochetes in order to assess the potential possibility of their supplementary use in Lyme disease therapy.

MATERIALS AND METHODS

PLANT MATERIALS

The plant materials used to prepare the extracts were purchased from producers of herbal products. The samples of dried plants were extracted using methanol/water (80:20). After extraction, the extracts were separated from the solid plant material by filtering process. Plant extracts were evaporated in rotary evaporator under reduced pressure, and then were freeze-dried to completely remove the solvents. The lyophilized powder was weighed and next, serial dilution of extracts were prepared. Tween 80 was added to dissolve lipophilic compounds (Liebold, 2011).

CELL CULTURES

Normal human dermal fibroblasts (NHDF cell line) were obtained from the Clonetics (CC-2511; San Diego, CA, USA). The reference strain of *Borrelia afzelii* (VS 461, ATCC 51567) was obtained from the National Institute of Public Health – National Institute of Hygiene in Warsaw (Poland).

The bacterial culture was carried out in BSK-H medium (Barbour'a, Stoenner'a, Kelly'ego; Sigma-Aldrich, St. Louis, MO, USA) at 35˚C in microaerophilic conditions. The microscopic analysis of culture was performed upon seven days of growth. Cell number was monitored by cell counting in the Bürker chamber.

Normal human dermal fibroblasts were routinely maintained in the FBM medium (Fibroblast Basal Medium; Lonza, Basel, Switzerland), supplemented with a human fibroblast growth factor-basic (hFGF-B), insulin and gentamicin (FGM™ SingleQuots™; Lonza, Basel, Switzerland) at 37˚C in a 5% CO_2 incubator (Direct Heat CO_2; Thermo Scientific, Waltham, MA, USA). Both, cell number and viability were monitored by cell counting in the Bürker chamber, after staining them with 0.2% trypan blue (Biological Industries, Beit HaEmek, Israel). The experiment was performed on cells in the logarithmic phase of growth under condition of ≥98% viability assessed by trypan blue exclusion. For the experiments, NHDF cells will be used at four – six passages.

ANALYSIS OF BIOACTIVE COMPOUNDS IN PLANT EXTRACTS

The content of total polar phenolic compounds in extracts was determined colorimetrically using Folin-Ciocalteu reagent. The reaction mixture contained of an extract, Folin-Ciocalteu reagent and a sodium carbonate solution. The final mixture was diluted with deionized water. The mixture was kept in the dark at ambient conditions for 60 min in order to complete the reaction (Dewanto, 2002). Then, the absorbance at 760 nm was measured using an Infinite 200

PRO NanoQuant (Tecan, Männedorf, Switzerland). The phenol content (mg/ml) was read from the calibration curve and was expressed in terms of gallic acid. All samples were analyzed in three replicates.

The content of flavonoids in extracts was determined colorimetrically using aluminum chloride solution (Dewanto, 2002). Then the absorbance of the mixture was measured at 415 nm by using an Infinite 200 PRO NanoQuant (Tecan, Männedorf, Switzerland). The flavonoid content (mg/ml) was read from the calibration curve and was expressed in terms of quercetin. All samples were analyzed in three replicates.

The total content of phenolic acids was determined spectrophotometrically using Arnova reagent and was read from the calibration curve and expressed in terms of caffeic acid. The absorbance at 490 nm was measured using an Infinite 200 PRO NanoQuant (Tecan, Männedorf, Switzerland). All samples were analyzed in three replicates.

The total content of tannins was determined spectrophotometrically (Sun 1998). The absorbance of the mixture was measured at 500 nm by using an Infinite 200 PRO NanoQuant (Tecan, Männedorf, Switzerland). The tannins content (mg/ml) was read from the calibration curve and was expressed in terms of catechin. All samples were analyzed in three replicates.

Determination of the antioxidant potential was determined spectrophotometrically using the ABTS solution. The absorbance at 734 nm was measured using an Infinite 200 PRO NanoQuant (Tecan, Männedorf, Switzerland). All samples were analyzed in three replicates. The value of the antioxidant potential was calculated from the standard curve prepared for the Trolox solution in the concentration range of 10-1000 μmol/l.

MIC (MINIMAL INHIBITORY CONCENTRATION)

Growth of *Borrelia burgdorferi* could be detected reliably by software-assisted kinetic measurement of the decrease of absorbance. MIC for *Borrelia burgdorferi* was determined by serial micro-dilution in BSK-H liquid medium (with the 25 μg/ml of phenol red) using 96-well titration plates (Hunfeld, 2000). A series of dilutions of the plants extract were made to concentrations ranging from 0.064 to 4 mg/ml. Final concentrations of the lyophilized plants extracts were reconstituted by adding of 200 μl of the final inoculum suspension in BSK containing phenol red as growth indicator. Microtitre plates with *Borrelia* samples and growth controls were sealed with sterile adhesive plastic and cultured at 35°C with 5% CO_2. The presence or absence of growth was examined after 0, 24, 48, 72, 96, 120, 144 and 168 h by kinetic measurement of indicator colour shift at 450:630 nm applying a commercially available ELISA-reader (Tecan Infinite 200 PRO; Tecan Austria, Grödig, Austria). Amoxycyline at a concentration of 0.5 μg/ml was used as a negative control (Sigma-Aldrich, St Louis, MO, USA) (Sicklinger, 2003).

CYTOTOXICITY

The MTT conversion method was used to determine whether plant extracts at concentrations between 0.05 and 1.0 mg/ml was toxic to the normal fibroblast cell cultures. The MTT assay is often used to measure metabolic activity of cells as an indicator of cell viablity and cytotoxicity of various compounds. It is based on the reduction of a yellow tetrazolium salt to purple formazan crystals by metabolically active cells. The absorbance of the formazan product is measured at a wawelength of 570 nm.

A stock solution of the plant extracts was prepared and then, diluted in cell culture medium. The viability of the cells was assessed after 24 h of plant extracts treatment. Fibroblasts were selected for cytotoxicity research because these cells have been widely used in cell culture as an *in vitro* model to tests of cell viability and toxicity of many compounds.

STATISTICAL ANALYSES

Statistical analyses were performed using Statistica 10.0 software (StatSoft, Tulsa, OK, USA), and the level of significance was set at $p<0.05$. Values were expressed as means and standard deviation (SD) of two independent experiments. A one-way ANOVA test, which was followed by Tukey's post hoc test or Dunnett's test, were used to assess any significant differences among the groups.

RESULTS

In this study, the content of active ingredients was determined, which are presented below (Tab. I). *Scutellaria baicalensis* extract is characterized by the greatest amount of active ingredients and antioxidant potential.

Table I. Concentration of active compounds (phenols, phenolic acids and flavonoids, tannins) and antioxidant potential

	Phenols [µg/ml]	**Phenolic acids [µg/ml]**	**Flavonoids [µg/ml]**	**Tannins [µg/ml]**	**AOP [µM/l]**
Scutellaria baicalensis	963	321	609	0.85	1431
Stevia rebaudiana	687	229	435	0.74	879
Eleutherococcus senticosus	421	194	246	0.38	781
Schisandra chinensis	889	211	544	0.63	1043
Boswellia serrata	721	183	317	0.42	970

AOP – antioxidant potential.

MIC

Growth of *Borrelia* spirochaetes was evaluated based on the decrease of absorbance after seven days (D7) in comparison to the initial absorbance values (first day, D1). The lowest concentration of the tested extracts that did not reduce the absorbance relative to the initial time was considered the MIC.

Compared to the control – amoxycilin (0.5 µg/ml), *Stevia rebaudiana, Scutellaria baicalensis* and *Eleutherococcus senticosus* (1.0 mg/ml) showed the greatest ability to inhibit the development of *Borrelia burgdorferi* spirochetes. Extracts of *Schisandra chinensis* and also *Boswelia serrata* were characterized by lower MIC index – 2.0 mg/ml that suggests their weaker antibacterial properties. The results are shown in Table II and Figs. 1-5.

