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Risk factors of neoplastic disease in patients with systemic rheumatic disorders

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Abstract

Systemic inflammatory rheumatic disorders are associated with an increased risk of malignancy. The mechanism linking malignancy and rheumatic diseases is complex and multidirectional, and is only partially understood. This review focused on the incidence of neoplastic diseases in patients with the most common systemic rheumatic disorders. Rheumatoid arthritis is associated with a risk of malignancy that is about 10% higher than in the general population, and this is more related to the disease itself than to medication. Systemic lupus erythematosus is associated with an increased risk of neoplasms, particularly haematological malignancies such as non-Hodgkin lymphoma. The risk increases with long-lasting active disease. Systemic sclerosis is associated with an increased risk of lung and liver cancer, as well as malignancies of the haematological system. Men and patients with RNA polymerase III antibodies are at a higher risk. Dermatomyositis and polymyositis are subgroups of idiopathic inflammatory myopathy associated with a high risk of malignancy. Male gender and old age are additional risk factors. Other rheumatic diseases are also thought to be associated with an increased risk of cancer. Currently, the data are insufficient for a clear distinction to be made between subgroups at risk. Most patients with systemic autoimmune disorders are at enhanced risk of malignancy to some degree. The management of these patients should include procedures for the early detection of age- and population-specific malignancies, as well as those which are more prevalent in the patient population suffering from the individual rheumatic disease. It is important to note that an atypical disease course or increased treatment resistance for a rheumatic disorder may indicate that the observed changes are an expression of a paraneoplastic syndrome or that a new neoplasm is modifying the clinical course of an already diagnosed rheumatic disease.

Keywords

Rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, idiopathic inflammatory myopathy, malignancy

Introduction

The relationship between systemic rheumatic diseases and malignancy is complex and has numerous aspects, both pathophysiological and clinical. This has resulted in the development of a new interdisciplinary field of medicine with clinical applications: oncorheumatology [1, 2]. Two main aspects of the mutual relationship of rheumatic musculoskeletal and neoplastic disorders are important. The first area of research focuses on the incidence, development, and course of malignancy in patients with systemic rheumatic disorders, including the role of anti-rheumatic management. The second research field comprises the development of rheumatic musculoskeletal diseases or syndromes akin to them in patients suffering from cancer, with or without concomitant oncological treatment.

The main problems comprise a few more specific questions, including the common etiopathogenetic factors of autoimmune rheumatic and neoplastic diseases, the role of pathological mechanisms, such as inflammation in the development of malignancy, and whether neoplastic phenomena can cause autoimmunity. Finally, the clinical aspects of oncorheumatology are important and lead to questions about factors or markers indicating predisposition in subgroups of rheumatic patients to develop malignancy, as well as differences in the clinical course of neoplastic diseases in patients with autoimmune rheumatic diseases. The main focus is on the early detection and management of such patients.

The aim of the study is to provide a narrative review of the various factors that predispose rheumatic patients to neoplastic diseases.

Incidence of malignancy in patients with rheumatic musculoskeletal diseases

Both groups of disorders—neoplastic and rheumatic—are relatively common. Thus, at first glance, the random coincidence of two independent diseases occurring in one patient cannot be ruled out. However, the human body is such a highly integrated system that there are several possible mechanisms facilitating the development of the disorders in question, and these are believed to be responsible for the altered incidence of neoplastic disorders in rheumatic patients.

The development of autoimmunity is significantly associated with genetic predisposition, but environmental factors also seem to play an essential role in the development of overt clinical autoimmunity [3]. These phenomena can be modified by various forms of rheumatic disease management, especially the administration of immunosuppressive, cytotoxic, and anti-inflammatory agents, as well as drugs that act specifically on various stages of immune reactivity or the inflammatory response.

