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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.

References

Abasolo L., Judez E., Descalzo M.A., Gonzalez-Alvaro I., Jover J.A., Carmona L. **Cancer in rheumatoid arthritis: occurrence, mortality, and associated factors in a South Euro-pean population**. Semin Arthritis Rheum. 2008; 37(6):388-397.

Abu-Shakra M., Buskila D., Ehrenfeld M., Conrad K., Shoenfeld Y. **Cancer and autoimmunity: autoimmune and rheumatic features in patients with malignancies**. Annals of the Rheumatic Diseases. 2001; 60:433-441.

Ahn S.S., Han M., Yoo J., Jung S.M., Song J.J., Park Y.B. et al. **Risk of Cancers in Antineutrophil Cytoplasmic Anti-Body-Associated Vasculitis: Results from the Korea National Health Insurance Claims**. Database 2010-2018. J Clin Med. 2019; 8(11):1871. doi:10.3390/jcm8111871

Airo P., Ceribelli A., Cavazzana I., Taraborelli M., Zingarelli S., Franceschini F. **Malignancies in Italian patients with systemic sclerosis positive for anti-RNA poly-merase III antibodies**. J Rheumatol. 2011; 38(7):1329-1334.

Baecklund E., Smedby K.E., Sutton L.A., Askling J., Rosenquist R. **Lymphoma develop-ment in patients with autoimmune and inflammatory disorders – what are the driving forces?** Semin Cancer Biol. 2014; 24:61-70.

Baecklund E., Sundstrom C., Ekbom A., Catrina A.I., Biberfeld P., Feltelius N. et al. **Lymphoma subtypes in patients with rheumatoid arthritis: increased proportion of dif-fuse large B cell lymphoma**. Arthritis Rheum. 2003; 48(6):1543-1550.

Baecklund E., Iliadou A., Askling J., Ekbom A., Backlin C., Granath F. et al. **Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthri-tis**. Arthritis & Rheumatism. 2006; 54(3):692-701

Baecklund E., Askling J., Rosenquist R., Ekbom A., Klareskog L. **Rheumatoid arthritis and malignant lymphomas**. Curr Opin Rheumatol. 2004; 16(3):254-261.

Bei R., Masuelli L., Palumbo C., Modesti M., Modesti A. **A common repertoire of autoantibodies is shared by cancer and autoimmune disease patients: Inflammation in their induction and im-pact on tumor growth**. Cancer Lett. 2009; 281(1):8-23. doi: 10.1016/j.canlet.2008.11.009, indexed in Pubmed: 19091462.

Bruni C., Lages A., Patel H., Nityanova S.I., Green B., AbuHial M. et al. **Resolution of paraneoplastic PM/Scl-positive system-ic sclerosis after curative resection of a pancreatic tumour**. Rheumatology (Oxford). 2017; 56(2):317-318.

Brito-Zerón P., Kostov B., Fraile G., Caravia-Durán D., Maure B., Rascon F.J. et al. **Characterization and risk estimate of cancer in patients with primary Sjögren syndrome**. J Hematol Oncol. 2017; 10(1):90. doi: 10.1186/s13045-017-0464-5.

Carmona L., Abasolo L., Descalzo M.A., Perez-Zafrilla B., Sellas A., de Abajo F. et al. **Cancer in patients with rheumatic diseases exposed to TNF antagonists**. Semin Arthritis Rheum. 2011; 41(1):71-80. doi: 10.1016/j.semarthrit.2010.08.005.

Choi M.Y., Flood K., Bernatsky S., Ramsey-Goldman R., Clarke A.E. **A review on SLE and malignancy**. Best Pract Res Clin Rheumatol. 2017; 31(3):373-96.

Chen Y.J., Chang Y.T., Wang C.B., Wu C.Y. **The risk of cancer in patients with rheuma-toid arthritis: a nationwide cohort study in Taiwan**. Arthritis Rheum. 2011; 63(2):352-358.

Clarke A., Pooley N., Marjenberg Z., Langham J., Nicholson L., Langham S. et al. **Risk of malignancy in patients with systemic lupus erythematosus: Systematic review and meta-analysis**. Seminars in Arthritis and Rheumatism. 2021; 6(51):1230-1241. doi: 10.1016/j. semar-thrit.2021.09.009.

David T., Ling S.F., Barton A. **Genetics of immune-mediated inflammatory diseases**. Clin. Exp. Immunol. 2018. doi: 10.1111/cei.13101.

Day D., Hansen A.R. **Immune-related adverse events associated with immune checkpoint inhibitors**. BioDrugs. 2016; 30:571-584.

De Cock D., Hyrich K. **Malignancy and rheumatoid arthritis: Epidemiology, risk fac-tors and management**. Best Pract Res Clin Rheumatol. 2018; 32(6):869-886. doi: 10.1016/j.berh.2019.03.011.