Table II. Change of absorbance value after seven days (D7) in comparison to the initial absorbance values (D1)

Extract	***Stevia rebaudiana***	***Eleutherococcus senticosus***	***Scutellaria baicalensis***	***Schisandra chinensis***	***Boswelia serrata***	***p**
	Absorbance $_{D7-D1}$ ± SD					
4 mg/ml	0.79 ±0.07^{a}	0.66 ±0.08^{ab}	0.43 ±0.09^{b}	0.70 ±0.16^{ab}	0.54 ±0.20^{ab}	p = 0.012
2 mg/ml	0.33 ±0.27^{a}	0.71 ±0.17^{b}	0.15 ±0.05^{acd}	**0.48 ±0.12^{abd}**	**0.10 ±0.18^{c}**	p < 0.001
1 mg/ml	0.11 ±0.16	0.11 ±0.09	0.01 ±0.05	-0.12 ±0.18	-0.18 ±0.18	NS
0.5 mg/ml	**-0.12 ±0.18**	**-0.08 ±0.04**	**-0.10 ±0.03**	-0.09 ±0.15	-0.22 ±0.15	-
0.25 mg/ml	-0.14 ±0.11	-0.24 ±0.17	-0.17 ±0.05	-0.17 ±0.18	-0.18 ±0.08	-
0.125 mg/ml	-0.21 ±0.14	-0.26 ±0.17	-0.19 ±0.07	-0.33 ±0.29	-0.33 ±0.15	-
0.065 mg/ml	-0.25 ±0.14	-0.32 ±0.13	-0.28 ±0.08	-0.39 ±0.06	-0.24 ±0.10	-
K (+)	-0.43 ±0.24	-0.43 ±0.18	-0.64 ±0.27	-0.47 ±0.12	-0.36 ±0.23	-
K (-)	1.21 ±0.21	1.12 ±0.37	1.33 ±0.07	1.20 ±0.21	1.19 ±0.27	-

the results are presented as the mean ± standard deviation;
MIC values are bolded;
one-way ANOVA test – *p < 0.05; NS – not significance
post hoc Tukey test – statistically different data groups are indicated using different letters.

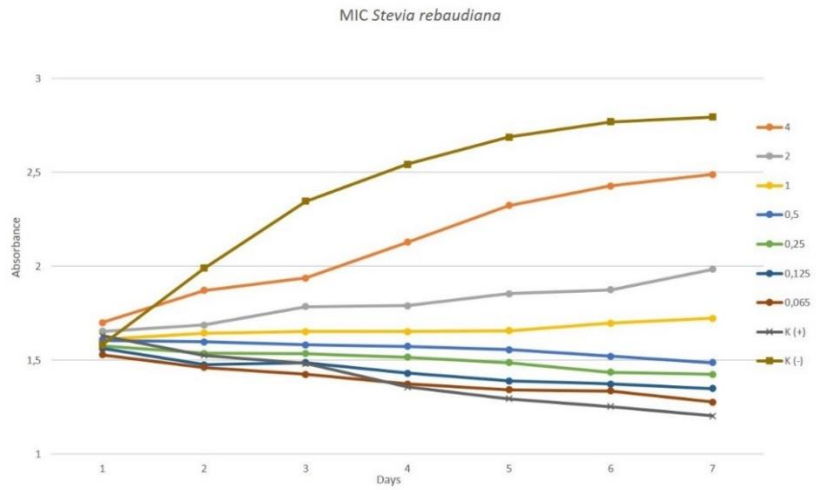

Figure 1. The Minimal Inhibitory Concentration of *Stevia rebaudiana* inhibiting the growth of *Borrelia burgdorferi* spirochetes after 7 days

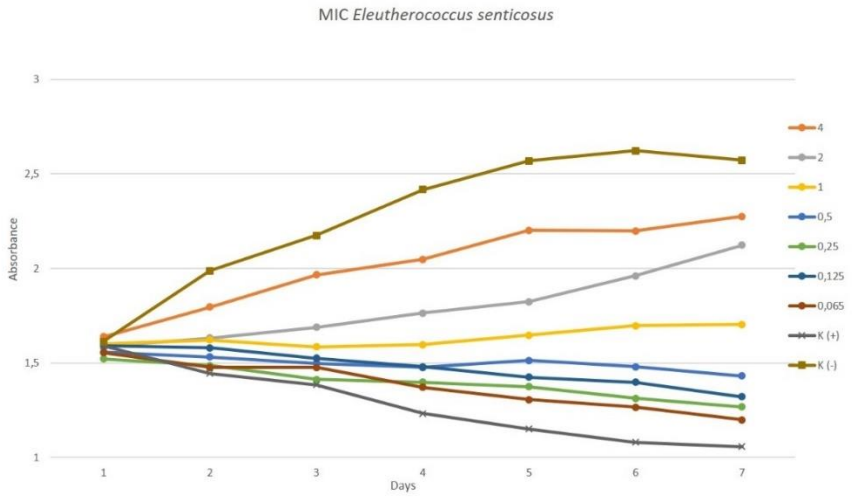

Figure 2. The Minimal Inhibitory Concentration of *Eleutherococcus senticosus* inhibiting the growth of *Borrelia burgdorferi* spirochetes after 7 days

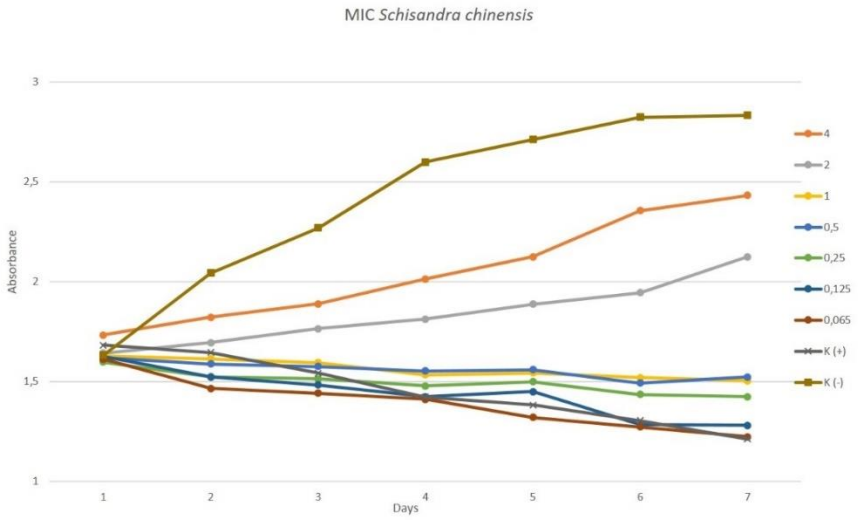

Figure 3. The Minimal Inhibitory Concentration of *Schisandra chinensis* inhibiting the growth of *Borrelia burgdorferi* spirochetes after 7 days

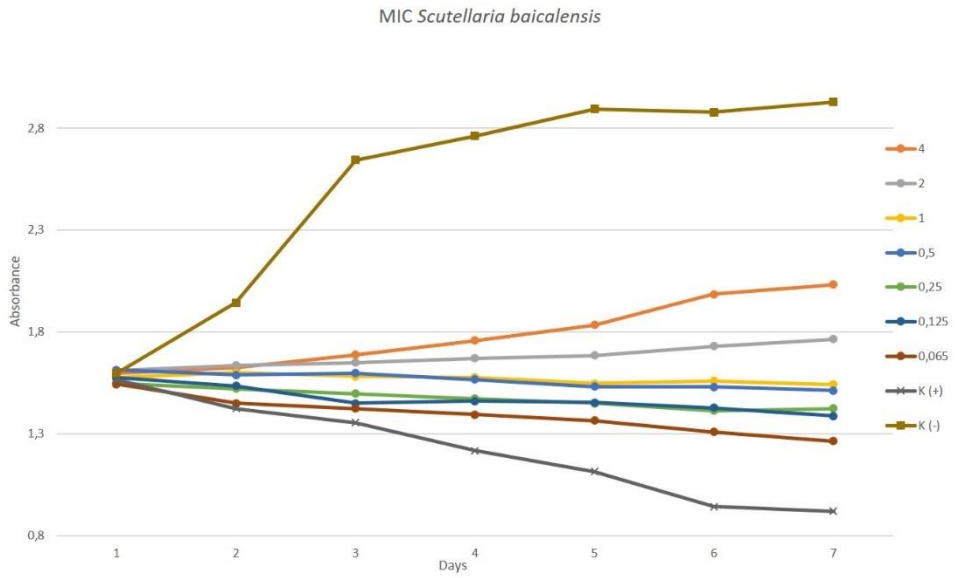

Figure 4. The Minimal Inhibitory Concentration of *Scutellaria baicalensis* inhibiting the growth of *Borrelia burgdorferi* spirochetes after 7 days