For several decades, inflammation has been known to be associated with the development of cancer, particularly when it is chronic. The detailed mechanism of this relationship remains unclear. There are numerous interactions between inflammation and carcinogenesis [4]. Autoimmune disorders are associated with chronic inflammation caused by immune response dysregulation. Inflammation can cause genomic instability, proliferative abnormalities, disturbed differentiation, and reprogramming of the microenvironment. Loss of homeostatic regulation can result from disturbed signalling due to inflammation. A number of phenomena linking inflammation and carcinogenesis have been described, but many of them remain unclear [4]. Such phenomena include oxidative or nitrosative stress resulting in an inflammatory response and DNA damage, the secretion of pro-inflammatory cytokines and growth factors, impaired DNA repair pathways, inflammation-induced chromosomal instability, and the secretion of angiogenic factors by inflammatory cells. These mechanisms are linked to inflammation and act as preceding events of carcinogenesis [5–8].

Rheumatoid arthritis

Rheumatoid arthritis is a chronic, immune-mediated, systemic disease characterised by progressive inflammation of multiple joints, associated with extra-articular manifestations, resulting in a shortened lifespan and severe disability due to progressive joint destruction. The course of rheumatoid arthritis is

usually progressive, although significant differences exist between patients, and the disease is considered heterogeneous. It is suggested that the disease results from the development of autoimmunity due to the coexistence of genetic and environmental factors. Overt rheumatoid arthritis is preceded by a preclinical phase and a period of nonspecific symptoms and signs referred to as very early rheumatoid arthritis [9].

The heterogeneity of rheumatoid arthritis is associated with the detection of certain autoantibodies in the patients' serum. The most common biomarkers are rheumatoid factor and autoantibodies against post-translationally modified proteins or peptides, such as those modified by citrullination. Other autoantibodies (e.g., those against proteins modified by carbamylation) have received less attention and are therefore considered less important. Autoantibodies can be detected years before the onset of the clinically overt disease. The pathophysiological role of autoantibodies remains only partially elucidated, and the mechanism causing their production remains unknown. Autoantibodies can affect the immune response in various ways, such as forming immune complexes that are deposited in the joints, subsequently attracting immune-competent cells and leading to the secretion of proinflammatory cytokines [10, 11]. Interestingly, the best-performing single anticitrullinated peptide autoantibody substrate is derived from the Epstein-Barr virus (EBV) nuclear antigen 2. This finding suggests a potential relationship between this oncogenic virus and rheumatoid arthritis [12].

Based on the presence of autoantibodies, the disease is categorised as seropositive or seronegative rheumatoid arthritis. It is suggested that both forms represent different nosological entities and are probably associated with different aetiologies, clinical presentations, and responses to medication. Currently, there is no different therapeutic strategy for patients with seropositive and seronegative rheumatoid arthritis, and no data indicate a different incidence of malignancy in patients in either group.

The risk of malignancy among patients with rheumatoid arthritis has been investigated over the last few decades. Since the first observations were made, it has been known that patients with rheumatoid arthritis suffer from cancer more frequently than the general population. A frequently asked question concerns the role of various forms of immunosuppressive therapy in the potential risk of malignancy. This issue has been raised in particular in investigations of the newly introduced, highly effective biological and targeted synthetic disease-modifying antirheumatic drugs. For obvious reasons, it is difficult to investigate the role of the disease as a risk factor for malignancy because there are no groups of patients with rheumatoid arthritis who are not receiving treatment and are thus free of the influence of medication. The isolated effect of various drugs used to manage rheumatoid arthritis was investigated in long-term studies, mostly based on national registries.

In 2015, Simon et al. [13] published a meta-analysis on the incidence of malignancy in adult patients with rheumatoid arthritis. The total number of patients included was high (more than 100,000), and the follow-up period ranged from 4 to 25 years. The pooled standardised incidence risk (SIR) for overall malignancy was 1.09 [95% confidence interval (CI): 1.06–1.13]. Similar results have been reported in almost all papers focusing on this subject, including both recent and older publications. Overall, rheumatoid arthritis patients have a 10% increased risk of malignancy compared to the general population.