Dias D., Isenberg D.A. **Susceptibility of patients with rheumatic diseases to B-cell non-Hodgkin lymphoma**. Nature Reviews Rheumatology, 2011; 7:360-368.

De Cock D., Hyrich K. **Malignancy and rheumatoid arthritis: Epidemiology, risk fac-tors and management**. Best Pract Res Clin Rheumatol. 2018; 32(6):869-886. doi: 10.1016/j.berh.2019.03.011.

Dejaco C., Singh Y.P., Perel P., Hutchings A., Camellino D., Mackie S. et al. **2015 Recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative**. Ann Rheum Dis. 2015; 74:1799-1807.

Deng C., Li W., Fei Y., Li Y., Zhang F. **Risk of malignancy in ankylosing spondylitis: a system-atic review and meta-analysis**. Sci Rep. 2016; 6:32063. doi: 10.1038/srep32063.

Ghaderi A. **CTLA4 gene variants in autoimmunity and cancer: a comparative review**. Iranian J Immunol. 2011; 8(3):127.

Hansen J.E., Chan G., Liu Y., Hegan D.C., Dalal S., Dray E. et al. **Targeting cancer with a lupus autoantibody**. Science Translational Medicine. 2012; 4:157ra142.

Hellgren K., Baecklund E., Backlin C., Sundstrom C., Smedby K.E., Askling J. **Rheumatoid Arthritis and Risk of Malignant Lymphoma: Is the Risk Still Increa-sed?**. Arthritis & Rheumatology. 2017; 69(4):700-708.

Hulvat M.C. **Cancer Incidence and Trends**. Surg Clin North Am. 2020; 100(3):469-481. doi: 10.1016/j.suc.2020.01.002.

Ichikawa A., Arakawa F., Kiyasu J., Sato K., Miyoshi H., Niino D. et al. **Methotrex-ate/iatrogenic lymphoproliferative disorders in rheumatoid arthritis: histology, Epstein-Barr virus, and clonality are important predictors of disease progression and regres-sion**. Eur J Haematol. 2013; 91(1):20-28.

Ioannidis J.P., Vassiliou V.A., Moutsopoulos H.M. **Long-term risk of mortality and lim-foproliferative disease and predictive classification of primary Sjögren's syndrome**. Ar-thritis Rheum. 2002; 46:741-747.

Jensen A., Thomsen H., Engebjerg M. Olesen A.B., Friis S., Karagas M.R. et al. **Use of oral glucocorticoids and risk of skin cancer and non-Hodgkin's lymphoma: a population-based case–control study**. Br J Cancer. 2009; 13;100(1):200-5. doi: 10.1038/sj.bjc.6604796.

Joseph R.M., Movahedi M., Dixon W.G., Symmons D.P. **Smoking-related mortality in patients with early rheumatoid arthritis: a retrospective cohort study using the clinical practice research datalink**. Arthritis Care Res (Hoboken). 2016; 68(11):1598-1606.

Kardes S., Gupta L., Aggarwal R. **Cancer and myositis: Who, when, and how to screen**. Best Pract Res Clin Rheumatol. 2022; 36(2):101771. doi: 10.1016/j.berh.2022.101771.

Kim S.C., Pawar A., Desai R.J., Solomon D.H., Gale S., Bao M. et al. **Risk of malignancy associated with use of tocilizumab versus other biologics in patients with rheumatoid arthritis: A multi-database cohort study**. Semin Arthritis Rheum. 2019; 49(2):222-228. doi: 10.1016/j.semarthrit.2019.03.002.

Khurana R., Wolf R., Berney S., Caldito G., Hayat S., Berney S.M. **Risk of development of lung cancer is increased in patients with rheumatoid arthritis: a large case control study in US veterans**. J Rheumatol. 2008; 35(9):1704-1708.

Lee H. **The Risk of Malignancy in Korean Patients with Rheumatoid Arthritis**. Yonsei Med J. 2019; 60(2):223-229. doi: 10.3349/ymj.2019.60.2.223

Lewandowska A.M., Rudzki M., Rudzki S., Lewandowski T., Laskowska B. **Environ-mental risk factors for cancer – review paper**. Ann Agric Environ Med. 2019; 22;26(1):1-7. doi: 10.26444/aaem/94299.

Li Y., Jia X., Sun X., Shi L., Lin F., Gan Y. et al. **Risk factors for cancer-associated myositis: A large-scale multicenter cohort study**. Int. J. Rheum. Dis. 2021, 24:268-273.

Lidar M., Giat E., Garelick D., Horowitz Y., Amital H., Steinberg-Silman Y. et al. **Rheumatic manifestations among cancer patients treated with immune checkpoint inhibitors**. Autoimmun Rev. 2018; 17(3):284-289.