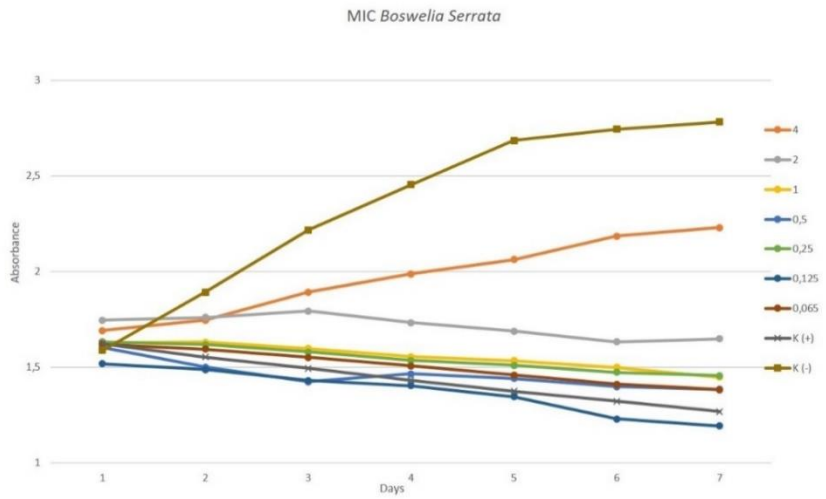

Figure 5. The Minimal Inhibitory Concentration of *Boswelia serrata* inhibiting the growth of *Borrelia burgdorferi* spirochetes after 7 days

EFFECT OF PLANT EXTRACTS ON NHDF VIABILITY

According to the results of a cell viability test. plant extracts was slightly cytotoxic to the normal human dermal fibroblasts at lower concentrations. Significant growth inhibition was observed in cultures incubated with higher concentrations of plant extracts except for *Boswelia serrata* (Tab. III).

Table III. Cell viability in normal human dermal fibroblast cultures in the presence of plant extracts for 24 h

NHDF cytotoxicity – *Scutellaria baicalensis*								
	Control	50 ug/ml	100 ug/ml	250 ug/ml	500 ug/ml	750 ug/ml	1000 ug/ml	Control -
% viability	100.00	104.64	103.36	60.01*	34.44*	33.53*	37.11*	88.56
% SD	10.76	12.39	7.56	5.65	1.75	1.63	2.17	9.73

NHDF cytotoxicity – *Stevia rebaudiana*

	Control	50 ug/ml	100 ug/ml	250 ug/ml	500 ug/ml	750 ug/ml	1000 ug/ml	Control -
% viability	100.00	77.76*	38.76*	46.51*	42.73*	36.08*	26.86*	84.96
% SD	9.96	14.53	2.60	5.32	7.18	8.51	2.17	11.90

NHDF cytotoxicity – *Eleutherococcus senticosus*

	Control	50 ug/ml	100 ug/ml	250 ug/ml	500 ug/ml	750 ug/ml	1000 ug/ml	Control -
% viability	100.00	104.69	39.49*	38.54*	40.43*	42.77*	49.92*	93.28
% SD	8.27	5.99	2.88	2.65	1.84	4.03	5.52	12.81

NHDF cytotoxicity – *Schisandra chinensis*

	Control	50 ug/ml	100 ug/ml	250 ug/ml	500 ug/ml	750 ug/ml	1000 ug/ml	Control -
% viability	100.00	90.30	82.80*	95.65	61.22*	24.34*	23.37*	99.12
% SD	14.65	11.35	15.34	7.52	6.97	1.06	0.42	11.03

NHDF cytotoxicity – *Boswelia Serrata*

	Control	50 ug/ml	100 ug/ml	250 ug/ml	500 ug/ml	750 ug/ml	1000 ug/ml	Control -
% viability	100	103.5	109.19	106.43	106.85	112.82	99.53	100.1
% SD	14.49	11.83	11.43	12.93	9.80	7.71	7.07	10.39

* Statistical significance: $p<0.05$ vs. Control.

DISCUSSION

Pharmacognostic methods may be effective in treating *Borrelia burgdorferi* infection. Standard antibiotic therapy is often supplemented by patients with plants that have antibacterial and strengthening effects on the body. Many plants. or pure substances extracted from them. are commercially available today and used to treat Lyme disease. However. the effect of plant extracts on *Borrelia burgdorferi* is still insufficiently studied especially since *in vitro* experiments predominate. The results of such experiments do not give a clear answer as to how the living organism will react and whether this will be reproducible in results obtained on cell lines. Nonetheless. they are essential for selecting plants with antimicrobial potential. An additional aspect to consider is the bioavailability of plant extracts due to instability of plant-derived compounds and their low bioavailability that results from the large size of compounds and their poor solubility. Nowadays. in order to improve the bioavailability of natural compounds and to achieve better therapeutic response. many methods are tested. such as nanoparticles or phytosome technology (Lu 2018; Rahman 2020; Myint 2021). This is very important for potential biomedical application of natural plant extracts. It should also be noted that the *in vivo* effect can be modulated by various factors for example biotransformation. pH or tissue properties hence *in vivo* studies with the use of an animal model are needed (Izah, 2018 Bubonja-Šonje 2020; Vaou 2021).

In the case of *Stevia rebaudiana*. Theophilus et al. confirmed that alcoholic extracts of stevia leaves exhibit chiropractic properties (Theophilus, 2015). Another research team also counts *Stevia rebaudiana* leaf extract as a natural agent that can kill spirochetes *in vitro*. However. in their compilation. *Stevia rebaudiana* extract is not as potent as the Theophilus et al. study (Feng. 2020). In this study. *Stevia rebaudiana* leaf extract showed the antibacterial efficacy with an MIC of 1.0 mg/ml. The safety of sugar-saccharose substitutes used in the food market has been confirmed (Bender. 2015; Sharma. 2016). Thus. it seems that steviosides isolated from *Stevia rebaudiana* or whole leaf extracts. in addition to their health-promoting properties. can be used as adjunctive preparations in the treatment of Lyme disease.

In the present study. extracts of *Scutellaria baicalensis* and *Eleutherococcus senticosus* were

shown to have similar ability to kill *Borrelia burgdorferi*. The relatively low toxicity in concentration up to 100 ug/ml to human cells in the case *of Scutellaria baicalensis*. allows us to suggest that this plant could also be used as an adjuvant therapy against *Borrelia burgdorferi*. This is also supported by the study of Feng et al. where the MIC for Baikal skullcap was determined to be >2% (Feng 2020). In addition to Lyme disease. flavonoids extracted from *Scutellaria baicalensis* could also potentially be used to treat Tick-Borne Encephalitis Virus (Leonova 2020).

However. there is little data on the antimicrobial activity of the other plants that were tested in this experiment. Of course. all of them showed antimicrobial activity. but examples were given mainly in relation to *Staphylococcus aureus* (Qian 2015; Mocan 2014; Ismail 2014). In the case of *Eleutherococcus senticosus*. which is often studied as an enhancing and adaptogenic plant. Extracts from the root stimulate bacterial migration and phagocytosis by macrophages. released increased amounts of TNF-α and IL-4. IL-6. IL-10 (Jin. 2020). In this study, the MIC with Siberian Ginseng was 1.0 mg/ml and the cytotoxicity against human cells was relatively high. However. it is important to note that *in vitro* studies are not equivalent to effects on the human body. The cytotoxicity of *Eleutherococcus senticosus* extracts was also tested against cancer cells (Chen 2021). Using Siberian Ginseng to treat Lyme disease may be a good choice especially because of its immunomodulatory potential.