Particular attention is paid to lymphoma and lung cancer. Lymphoma is a form of malignancy which, in almost all studies on rheumatoid arthritis, is reported to be at a higher risk than in the general population. The risk ranges from 1.75 to 12.85, with a pooled risk of 2.46 (95% CI: 2.05–2.96) being reported [8]. Attempts to explain the enhanced risk suggest a role for increased immune system activity and a higher probability of malignant transformation of immune-competent cells. Long-lasting immune stimulation and a decrease in the number of T-suppressor lymphocytes are suggested to contribute to an increase in lymphomas [14].

Lung cancer is also relatively common among patients with rheumatoid arthritis [15]. Interestingly, smoking (both current and past) is associated with an increased incidence of rheumatoid arthritis. The mechanism of this relationship remains unclear. Chronic periodontitis enhances the risk of developing rheumatoid arthritis [16]. Chronic periodontitis lasting at least two years may independently elevate the risk of rheumatoid arthritis, but the role of the microbiota associated with chronic periodontitis and

smoking is currently a subject of controversy [17]. Other mechanisms by which nicotine influences the development of rheumatoid arthritis have also been suggested, including disruption to cellular regulatory activity and inflammatory, morphological, physiological, biochemical, and enzymatic responses [18]. It is well known that smoking is a risk factor for lung cancer [19]. Unfortunately, most studies on lung cancer risk in patients with rheumatoid arthritis did not separate smokers and non-smokers, making it impossible to rule out an indirect association. The open question is the pathophysiological relationship between the pro-oncogenic action of smoking and the risk of rheumatoid arthritis. The prognosis for lung cancer in patients with rheumatoid arthritis is associated with disease activity, seropositive arthritis, corticosteroid administration, and interstitial lung disease [15].

The risk of melanoma in patients with rheumatoid arthritis has only been evaluated in a few studies. It was found that the risk is increased, with a pooled SIR of 1.23 (95% CI: 1.01–1.49). There is also controversy about the role of medication in increasing the risk of melanoma. A low dose of methotrexate administered to patients with rheumatoid arthritis and other inflammatory rheumatic diseases was found to be associated with a slight but significant increase in the risk of melanoma [20].

The introduction of biologic disease-modifying antirheumatic drugs for the management of patients with rheumatoid arthritis, despite their effectiveness in decreasing disease activity, has been controversial. Immune incompetence can result in reduced control of neoplastic transformation, but immunosuppressive agents are also used to treat some malignancies. Furthermore, the term “anti-tumour necrosis factor alpha (anti-TNF-alpha)” can incorrectly suggest that the medication “decreases anti-tumour activity”. Several studies based on long-term observations of a large population of rheumatoid arthritis patients receiving therapy consisting of TNF-alpha inhibitors have clearly revealed that these biologic drugs do not increase the risk of cancer. These findings were confirmed in recent observations [21]. Additionally, biologic medications that are less well-investigated and which are used to treat rheumatoid arthritis (tocilizumab, abatacept, and rituximab) have also been reported to have no effect on the overall risk of cancer. The only exception is an increased risk of squamous skin cancer in patients receiving abatacept [9]. Similar findings suggesting an enhanced risk of non-melanoma skin cancer were reported in studies on other biologic drugs used to manage rheumatoid arthritis [22, 23]. There was no difference in the risk of malignancy for patients with rheumatoid arthritis who initiated TNF-alpha inhibitors as their first or second biologic therapy, compared to those who received other biologic agents or conventional synthetic disease-modifying antirheumatic drugs [9]. Additionally, there was no change in cancer risk for patients treated short-term with targeted synthetic disease-modifying antirheumatic drugs, except for non-melanoma skin cancer [24, 25].

Only a few studies have addressed the issue of cancer risk in patients with rheumatoid arthritis who have had a previous malignancy. It has been suggested that the administration of TNF-alpha inhibitors is not associated with recurrence [26]. Similar findings were reported in a large-scale study by Molina-Collada et al. [27], published in 2024.

Several studies have shown that patients with rheumatoid arthritis have a decreased risk of breast cancer. The incidence of breast cancer diminishes even before the diagnosis of rheumatoid arthritis, and the mechanism by which this occurs remains unclear. However, the reduced risk cannot be readily explained by hormonal risk factors. Studies by Wadström et al. [28] showed that adjuvant antihormonal therapy administered for breast cancer does not seem to increase the risk of rheumatoid arthritis.