Mahr A., Heijl C., Le Guenno G., Faurschou M. **ANCA-associated vasculitis and malig-nancy: current evidence for cause and consequence relationships**. Best Pract Res Clin Rheumatol. 2013; 27(1):45-56. doi: 10.1016/j.berh.2012.12.003.

Calatroni M., Buzio C., Vaglio A. **The evolving paradigm of cancer risk related to cyclophosphamide therapy in granulomatosis with polyangiitis**. Rheumatology 2015; 54(8):1339-1341. doi.org/10.1093/rheumatology/kev196

Moghadam-Kia S., Oddis C.V., Ascherman, D.P., Aggarwal R. **Risk factors and cancer screening in myositis**. Rheum. Dis. Clin. N. Am. 2020, 46:565-576.

Moutsopoulos H.M. **Autoimmune rheumatic diseases: One or many diseases?**. J Transl Autoimmun. 2021; 28(4):100129. doi: 10.1016/j.jtauto.2021.100129.

Muellenhoff M.W., Koo J.Y. **Cyclosporine and skin cancer: an international dermatologic perspective over 25 years of experience. A comprehensive review and pursuit to de-fine safe use of cyclosporine in dermatology**. J Dermatolog Treat. 2012; 23(4):290-304. doi: 10.3109/09546634.2011.590792.

Muller S., Hider S.L., Belcher J., Helliwell T., Mallen C.D. **Is cancer associated with polymyalgia rheumatica? A cohort study in the General Practice Research Database**. Ann Rheum Dis. 2013. Epub ahead of print July 18] DOI: 10.1136/annrheumdis-2013-203465.

Nocturne G., Virone A., Ng W.F. Guern V.L., Hachulla E., Cornec D. et al. **Rheumatoid factor and disease activity are in-dependent predictors of lymphomas in primary Sjogren's syndrome**. Arthritis Rheum. 2016; 68:977-985.

Oldroyd A.G.S., Allard A.B., Callen J.P., Chinoy H., Chung L., Fiorentino D. et al. **A systematic review and meta-analysis to inform cancer screening guidelines in idiopathic inflammatory myopathies**. Rheumatology. 2021; 60:2615-2628. doi: 10.1093/rheumatology/keab166.

Parikh-Patel A., White R.H., Allen M., Cress R. **Risk of cancer among rheumatoid arthritis patients in California**. Cancer Causes Control. 2009; 20(6):1001-1010.

Ramos-Casals M., Brito-Zeron P., Camps M.T., Casanovas A., Sophena B., DiazLopez B. et al. **Systemic involvement in primary Sjogren's syndrome evaluated by the EULAR-SS disease activity index: analysis of 921 Spanish patients (GEAS-SS Registry)**. Rheumatology (Oxford). 2014; 53:321-331.

Requena C., Alfaro A., Traves V., Nagore E., Llombart B., Serra C. et al. **Dermatomiositis paraneoplásica: Estudio de 12 casos. Actas Dermo-Sifiliográficas**. 2014; 105:675-682. doi: 10.1016/j.ad.2013.11.007.

Rosenblum M.D., Remedios K.A., Abbas A.K. **Mechanisms of human autoimmunity**. J. Clin. Invest. 2015; 125(6):2228-2233. doi: 10.1172/JCI78088.

Saigusa R., Asano Y., Nakamura K., Miura S., Ichimura Y., Takashashi T. et al. **Association of anti-RNA polymerase III an-tibody and malignancy in Japanese patients with systemic sclerosis**. J Dermatol. 2015; 42(5):524-527.

Shang W., Ning Y., Xu X., Li M., Guo S., Han M. et al. **Incidence of Cancer in ANCA-Associated Vasculitis: A Meta-Analysis of Observational Studies**. PloS one 2015; 10,5:e0126016.14 doi:10.1371/journal. pone. 0126016.

Simon T.A., Thompson A., Gandhi K.K., Hochberg M.C., Suissa S. **Incidence of malig-nancy in adult patients with rheumatoid arthritis: a meta-analysis**. Arthritis Res Ther. 2015; 15(17):212.

Simon T.A., Boers M., Hochberg M., Baker N., Skovron M.L., Ray N. et al. **Comparative risk of malignancies and infections in patients with rheumatoid arthritis initiating abatacept versus other biologics: a multi-database real-world study**. Arthritis Res Ther. 2019; 8;21(1):228. doi: 10.1186/s13075-019-1992-x.