Schisandra chinensis has the higher MIC than *Eleutherococcus senticosus* but lower cytotoxicity to human cells. In scientific reports there is no information whether the plant can be used as a raw material in the therapy of Lyme disease. However, there is quite a lot of information about its antibacterial potential against e.g. *Salmonella* (Kwon 2008). *Escherichia coli* (Cui 2020). *Chlamydia pneumoniae* and *Chlamydia trachomatis* (Hakala 2015) and in an animal model of sepsis (Lee 2012).

Boswellia Serrata has the same MIC as *Schisandra chinensis*. but has virtually no cytotoxicity to human cells. The antimicrobial activity of this plant is limited to the few bacterial strains tested. while the mainstream research seems to oscillate around the anticancerogenic properties of this plant (Feng 2021; Ahmed 2015).

SHORT CONCLUSION

In conclusion. our study showed that *Stevia rebaudiana. Scutellaria baicalensis* and *Eleutherococcus senticosus* have the greatest ability to inhibit the growth of *Borrelia burgdorferi.* but *Boswelia serrata* extract may be of interest in the context of application in Lyme disease therapy due to the lack of cytotoxic activity against human cells. Further studies would be recommended due to the relatively high toxic effects of higher concentrations of other plant extracts on human fibroblasts.

Acknowledgments

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Conflicts of Interest

The authors declare no conflict of interest.

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Autoimmune inflammatory rheumatic diseases and malignancy

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ABSTRACT

Autoimmune inflammatory rheumatic diseases (AIRDs) have a complex and not fully understood patho-genesis. They include systemic lupus erythematosus (SLE), primary Sjögren's syndrome (pSS), dermatomyositis (DM), polymyositis (PM), IgG4 related disease and vasculitides (with anti-neutrophil cytoplasmic antibodies – ANCA and non-ANCA associated). The development and activity of the autoimmune process in AIRDs are influenced by genetic, epigenetic, hormonal, and environmental (infections, smoke, ultraviolet radiation) factors. The severity of the inflammatory process varies depending on the type of the disease, activity of specific proinflammatory and anti-inflammatory cytokines and activation of several pathways related to inflammation.

Autoimmune inflammatory rheumatic diseases affect various organs and systems. The course of AIRDs may be mild as well as severe and life-threatening. The treatment of AIRDSs includes immunosuppressive drugs, biologics, symptomatic drugs, immunoglobulins, plasmapheresis and haemopoietic stem-cell transplantation. The choice of the therapy depends on the activity of inflammation, the type of organs being affected, the severity of systemic symptoms (weakness, fever, weight loss), changes present in the peripheral blood picture and the severity of lymphadenopathy. Currently AIRDs cannot be cured completely.

The presence of the chronic inflammation is known to play a role of a triggering factor for neoplasmogenesis. The combination of chronic inflammation with autoimmune phenomena, occurring in AIRDs, significantly increases the risk of cells escaping the regulatory mechanisms, which control their formation, development and differentiation. Therefore, some AIRDs are particularly associated with a risk of cancer development e.g. DM with a risk of breast, lung and renal cancers and pSS with a risk of lymphomas. The aim of this chapter is to present the associations of AIRDs with certain neoplastic diseases and factors contributing to this serious complication of AIRDs.

INTRODUCTION

The autoimmune inflammatory rheumatic diseases (AIRD) constitute a heterogenous group of diseases associated with the presence of general symptoms, as well as affecting various organs and systems (Abasolo, 2008). In certain diseases from this group e.g. rheumatoid arthritis (RA) or spondyloarthropathies (SpA), the peripheral or axial joints inflammation precedes other symptoms and organ complications. In others – such as systemic lupus erythematosus (SLE), systemic sclerosis (SSc), different types of vasculitis and inflammatory myositis – the beginning is more insidious, with the involvement of various organs, thus often taking "a mask" of other diseases.

Although the activation of the innate and acquired immune system is crucial for the pathogenesis of AIRDs, the level of inflammation and effect of its chronicity on the immune system varies depending on the type of the disease involved. Environmental factors, such as bacterial and viral infections, ultraviolet radiation, vitamin deficiency or hormonal imbalance also play an important role in development AIRDs in susceptible individuals (Moutsopoulos, 2021; Rosenblum, 2015; David, 2018).

However, the clinical picture suggestive of AIRDs may be in fact "a mask" of malignancies, especially when the picture of the disease differs to some extent from its typical course, the relevant immunological criteria are not met, or the basic treatment turns out to be ineffective.

Although the connection between the autoimmunity and tumorigenesis is still widely discussed, in AIRDs the clinical features, which point to a potential presence of a neoplasm, should always be closely analyzed, to potentially redirect the focus of the diagnostics as soon as possible.

AUTOIMMUNE DISEASES AND TUMORIGENESIS

In rheumatic diseases (RD) the systemic inflammation plays a crucial role in the link between RDs and neoplasms, being a triggering factor of neoplasmogenesis. While the innate and acquired immune systems – apart from being a defense against pathogens (microbials, viruses, fungi and helminths) – constitute a barrier to the uncontrolled development of the malignancy,

their role in this respect is altered in RDs as the systemic inflammation leads to the chronic stimulation of T and B cells. This in turn may result in the development of lymphoproliferative diseases. The autoinflammatory process may also lead to the cancerogenesis. The differences in a risk of cancer development in particular RDs depend on type of cells and immune system pathways which are hyperactivate in each of those diseases (Yu, 2022; Brito-Zeron, 2017; Takakubo, 2012).

At the center of AIRD phenomenon lays the balance between the type 1 and type 2 chronic immunity. The former is associated with the production of IFNγ and other inflammatory cytokines, the latter – with IL4 and IL13 activity. While the type 2 immunity plays a vital inhibitory role in the development of the immune response, its excessive activity may also induce metaplasia and cellular transformation in susceptible persons, finally leading to malignancy (Yu, 2022; Takakubo, 2012).

An increased risk of malignancy is also associated with individual features of patients, such as: age, gender, previous medical history of cancer and genetic susceptibility. It also depends on geoepidemiological circumstances – the incidence of infections in a given area, their prevention and availability of – or more often the lack of – an effective AIRD treatment (Jensen, 2009; Calatroni, 2015; Vanni, 2020). The overall risk factors associated with a lifestyle, such as smoking, alcohol abuse and contact with toxins should also be taken under consideration (Lewandowska, 2019; Hulvat, 2020).

The treatment of AIRDs rests upon the various ways of the inhibition of the autoimmune process. The main method of treatment is a non-specific inhibition of T and B cell activity or antigen presentation, mainly by classic synthetic disease-modifying drugs (DMARDs), such as: methotrexate, azathioprine, leflunomide and antimalarial drugs. The same immunologic mechanisms can also be a subject of a targeted inhibition with synthetic drugs (target-directed systemic drugs) – mainly with inhibitors of Janus kinases (among others: upadacitinib, baricitinib, tofacitinib). It is important to note, that the immunosuppressive therapy may influence tumor development to an extent depending on the patient's susceptibility, the drug itself and the influence of additional environmental factors. Biological DMARDs (bDMARDs) target different elements of the immune process, inhibiting the autoimmune process through inhibition of e.g. tumor necrosis factor (TNF), IL-6, IL-12/23, IL17 or CD20 cells. They may exert various side effects, including the triggering of a neoplastic process.

THE RISK OF DEVELOPING MALIGNANCY IN PARTICULAR RHEUMATIC DISEASES

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic autoimmune disease with a joint inflammation being a dominant symptom, although its complications may affect various internal organs. It is the most common type of a non-infectious arthritis. Rheumatoid arthritis raises the risk of the development of several other diseases – compared to the general population. The number of comorbidities in RA increases with patient's age, disease duration and activity of inflammatory process. Cardiovascular diseases, infections and cancers constitute the most important comorbidities of RA patients, as they can lead to an increased risk of death. The overall malignancy risk in patients with RA is similar to that of the general population (Wilton, 2012).