Most studies indicate that patients with rheumatoid arthritis have a lower risk of developing colorectal cancer. The pooled SIR is 0.78 (95% CI: 0.71–0.86). However, some increase in risk was reported in a few older studies only [13]. It has been suggested that the decreased risk of colorectal cancer is related to the use of non-steroidal anti-inflammatory drugs. These drugs can reduce the development of inflammatory polyps in the colon. These polyps are considered a precancerous state.

A decrease in the risk of cervical cancer in patients with rheumatoid arthritis has also been reported. This cancer is attributed to a viral infection. One hypothetical explanation for this phenomenon may be the role of vaccination in patients.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune inflammatory disease accompanied by immune phenomena such as autoantibodies, immune complex deposition, complement activation, and disturbed interferon activity. It can affect almost all organs and systems in the body, and is usually severe and progressive [29].

SLE is associated with various forms of neoplastic disease, including haematological malignancies and solid cancers of various organs. The lungs, liver, urinary bladder, and prostate are common locations for cancer in SLE patients. Conversely, a decrease in certain cancers in SLE patients has been reported (e.g., breast and ovarian cancer). A meta-analysis published by Apor et al. [30] revealed that SLE is associated with an increased risk of all haematological malignancies. The pooled SIR was 2.9 (95% CI: 2.0–4.4); however, data from various studies have shown significant heterogeneity in the results obtained. An increased risk of non-Hodgkin lymphoma was found, with a relatively high pooled SIR of 5.7 (95% CI: 3.6–9.1). The risk of Hodgkin lymphoma appears to be lower. Its SIR was reported to be 3.1 (95% CI: 2.1–4.4). A lower risk of leukaemia and myeloma was described compared to lymphoma. The SIR for leukaemia was calculated as 2.3 (95% CI: 1.9–2.7) and for myeloma as 1.5 (95% CI: 1.0–2.0) [30].

There are geographical differences in the risk of haematological malignancies in SLE. Asian studies reported the highest risk of non-Hodgkin lymphoma, while the risk was almost twice as low in European studies as compared to those from Asia. A higher risk was also shown in patients younger than 40 years, and one study indicated a risk more than twice as high in male patients. The most common forms of non-Hodgkin lymphoma diagnosed in SLE patients were diffuse large B-cell lymphoma and follicular lymphoma [30].

A higher risk of Hodgkin lymphoma was suggested in European patients compared to those in the US/Canada. Long-lasting SLE was found to be associated with a higher incidence of Hodgkin lymphoma, but not of leukaemia. Leukaemia incidence was shown to be highest in SLE patients 1–5 years after SLE diagnosis. Incidence of myeloma in SLE patients was reported to be higher in US/Canadian studies than in European studies [30].

A long-term follow-up study of potentially virus-induced malignancies in SLE patients was published in Denmark. The study included 576 SLE patients, with a median follow-up duration of 13.2 years [31]. Overall, the risk of malignant neoplastic disease increased (SIR 1.6, 95% CI: 1.2–2.0), as did the risk of malignant and premalignant conditions associated with papillomavirus. A high risk was found for anal cancer (SIR 26.9, 95% CI: 8.7–83.4) and vaginal/vulvar cancer (SIR 9.1, 95% CI: 2.3–36.6). An increased risk was also reported for epithelial dysplasia/carcinoma in situ of the uterine cervix and non-melanoma skin cancer. Other potentially virus-induced cancers with an increased risk in SLE patients were liver cancer (SIR 9.9, 95% CI: 2.5–39.8) and bladder cancer [32]. These observations were published before the widespread introduction of HPV vaccination.

Systemic sclerosis

Systemic sclerosis is a connective tissue disease characterised by excessive fibrosis of the skin and internal organs, preceded by autoimmune phenomena, vasculopathy, and inflammation. The disease becomes clinically apparent in a relatively late phase and affects almost all organs and systems in the body [33]. It is classified into subgroups, including diffuse and limited systemic sclerosis, as well as systemic sclerosis sine scleroderma and overlapping syndromes, which are characterised by symptoms and signs of two or more systemic connective tissue disorders. The most common of these are systemic sclerosis and polymyositis (scleromyositis) [34, 35]. The heterogeneity of the disease remains unclear.