Solans-Laqué R., Pérez-Bocanegra C., Salud-Salvia A., Fonollosa-Pla V., Rodrigo M.J., Armadans L. et al. **Clinical significance of an-tinuclear antibodies in malignant diseases: association with rheumatic and connective tissue paraneoplastic syndromes Lupus**. 2004; 13(3):159-164. doi: 10.1191/0961203304lu521oa,

Song L., Wang Y., Zhang J., Song N., Xu X., Lu Y. **The risks of cancer development in systemic lupus erythematosus (SLE) patients: a systematic review and meta-analysis**. Arthritis research & therapy. 2018; 1(20):270. doi:10.1186/s13075-018-1760-3

Szekanecz E., András C., Sándor Z., Antal-Szalmas P., Szanto J., Tamasi L. et al. **Malignancies and soluble tumor antigens in rheumatic diseases**. Autoimmun Rev. 2006; 6(1):42-47, doi: 10.1016/j.autrev.2006.03.007,

Świerkocka K., Łącki J.K. **Review paper Lymphoma in Sjögren's syndrome**. Reumatologia. 2008; 1(46):16-20.

Takakubo Y., Konttinen Y.T. **Immune-regulatory mechanisms in systemic autoimmune and rheumatic diseases**. Clin Dev Immunol. 2012; 2012:941346. doi: 10.1155/2012/941346.

Theander E., Henriksson G., Ljungberg O., Mandl T., Manthorpe R., Jacobsson L.T.H. **Lymphoma and other malignancies in primary Sjögren's syndrome: a cohort study on cancer incidence and lymphoma predictors**. Ann Rheum Dis. 2006; 65:796-803.

Tison A., Quéré G., Misery L., Funck-Brentano E., Danlos F.X., Routier E. **Safety and Efficacy of Immune Checkpoint Inhibitors in Patients with Cancer and Preexisting Autoimmune Disease: A Nationwide, Multicenter Cohort Study**. Arthritis Rheumatol. 2019; 71(12):2100-2111. doi: 10.1002/art.41068.

Vanni K.M.M., Berliner N., Paynter N.P., Glynn R.J., Mac Fadyen J., Colls J. et al. **Adverse Effects of Low-Dose Methotrexate in a Random-ized Double-Blind Placebo-Controlled Trial: Adjudicated Hematologic and Skin Can-cer Outcomes in the Cardiovascular Inflammation Reduction Trial**. ACR Open Rheumatol. 2020; 2(12):697-704. doi: 10.1002/acr2.11187.

Vaengebjerg S., Skov L., Egeberg A., Loft N.D. **Prevalence, Incidence, and Risk of Cancer in Patients with Psoriasis and Psoriatic Arthritis: A Systematic Review and Meta-analysis**. JAMA dermatology 2020; 156,4:421-429. doi:10.1001/jamadermatol.2020.0024

Vogelzang N.J., Bosl G.J., Johnson K., Kennedy B.J. **Raynaud's phenomenon: a common toxicity after combination chemotherapy for testicular cancer**. Ann Intern Med. 1981; 95(3):288-292. doi: 10.7326/0003-4819-95-3-288.

Weeding E., Casciola-Rosen L., Shah A.A. **Cancer and Scleroderma**. Rheumatic diseases clinics of North America. 2020; 46(3):551-564. doi: 10.1016/j.rdc.2020.03.002.

Wilton K.M., Matteson E.L. **Malignancy Incidence, Management, and Prevention in Pa-tients with Rheumatoid Arthritis**. Rheumatol Ther. 2017; 4(2):333-347. doi: 10.1007/s40744-017-0064-4.

Winthrop K.L., Cohen S.B. **Oral surveillance and JAK inhibitor safety: the theory of relativity**. Nat Rev Rheumatol 2022; 18:301-304. doi: 10.1038/s41584-022-00767-7.

Wolfe F., Michaud K. **Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients**. Arthritis Rheum. 2004; 50:1740-1751.

Wu C.Y., Chen D.Y., Shen J.L., Ho H.J., Chen C.C., Kuo K.N. et al. **The risk of cancer in patients with rheumatoid arthritis taking tumor necrosis factor antagonists: a nationwide cohort study**. Arthritis Res Ther. 2014; 30;16(5):449. doi: 10.1186/s13075-014-0449-5. Erratum in: Arthritis Res Ther. 2016; 18(1):110.

Yu T., Wu Y., Liu J., Zhuang Y., Jin X., Wang L. **The risk of malignancy in patients with IgG4-related disease: a systematic review and meta-analysis**. Arthritis Res Ther. 2022; 5;24(1):14. doi: 10.1186/s13075-021-02652-2.

Zucca E., Conconi A., Pedrinis E. **Non-gastric marginal zone B-cell lymphoma of ultrasonographic examinations of the parotid gland in the diagnosis and follow-up of primary Sjögren's syndrome**. Rheumatology. 2000; 39:97-104.