There is an increased risk of the development of certain neoplasms in RA, concerning lung, renal cancer and lymphoma in particular. The etiopathogenesis of this increased risk is likely multifactorial and depends on the presence of a chronic inflammation along with other risk factors (Wilton, 2012; Muellenhoff, 2012; Kim, 2019; Winthrop, 2022; Wu, 2016; Simon, 2019). Interestingly, there are cancers, that occur less frequently in RA than in the general population, such as breast, gastrointestinal and – in particular – a colorectal cancer. In RA the risk of development of cancer is higher for males and older individuals, however compared to the general population, the effect of RA on cancer risk is more pronounced in the younger age groups (Lee, 2019; Simon, 2015; Wilton, 2017; Carmona, 2010; De Cock, 2018). The highest incidence of cancer in patients with RA is in the first 5 years after the establishment of the diagnosis of RA. At the later stages of the disease the risk of developing cancer gradually decreases, however still active inflammation often associated with an increased number of white blood cells is related to the malignancy (Parikh-Patel, 2009; Wolfe, 2004; Chen, 2011). The risk of developing lymphoproliferative diseases, including Hodgkin's lymphoma (HL)

and non-Hodgkin's lymphoma (NHL), is increased in patients with RA. The patients with RA and NHL have survival rate similar to the overall population of NHL patients. In RA patients lymphomas tend to be low-stage and lymphoma effect on mortality of RA patients is minimal (Abasolo, 2008; Baecklund, 2014). Risk factors for the lymphoma developement in RA patients are the same as those in the general population, including increased age and male gender. Histologically, diffuse large B cell lymphoma (DLBCL) is the most frequent type of lymphoma in patients with RA (Abasolo, 2008; Baecklund, 2014; Hellgren, 2017; Baecklund, 2003). All types of DLBCL are associated with an increased RA disease activity. Immunoglobulin heavy chain clonality reduces survival rate of DLBCL patients. The development of lymphoma in patients with RA is associated with the high disease activity (the disease activity index-28 (DAS 28) for RA >5.7), as well as with an immunosuppressive treatment, which may result in the development of certain lymphomas (Ichikawa, 2013; Baecklund, 2006). It was confirmed that a proper control of the disease activity reduces the risk of lymphoma development (Ichikawa, 2013; Baecklund, 2006). The incidence of lung cancer in RA patients is generally higher than in the general population, especially in patients over 55 years of age and it is more common in male, especially in individuals with Fealty's syndrome (Baecklund, 2006; Baecklund, 2004). The prognosis for survival of RA patients with lung cancer is worse than in the general population (Khurana, 2008; Joseph, 2016).

PRIMARY SJÖGREN'S SYNDROME

The primary Sjögren's syndrome (pSS) is a chronic autoimmune disease characterized by a progressive mononuclear cells infiltrations and hyperreactivity of B cells with autoantibodies production (mainly anti-SSA/Ro, anti-SSB/La antibodies). The disease affects mainly exocrine glands – salivary and lachrymal glands in particular – causing xerostomia and xerophthalmia. The activity of B cells and other immune cells increases the risk of development of lymphoproliferative malignancies (LM) especially lymphomas, the mucosa associated lymphoid tissue (MALT) lymphoma being most common.

The pSS activity is evaluated with the EULAR Sjögren's syndrome disease activity index (ESSDAI), based on the assessment of the general, glandular and articular symptoms, immunological findings and lymphadenopathy using scoring system. In about 20-40% of patients with pSS multiple organs and systems are affected, resulting in a high ESSDAI score (Ramos-Casals, 2014) – such patients have also a higher risk of lymphoma development.

About 4-8% of patients with Sjögren's syndrome develop non-Hodgkin's lymphoma within the first 10 years of disease duration. It is most often localized in the main salivary glands. Most lymphomas in pSS are MALT lymphomas. MALT lymphomas are usually slow-growing and their course mild, with a 90% five-year survival rate. Tertiary lymphoid structures and transformation to lymphomas may be present in a variety of organs, however the parotid glands are quite common involved in it (Nocturne, 2016). Non-Hodgkin's lymphomas usually occur in patients with enlarged salivary glands, splenomegaly and lymphadenopathy, although they can also develop in patients with undiagnosed asymptomatic pSS. Palpable purpura, peripheral neuropathy, glomerulonephritis, low serum concentration of the C3 or C4 complement component and presence of cryoglobulins (mixed cryoglobulinemia) are associated with the high-risk of development the lymphoproliferative process, what may concern approximately 20% of all patients with pSS (Nocturne, 2016; Świerkocka, 2008). Additionally, a decreased number of CD4 + lymphocytes in blood and the index of CD4 / CD8 lymphocytes lower than 0.8 are significant risk factors for the development of lymphoma (Świerkocka 2008). Even up to 80-100% of patients with extraglandular symptoms occurring in the course of pSS have monoclonal light chains or monoclonal immunoglobulins present in serum and / or urine, what may be a useful indicator of lymphoproliferative disease development. B-cell marginal zone lymphomas develop more frequently in pSS than other lymphomas and usually emerge in places with chronic inflammation, often extranodally, in the lymphatic tissue associated with the mucous membranes (MALT), not only in the salivary glands, but also at other sites e.g. stomach or lungs. T-cell lymphomas occur much less frequently in pSS. The prognosis for lymphoproliferative diseases in pSS depends on the type of lymphoma that develops. The MALT B cell lymphomas are usually slow-growing course and the 5-year

survival in this group of patients is over 90% (Ioannidis, 2002; Theander, 2006; Zucca, 2000). Certain lymphomas have a poor prognosis e.g. giant cell B-cell lymphoma of the type of spilled growth, which in some cases may be a result of the transformation from MALT lymphomas.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease, occurring predominantly in young and middle-aged individuals, significantly more often affecting females (female/male ratio of 10:1). The main symptoms of this disease include skin lesions (characteristic butterfly-shaped erythema, disc erythema, hair loss), pleuritis, pericarditis and proteinuria in kidney involvement (lupus nephritis). Systemic lupus erythematosus may also manifest itself through a wide spectrum of immunological phenomena (including antiphospholipid spectrum antibodies) and hematological changes (leukopenia, lymphopenia, antihemolytic anemia, thrombocytopenia). The elevated titer of antinuclear antibodies, with a homogenous nucleolar indirect immunofluorescence (IIF) pattern, is characteristic for SLE. Systemic lupus erythematosus is also characterized by the production of specific autoantibodies, mainly anti double strand DNA antibodies (anti-dsDNA Ab) and anti-Smith antibodies (anti-Sm), complement activation and emergence of deposits of immune complexes. The autoantibodies can be directed against almost any organ or system, being responsible for a heterogeneous array of clinical manifestations. The main causes of morbidity and mortality in SLE are: infection, cancer or other type of neoplasm, lymphoproliferative diseases, renal failure, myocardial infarction and central nervous system disease (Choi, 2017).

Systemic lupus erythematosus is associated with an increased risk of the development of different types of malignancies, including lymphoproliferative diseases (non-Hodgkin's lymphoma, Hodgkin's lymphoma, leukemia, multiple myeloma), cancers of cervix, vagina/vulva, bladder, esophagus, lung, oropharynx, larynx, skin (non-melanoma) and renal, hepatobiliary and thyroid cancers. In SLE the risk of Hodgkin lymphoma is >3-fold; of myeloma and liver cancer >2-fold; of cervical, lung, bladder and thyroid cancers ≥1.5-fold; of stomach cancer >1.3-fold higher than in a general population (Song, 2018). Patients with SLE have a decreased risks of prostate cancer and cutaneous melanoma and there is no significant associations between SLE and breast, uterus, ovarian, pancreatic and colorectal cancers. Because the ultraviolent sunlight exacerbates SLE activity, patients generally avoid sun overexposure, which may provide the benefit of a lower risk of ultraviolet-related cancers like melanoma. Several potential mechanisms could explain the increased risk of malignancy development in SLE patients. Patients with SLE have basic defects in immune cell functions, resulting in an immune dysregulation, which might prevent aberrant cells from being removed. This potentially contributes to an increased risk of neoplasmogenesis. The combination of a chronic inflammation and genetic predisposition to an impaired DNA repair may also contribute to the increased DNA damage and a heightened risk of malignancy in SLE patients. Some studies also reported the existence of several important co-stimulatory molecules, including OX40L and CTLA4, which play crucial roles in both the pathogenesis of SLE and carcinogenesis (Clarke, 2021). CTLA4 predisposes to tumor growth and / or progression and accelerates the formation and / or manifestation of inflammatory autoimmune disorders. Some auto-antibody profiles may alter the malignancy risk, for example, antiphospholipid antibodies are associated with increased risk of all hematologic neoplasms including NHL (Ghaderi, 2011; Dias, 2011). It has been shown that the risk of hormone-sensitive neoplasms is reduced: breast, uterine and prostate cancer (by 13%, 36% and 20%, respectively), which may also be the result of autoantibody profile in particular patient. It was demonstrated that the presence of cell-penetrating anti-double-stranded DNA is associated with a reduced risk of breast cancer (Hansen, 2012). The reduced risk of hormone-sensitive cancers may also be a result of a lower exposure to endogenous and / or exogenous hormones.