Systemic sclerosis is known to be associated with an increased incidence of cancer, but the available data are inconsistent. In 2013, Onishi et al. [36] published a meta-analysis of population-based cohort studies. They found SIR for overall cancer incidence of 1.41 (95% CI: 1.18–1.68). Systemic sclerosis is diagnosed about seven times more commonly in females than in males, but the SIR for overall cancer risk was higher in men than in women (1.85 versus 1.33). There was no difference in cancer risk between the

limited and diffuse forms of the disease. The most common malignancies in systemic sclerosis were lung cancer, liver cancer, and cancers of the haematological system (non-Hodgkin lymphoma and leukaemia), as well as urinary bladder cancer [37]. It is possible that cyclophosphamide, a medication widely used in systemic sclerosis treatment, can be associated with some forms of malignancy (bladder cancer). Similar findings were observed by Szekanecz et al. [38]. They reported the highest incidence of lung cancer and suggested that organs affected by fibrosis are at risk of developing cancer. Studies based on the Spanish Scleroderma Registry revealed a similar tendency in the risk of cancer, but showed that cancer in systemic sclerosis patients was associated with an older age at disease onset [39].

In recent years, significant progress has been made in understanding specific autoantibodies and distinguishing subgroups of patients with systemic sclerosis who are at a higher risk of malignancy. The ACR/EULAR classification criteria for systemic sclerosis include the following specific autoantibodies: antibodies against topoisomerase I (Scl-70), centromere (ACA), and RNA polymerase III (RNA P3). The latter is associated with an increased risk of cancer in the early years of overt systemic sclerosis [40]. Conversely, the presence of ACA or anti-Th/To antibodies suggests a decreased risk of malignancy. Th/To autoantibodies react with ribonuclease P protein subunits p25 and p38 [41]. Antibodies against the Sjögren/scleroderma autoantigen 1 (anti-SSSCA1) have been identified as a potential serum marker for cancer risk, but this finding requires further evaluation in a larger population [42].

In recent years, significant progress has been made in understanding specific autoantibodies and distinguishing subgroups of patients with systemic sclerosis who are at a higher risk of malignancy [41, 43].

Idiopathic inflammatory myopathies

Idiopathic inflammatory myopathies (IIMs) are a group of chronic systemic autoimmune disorders primarily involving the muscles and associated with various extramuscular manifestations, particularly cutaneous, cardiac, and pulmonary. The two main subgroups of IIM are dermatomyositis and polymyositis. These conditions have been recognised for a long time, and in recent decades, additional subgroups such as juvenile myositis, inclusion body myositis, immune-mediated necrotising myopathy, amyopathic dermatomyositis, and anti-synthetase syndrome have been classified as IIMs [44, 45]. The high incidence of malignancy in patients with dermatomyositis or polymyositis has been recognised since the early years of the 20th century. The reported SIR varies from 2 to 7 for dermatomyositis and from 1.3 to 2.1 for polymyositis. Although there are geographical variations in risk, all analyses clearly indicate a very high risk of cancer development in patients with dermatomyositis. Most cancers are detected within one year before or after the IIM diagnosis. Other IIM subgroups are characterised by a different malignancy risk. No altered risk of cancer was found in patients with juvenile myositis, inclusion body myositis, or overlap syndrome. A high risk of malignancy was reported in patients with amyopathic dermatomyositis (only slightly lower than in patients with dermatomyositis). In patients with immune-mediated necrotising myositis, the risk of cancer is associated with the type of autoantibody present. Antisynthetase syndrome is characterised by a lower risk of malignancy [45].

A higher risk of cancer is associated with male gender, an older age at onset of IIM, and a severe disease course, as indicated by cutaneous necrosis and/or concomitant vasculitis. Interestingly, pulmonary involvement in the form of interstitial lung disease, Raynaud's phenomenon, and joint manifestations are considered clinical factors associated with a lower risk of cancer, and are referred to as 'protective factors' [46].