SYSTEMIC SCLEROSIS

Systemic sclerosis (SSc) is a chronic autoimmune disease characterized by a skin and tissue fibrosis with an increased activity of fibroblast growth factors (FGFs) and inflammatory activity, subsequent atrophy of the skin, subcutaneous tissue and muscles. The inflammatory process with fibrosis also takes place in internal organs such as: esophagus, lungs, heart (inclu-

ding the conduction system of the heart) and kidney vessels and the central nervous system. Although interstitial lung disease and pulmonary fibrosis are the most common manifestations of the extracutaneous organ involvement in SSc, also the vasculopathy constitutes an important clinical problem, as it can lead to ischemia of extremities with digital ulcers and ischemia of internal organs. There are two major types of SSc based on the extent of skin involvement: the limited systemic sclerosis (lSSc) with skin thickening of the extremities (hands, legs) and face accompanied by fibrosis of lungs and esophagus and the diffuse systemic sclerosis (dSSc) with skin lesions not restricted to any specified locations. The prognosis is determined by the type of the disease and the extent of visceral involvement – the prognosis is better for patients with lSSc. Death is most often caused by lungs, heart and kidneys being affected. The risk of developing cancer is for patients suffering from SSc 1.5 to 4 times higher than that of the general population (Weeding, 2020). In SSc there is an overall increased risk of a development of lung, liver and hematologic malignancies, as well as an increased risk of bladder cancer in women and non-melanomatous skin cancer in men. This heightened risk may be caused by a chronic inflammation and tissue damage, or malignant transformation provoked by immunosuppressive therapies. In some subsets of SSc patients there is a close temporal relationship between the onset of cancer and SSc, suggesting that cancer is inducing autoimmunity (Weeding, 2020) and in such cases scleroderma should be considered a paraneoplastic disease. There is a particularly striking temporal connection between a breast cancer and scleroderma. It was shown that individuals with both cancer and SSc with anti-POLR3 antibodies have a significantly shorter time interval between the onset of each of these diseases, compared to the patients with anti-topoisomerase 1 or anti-centromere antibodies. Patients with anti-POLR3 antibodies have also a robust nuclear expression of RNA polymerase III in their cancerous cells, which was not found in healthy control tissues or in cancer cell from the other antibody groups (Bruni, 2017). Cancer is significantly more common in the anti-POLR3 positive group, particularly with respect to cancers diagnosed within two years of scleroderma onset. It was also revealed that individuals with the presence of anti-POLR3 antibodies with a synchronous onset of cancer and scleroderma were significantly older at the time of SSc onset and more likely to have diffuse cutaneous disease (Airo, 2011; Saigusa, 2015). The risk of a concurrent onset of non-breast cancers and scleroderma is also significantly higher in men than in women. Data suggest that the risk of developing a cancer may be related to the disease activity and organ damage in SSc. Patients with SSc may have a higher risk of esophageal cancer associated with severe Barrett's esophagus and acid reflux, of lung cancer associated with interstitial lung disease (ILD), of hepatocarcinoma – especially patients with primary biliary cirrhosis and of thyroid cancer, in case of patients suffering from autoimmune thyroiditis (Weeding, 2020).

IDIOPATHIC INFLAMMATORY MYOPATHIES

The idiopathic inflammatory myopathies (IIMs) are a group of relatively rare connective tissue diseases, that can be divided into several subtypes, such as polymyositis (PM), dermatomyositis (DM), inclusion body myositis, antisynthetase syndrome and immunemediated necrotizing myopathy (IMNM). Muscle weakness is a common symptom of IIM, but internal organs may also be affected. Polymyositis and dermatomyositis usually occur in children between 5 and 15 years old and in adults between 40 and 60 years old, with DM being more common than PM. Both PM and DM are characterized by acute or subacute onset, symmetrical proximal muscle weakness, the presence of infiltrating mononuclear cells in histological examination of muscle biopsy and by an increased activity of muscle enzymes: creatine phosphokinase (CK), alanine aminotransferase (ALT), transaminase aspartic acid (AST) and lactate dehydrogenase (LDH) – as a result of a muscle damage. Studies have identified numerous myositis-specific autoantibodies (MSAs), which can be useful not only in the diagnosis, but for the classification of IIM as well. The antibodies targeting aminoacyl-tRNA synthetases (Anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-KS, anti-OJ, anti-Ha, and anti-Zo) (McHugh, 2018) are typical for antisynthetase syndrome, which is characterized by myositis, interstitial lung disease, arthritis, fever, Raynaud's phenomenon and mechanic's hands. The antibodies specific for dermatomyositis include Anti-Mi-2, anti-MDA5 (anti-CADM140), anti-TIF1 (anti-155/140, anti-p155), anti-NXP-2 (anti-MJ) and anti-SAE. Anti-MDA5 antibodies are clinically associated with amyopathic dermatomyositis developing into rapidly progressive interstitial lung disease,

while anti-TIF1 and anti-NXP-2 antibodies correlate closely with a cancer-associated dermatomyositis in adults. Anti-TIF1 and anti-NXP-2 antibodies are predominant MSAs found in juvenile dermatomyositis, especially with a high incidence of calcinosis. Anti-SRP and anti-3-hydroxy-3-methylglutaryl-coenzyme A (anti-HMG-CoA) antibodies have been found in patients with IMNM. The diagnosis of cancer-associated myositis (CAM) can be posed if cancer occurs within three years after or prior to the diagnosis of inflammatory myopathy being established (Moghadam-Kia 2020). Most of the cancer cases emerge within a year of IIM diagnosis, and the risk of malignancy decreases over time (Li, 2021). The highest risk of malignancy in IIM is observed in the course of DM. The cancer risk factors in patients with PM/DM include: an age over 60, male sex, dysphagia, skin necrosis, cutaneous vasculitis, rapid disease onset (< 4 weeks), elevated CK, an increase in the ESR and a high level of C-reactive protein. Additionally, patients with IIM and diabetes mellitus, have an increased risk of developing a cancer. On the other hand, the presence of arthritis, interstitial lung disease, Raynaud's syndrome or anti-Jo-1 antibody indicates less than average risk of developing a neoplasm. In the course of IIMs, different types of cancers have been observed, although adenocarcinoma seems to be the most prevalent tumor type, as it accounts for approximately 70% in CAM. Breast, lung, gastrointestinal, cervical, ovarian, bladder, uterine, pancreatic and prostatic tumors, as well as Hodgkin's lymphomas, are listed among the most frequent malignancies associated with IIM (Kardes, 2022). The prevalence of cancers depends on the subtype of myositis, as specific neoplasms occur more frequently in patients with DM, while others are predominantly diagnosed in patients with PM. It was observed that the most frequently detected tumors in patients with DM include ovarian, pancreatic, colorectal and stomach cancer, as well as non-Hodgkin's lymphoma. The relative risk of hematologic neoplasms was found to be higher in PM than in DM, with non-Hodgkin's lymphoma being the most prevalent malignancy, preceding lung and bladder cancers (Marie, 2012). Patients with severe muscle involvement are more likely to develop malignant neoplasm, particularly those with marked skeletal muscle weakness, involving distal skeletal limb muscles, respiratory skeletal muscles, and esophageal muscle. Malignancy may be associated with severe cutaneous lesions such as cutaneous ulceration, skin necrosis and leukocytoclastic vasculitis. It was also reported that CAM patients presents periungual erythema, violaceous and heliotrope rash, Gottron's papules and essential derangement of nailfold capillaries (Requena, 2014). Biochemical and serological test results may also indicate an increased risk of cancer in MII patients, but in some studies also those with lower levels of CK and LDH had an increased risk of malignancy, if they have elevated inflammatory markers such as C-reactive protein and sedimentation erythrocytes rate (Oldroyd, 2021).

POLYMYALGIA RHEUMATICA

Polymyalgia rheumatica (PMR) is an inflammatory disease in which pain and stiffness of muscles of shoulders and hips occur, especially in the morning. The most of patients who develop polymyalgia are over 65 years of age and according to classification criteria the PMR diagnosis can be established for patients no younger than 50 years old.

This condition is associated with another inflammatory disease called giant cell arteritis, which causes inflammation of the arteries resulting in headaches, vision problems, jaw pain and scalp tenderness. It is possible for both conditions to coexist at the same time. Polymyalgia rheumatica may be initially hard to diagnose, although typically the lab results of blood inflammatory markers are usually abnormally high. In order to diagnose PMR, it is necessary to exclude a significant number of other conditions, which may mimic the symptoms of PMR, including rheumatoid arthritis and numerous endocrine, infective and neoplastic conditions (Dejaco, 2015). On the other hand, PMR can repre-sent a paraneoplastic syndrome. Comorbidities are very common in the age group affected by PMR and therefore the coexistence of one of these comorbidities with PMR should not necessarily invalidate the diagnosis of PMR itself. People with cancer experience some of the symptoms associated with PMR, including fever, weight loss, fatigue and loss of appetite. Cancer risk among patients with PMR appears unrelated to sex, age or smoking status, or even to treatment with glucocorticosteroids. The data suggest an increased risk in PMR of hemopoietic malignancies and malignancies of the

lymphatic, genitourinary, nervous and female reproductive systems (Muller, 2013). As the cancer is more common in the general population in the elderly and the symptoms can be similar both in the PMR and in the course of cancer, it is especially important, that every PMR patient should also be carefully observed for any indication of cancer development in the 6 months after the initial PMR diagnosis.

PSORIASIS ARTHRITIS

This form of arthritis usually develops years after the initial diagnosis of psoriasis; however, some joint problems may occur before or concurrently with the observation of skin lesions. Patients with psoriatic arthritis (PsA), similarly to those suffering from RA, present mainly joint pain, stiffness and swelling as main symptoms of the disease. Psoriatic arthritis can affect any part of the body where ligaments and tendons connect to bone, including fingertips, spine and sacroiliac joints, with the intensity of the disease ranging from relatively mild to severe. Psoriasis arthritis is classified as a type of seronegative spondyloarthropathy. Approximately 40-50% of individuals with psoriatic arthritis have the human leukocyte antigen (HLA) B27 genotype. The overall incidence of malignancy is higher in patients with PsA than in the general population. Patients with psoriasis appear to present an increased risk of malignancies, particularly keratinocyte cancer, lymphomas, bladder and lung cancer (Muller, 2020). It was found that patients with psoriasis are at an increased risk of developing both non-Hodgkin and Hodgkin lymphoma, it can be partly explained by an increased risk of cutaneous T-cell lymphoma (CTCL) in patients with psoriasis. In PsA particularly the risk of developing keratinocyte cancer is associated with an exposure to sunlight.

ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is a disease in which an abnormal immune response triggers chronic inflammation particularly in sacroiliac joint, spine (longitudinal ligaments), as well as in peripheral joints. Ankylosing spondylitis is an HLA-B27-related disease, that predominantly affects adolescent men. It initially manifests itself with pain in sacroiliac joints (with inflammation confirmed with X-ray and MRI) and spine involvement resulting in pain and morning stiffness. This disease may also affect heart, lungs and colon (AS is associated and can coincide with the inflammatory bowel disease). It can lead to complications such as eye involvement (anterior uveitis, iridocyclitis) and osteoporosis. Ankylosing spondylitis in combination with severe comorbidities is a risk factor for the development of cancer in females and males and is associated with a 14% increase in the for overall risk of malignancy (Deng, 2016). An oncological screening during the first 3 years following the diagnosis of AS provides a chance for an early detection of hematological malignancies in males and females, prostate cancer in males and colon cancer in females. Young patients with a high disease activity and long disease duration with high activity of inflammation are particularly at this risk (Chang, 2017).

ANCA-ASSOCIATED VASCULITIS

The anti-neutrophil cytoplasm antibody associated vasculitides (AASVs or AAV-ANCA associated vasculitis), which include granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), are characterized by a necrotizing inflammation of small blood vessels with predilection for kidneys, lungs and nutrient vessels of nerve fibers with symptoms of peripheral neuropathy in most of the patients. In course of AAVs any organ or system can be affected. The ANCA-associated vasculitis are rare multisystem autoimmune diseases, occurring more frequently in men and in the older people. AAV should be considered as a chronic disease needing long-term immunosuppressive therapy. The mortality remains high, and late death is due to infection (often secondary to immunosuppressive treatment), cardiovascular disease and malignancy. Data suggest a standar-dized incidence ratio of cancers in AAV of 1.6-2.0 compared to the general population and a possibly higher risk in GPA than in MPA (Mahr, 2013). The most prominent neoplasms observed in AAV include leukemia and non-melanoma skin cancer, urinary tract cancer. Individual drugs may increase the development of cancer in AAV among these the first place belongs to cyclophosphamide due to its direct carcinogenic properties. There was no significant association between AASV and colon, kidney, prostate and breast cancer (Shang, 2015). Some studies have shown AAV patients

have an increased overall risk of malignancy especially increased risks of site-specific cancers such as lung cancer or hematological malignancy. Men with AAV have an increased risk of gallbladder cancer while women have increased risk of bladder (Ahn, 2019). Regular monitoring of cancers and if it is possible to minimize the administration of immunosuppressive agents in the treatment of AAV are necessary to improve survival in AAV patients.

IgG4-RELATED DISEASE

IgG4-related disease (IgG4-RD) is a chronic, systemic, inflammatory disease characterized by elevation serum levels of IgG4, infiltration of IgG4 positive plasma cells, presence of pseudotumors, multiorgan involvement with inflammation and storiform. In the new classification criteria for diagnosis of IgG4-RD one of the exclusion criteria is cancer (Wallace, 2020). This disease entity is not yet fully understood and the researched are also its dependencies, inter alia, as a risk factor for the development of certain neoplasms. At present, it has been shown that with IgG4-RD the overall risk of neoplasms (especially lymphomas and pancreatic cancer) is increased (Yu, 2022).

The summarize of rheumatic diseases and associated malignancy was presented in table 1.

Rheumatic disease	Type of cancer with an increased develop risk
Rheumatoid arthritis	Lung cancer, renal cancer, lymphomas (non-Hodgkin lymphoma; especially diffuse large B cell lymphoma and HL)
Primary Sjögren's syndrome	Lymphoma (especially MALT lymphoma), B-cell non-MALT, non-hematological cancers (thyroid, oral cavity, stomach)
Systemic lupus erythematosus	Lymphoma, cervix, vagina/vulva cancer, renal and bladder cancer, esophagus and gastric cancer, lung cancer, oropharynx and larynx cancer, non-melanoma skin cancer, thyroid cancer
Systemic sclerosis	Lung cancer, liver cancer, hematologic cancers overall, bladder cancer, non-melanomatous skin cancer
Idiopathic inflammatory myopathies	Breast cancer, lung cancer, gastrointestinal cancer, cervical and ovarian cancer, bladder cancer, pancreatic and prostatic tumors, lymphomas
Polymyalgia rheumatica	Lymphomas, genitourinary cancers, nervous system cancer, hematological cancers, female reproductive tract cancers
Psoriasis arthritis	Keratinocyte cancer, lymphomas, bladder cancer, lung cancer
Ankylosing spondylitis	Hematological malignancies, prostate cancer, colon cancer
ANCA-Associated Vasculitis	Leukemia, non-melanoma skin cancer, urinary tract cancer, lung cancer, bladder cancer, hematological cancers
IgG-4 related disease	Lymphoma, pancreatic cancer

Some of the autoimmune rheumatic diseases mentioned above are more closely related to the development of neoplasms, such as Sjogren's syndrome (mainly non-Hodgkin lymphoma) and scleroderma or dermatomyositis, which may be tumor revelators. Particular diagnostic vigilance should be shown in the case of unclear syndromes imitating the symptoms of rheumatic disease. All "gaps" in meeting the classification criteria, often the lack of a typical immune profile, with the presence of autoantibodies closely associated with the neoplastic process, such as TIF-1 in systemic sclerosis or anti-TIF1, anti-NXP-2 antibodies in dermatomyositis or polymyositis.