The detection of certain autoantibodies is associated with an increased risk of cancer. These include the anti-transcriptional intermediary factor-1-gamma antibody, also known as the anti-p155/140 antibody, which is associated with a significant cancer risk (SIR 4.68, 95% CI: 3.37–6.48) [46]. The most common cancers are breast cancer, ovarian cancer, and lymphoma. Kilinc and Ugurlu [47] found that 42.6% of dermatomyositis patients with anti-TIP1γ had malignancy.

The anti-nuclear matrix protein 2 autoantibody (anti-NXP2) has been suggested to be associated with an increased risk of malignancy, but this has not been confirmed by all studies [47]. Contradictory results have been published regarding the estimation of cancer risk for the following autoantibodies: anti-3-hydroxy-3-methylglutaryl-CoA reductase, anti-Mi-2, and anti-small ubiquitin-like modifier 1. A lower risk of malignancy was found in patients with lung involvement and associated autoantibodies (anti-synthetase and anti-melanoma differentiation-associated gene 5, or anti-MDA5) [47, 48].

The most common malignancies associated with IIM are lung, ovarian, colorectal, breast, and nasopharyngeal cancers, as well as lymphoma. Melanoma is also a common malignancy in IIM patients [47]. A meta-analysis by Luo et al. [49] revealed that the SIR for melanoma is 6.30 (95% CI: 1.59–11.02).

In 2023, international guidelines for IIM-associated cancer screening were published [50]. The list of 18 recommendations indicates how to stratify individual patients into risk groups according to IIM subtype. The lowest risk is for juvenile-onset IIM and inclusion body myositis. High-risk factors include clinical factors and autoantibody status. Patients with dermatomyositis are generally classified as high risk, while those with clinically amyopathic dermatomyositis, polymyositis, and immune-necrotising myopathy are classified as intermediate risk. Patients with antisynthetase syndrome, inclusion body myositis, and juvenile-onset IIM are classified as low risk. There is also a list of recommended screening procedures for patients [50].

Sjögren's syndrome

Sjögren's syndrome is a chronic, heterogeneous autoimmune systemic connective tissue disease involving the exocrine glands, among other symptoms and signs. Symptoms include dry eyes and mouth, as well as systemic manifestations such as musculoskeletal pain and fatigue. The exocrine glands are affected, and lymphocyte infiltrations can be found. Primary Sjögren's syndrome is associated with a significant risk of lymphoma. A meta-analysis revealed a substantial link between the syndrome and the risk of non-Hodgkin lymphoma: the SIR was 8.78 (95% CI: 5.51–13.99) [51]. A similar trend was found in both sexes and different age groups. An earlier study by Zhong et al. [52] revealed slightly higher. They found that the SIR for overall malignancy in patients with primary Sjögren's syndrome was 2.17 (95% CI: 1.57–3.00) and the SIR for pooled haematological malignancy was 11.55 (95% CI: 4.32–30.90). In addition to non-Hodgkin lymphoma, the haematological malignancies included Hodgkin lymphoma, multiple myeloma, and leukaemia. Common cancers in patients with Sjögren's syndrome include thyroid, kidney, and urinary tract cancers, as well as non-melanoma skin cancer [53]. A number of factors were associated with an increased risk of malignancy. These included salivary gland enlargement, vasculitis or purpura, peripheral neuropathy, glomerulonephritis, splenomegaly, cytopenias, hypocomplementemia, cryoglobulinemia, and a high biopsy focus score [54, 55]. Nocturne et al. [56] suggested that high rheumatoid factor levels and high disease activity are simple yet important predictors of lymphoma in primary Sjögren's syndrome. A novel marker, the microRNA miR200b-5p, was described. A low level of this biomarker is suggested to be a sensitive indicator for distinguishing between patients with and without non-Hodgkin lymphoma [57].