Some variables may be factors that increase the risk of neoplasms in rheumatic diseases, such as older age of patients, longer-lasting disease, lymphadenopathy or purpura and multi-organ involvement. Some immunological deviations are more strongly associated with the development of neoplasms, especially hematological: leukopenia, raised levels of BAFF and beta2-microglobulin, cryoglobulins, monoclonal band, and hypocomplementemia.

Disease-related risk factors may overlap with population risk factors, both physical, chemical and biological with mutagenic effects, such as cigarette smoking, radiation exposure, environmental pollution, exposure to aflatoxins, nitrates, aromatic amines, coal combustion products or asbestos. Viruses play a special role among biological factors.

TREATMENT OF AUTOIMMUNE RHEUMATIC DISEASES AND MALIGNANCY

In discussion about malignancy and RD the immunosuppressive and immunomodulatory treatment also should be considered as a factor influencing cells and immune system toward tumorigenesis. However, anti-inflammatory properties of different disease modifying anti-rheumatic drugs (DMARDs) in general have positive effect on disease activity and on this way should lowering risk of malignancy. Some of drugs have unique abilities and even positive effect on autoimmune disease may enhance this risk.

We take into account that some drugs are use in severe and life-threatening stage of the disease such as cyclophosphamide (CyC) which particularly use in severe diseases complications such as: vasculitis, central nervous system involvement. This risk may cumulate along with disease activity and higher immune system dysregulation.

In table 2 the main drugs used in the treatment of AIRDs, and their potential risk of triggering malignancy are presented.

The risk of cancer in connection with drugs used in the treatment of rheumatic diseases	
Cyclophosphamide	bladder cancer, non-melanoma skin cancer, lymphoma and leukemia;
Methotrexate	overall skin cancer risk is increased, especially risk of squamous cell skin cancer; lung cancer, NHL;
Glucocorticosteroids	overall glucocorticosteroids do not increase malignancy risk; generally, glucocorticosteroids use appears to decrease lymphoma risk;
Leflunomide	pancreatic cancer;
Cyclosporine	lymphoma, skin cancer;
Azathioprine	lymphoma, leukemia;
TNF inhibitors *	skin cancer, lymphoma;
Rituximab (anti-CD-20)	no evidence of increased risk of malignancy;
Tocilizumab (anti-IL-6)	no evidence of increased risk of malignancy;
JAK inhibitors	an increased risk of non-melanoma skin cancer with use of the tofacitinib 10-mg dose;

***** There are studies presented that treatment with TNF antagonist of RA patients was associated with a lower risk of cancer, but not for hematologic cancers in comparison of RA patients taking non biological DMARDs (Wu, 2016).

Glucocorticosteroids (GCs) are often used drugs in treatment of AIRDs, in some diseases they are primary drugs and equivalent in combination therapy (PM, SLE, IgG4-RD), in some they are adjunctive therapy for inhibition of inflammation (RA).

There are also signs that, apart from the obvious metabolic complications of GCs that they may increase the risk of cancer, but this has not been shown to be statistically significant, some studies have indicated a certain risk of basal skin cancer or breast cancer, but this is subject to further discussion. As well as GCs are often used in combined therapy of cancers. At the same time, the lack of response to GCs may be a signal of an atypical course of the disease, incorrect diagnosis and a signal for diagnosis to exclude the neoplastic process. This applies especially to rheumatic polymyalgia, SLE, DM / PM or dependent IgG4 disease.

THE OTHER SIDE OF THE COIN – RHEUMATIC DISEASES DURING MALIGNANCY AND AFTER ONCOLOGICAL THERAPY

Autoantibodies associated with autoimmune rheumatic diseases may appear in the serum of cancer patients. The most common are anti-nuclear antibodies (ANA) and rheumatoid factor, as well as dsDNA, histones, anti-SS-A / Ro and anti-SS-B / La antibodies, Sm and RNP antibodies (Solans-Laqué, 2004). Similarly antiphospholipid autoantibodies (aPL) were also found. The latter have been shown to significantly increase the risk of thrombosis in cancer patients. Patients with hematological neoplasms such as myeloma or lymphomas often have rheumatoid factor and cryoglobulins present. The occurrence of autoantibodies may also be associated with the occurrence of paraneoplastic syndrome in the form of rheumatic disease, as already mentioned, especially in the case of dermatomyositis, polymyositis, vasculitis, and systemic sclerosis. In some cases, the clinical components of neoplastic disease and rheumatic

disease overlap, such as, for example, autoimmune hemolytic anemia and thrombocytopenia. In conclusion, tumor-induced immune dysregulation may influence the development of autoimmune phenomena and autoimmune rheumatic disease symptoms over time. Patients with hematological neoplasms such as myeloma or lymphomas often have rheumatoid factor and cryoglobulins present (Bei, 2009; Szekanecz, 2006).

Oncological treatment can induce symptoms of rheumatic disease in a variety of ways. One of the most frequently mentioned drugs used in cancer therapy that can induce autoimmune phenomena is cyclophosphamide combined with methotrexate, fluorouracil or doxorubicin (Abu-Shakra, 2001). In addition to joint and muscle pain, arthritis and tenosynovitis have been reported following this treatment.

Oncological drugs such as bleomycin, vinblastine and cisplatin may trigger the Raynaud's phenomenon (Abu-Shakra, 2001; Vogelzang, 1981). After 5-fluorouracil, digital ischemia and necrosis may occur. These drugs can cause SSc-like disease, especially bleomycin, then with thickening of the skin and lung fibrosis.

In this context, much attention is currently paid to checkpoint inhibitors aimed at the inhibition of CTLA-4 and PD-1 receptors and are nowadays an element of cancer therapy among others: melanoma, breast cancer, Hodgkin lymphoma, bladder and renal cell cancer and skin cancer. These drugs enhance the patient's immune system, resulting in the destruction of tumor cells (Menzies, 2017).

In group of patients with previous autoimmune disease the disease flare during checkpoint inhibitor therapy was observed especially in psoriasis/psoriatic arthritis (in 68% of patients) and rheumatoid arthritis (in 65%) (Lidar, 2018). However also autoimmunity may develop in patients without previous autoimmune disease (autoimmune side effect) and it was more frequently observed in a group treated with first approved checkpoint inhibitor – ipilimumab (79%) (Tison, 2019). In this group colitis, pituitaritis, vitiligo, or thyroiditis were described (Tison, 2019). The development of autoimmune rheumatic disease is rare, however psoriasis/ psoriatic arthritis (in 68% of patients) and rheumatoid arthritis (in 65%) were reported (Day, 2016). Arthralgia or arthritis are the most often described symptoms during checkpoint inhibitors treatment.

CONCLUSIONS

In AIRDs diagnostics, differentiation from the neoplastic process may be necessary, especially in the case of an atypical course of an autoimmune disease or known connection between it and the occurrence of a specific type of neoplasm. In addition, the individual predisposition of the patient, the influence of environmental factors or the effect of the applied immunosuppression are additional factors favoring the development of cancer. Some of the rheumatic diseases are particularly associated with the risk of malignancy, such as polymyalgia rheumatica, Sjogren's syndrome and dermatomyositis. Treatment of AIRDs with synthetic as well as biological DMARDs may also increase the risk of malignancy development. On the other hand, in the oncological treatment there are drugs that can stimulate the development of the autoimmune process and thus the occurrence of symptoms of rheumatic diseases.

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