Vasculitides

Vasculitides are a very heterogeneous group of disorders, the only main pathological feature of which is inflammatory cell infiltration of the vessel walls. Vasculitides are classified as either having a known cause (e.g., infectious or drug-induced) or as systemic vasculitis. In the most recent classification, from 2012, a subgroup of vasculitides associated with the presence of autoantibodies against cytoplasmic neutrophil components is categorised as the first group of systemic vasculitis with a suggested aetiology [56].

There are only a few studies indicating the relationship between some forms of systemic vasculitis and malignancy. Giant cell arthritis can be accompanied by polymyalgia rheumatica. The last disease is believed to be associated with a risk of cancer [57]. Meta-analysis showed a pooled risk ratio SIR 1.14 (95% CI: 1.05–1.22). The higher risk was in the first 6–12 months after diagnosis, although a number of factors can affect the results of the study. It is also interesting that patients with positive temporal artery biopsy were

found to have a higher risk of malignancy. The cause of such findings remains unclear. Some relationship between IgA vasculitis and cancer was also suggested [58].

From a practical point of view, it should be remembered that vasculitis secondary to malignancy in various locations is common. In some cases, vasculitis may be the only symptom of cancer, with the neoplastic disease being diagnosed at a later stage. In such cases, cancer can be considered a new disease that is both complicated by and predisposed to vasculitis.

Other systemic musculoskeletal rheumatic disorders

There are very few studies on the occurrence of malignancy in patients with these diseases. A meta-analysis of cancer in patients with ankylosing spondylitis, which included a large cohort (> 330,000 patients), revealed a higher cancer risk in Asia. However, this association was not significant in Europe [59]. Ankylosing spondylitis has been found to be associated with an increased risk of bone cancer, thyroid cancer, multiple myeloma, leukaemia, kidney cancer, prostate cancer, and non-Hodgkin lymphoma. Previous studies have shown that patients with ankylosing spondylitis are at an increased risk of developing malignancies of the digestive system, multiple myeloma, and lymphoma. Subgroup analysis of high-quality cohort studies indicated that patients with ankylosing spondylitis from Asia are at the highest overall risk of malignancy [60]. Ankylosing spondylitis was not associated with an increased risk of lung cancer in either European or non-European patients [61]. There is some suggestion that psoriasis and psoriatic arthritis are associated with an increased risk of breast cancer [62].

The association between gout and malignancy remains unclear. While some observations have suggested a link between advanced gout and a higher incidence of cancer, there is currently no data based on large-scale studies to support this. Chronic, persistent inflammation may facilitate the development of neoplasia. It is possible that advanced gout is commonly found in patients exposed to other factors that affect the rate of malignancy, such as diet, smoking, and alcohol consumption. No correlation was found between serum uric acid and colorectal cancer in the European population [63]. Further studies are needed in this field.

Conclusions

It is difficult to draw conclusions from various studies on the risk of malignancy in patients with systemic rheumatic diseases. Almost all studies have shown a relationship between the development of an autoimmune disorder and the risk of malignancy. The biggest problem in interpreting the results is the heterogeneity of the analysed populations and the number of factors that can affect both autoimmunity and malignancy. Many aspects of the aetiopathogenesis and pathophysiology of the observed clinical outcomes remain unknown.

The key finding of the reviewed studies is that most patients with systemic autoimmune disorders are at an enhanced risk of malignancy. When treating these patients, it is essential not only to carry out age- and population-specific cancer screening, but also to pay attention to procedures for the early detection of malignancies that are more prevalent in specific patient populations. This is more clearly defined in some diseases (systemic sclerosis and inflammatory myopathy), but in others, the available data do not allow for the simple separation of subgroups at increased risk of developing cancer. An individualised approach to each patient is essential.

It is important to note that an atypical course of disease or increased resistance to treatment for a rheumatic disorder may indicate that the observed changes are an expression of a paraneoplastic syndrome, or that a new neoplasm is modifying the clinical course of an already-diagnosed rheumatic disease.

The clinical problems described are the subject of further research, and it is hoped that in the coming years, a better understanding will emerge of the mechanisms involved in autoimmunity and cancer development, as well as new cancer risk biomarkers and more detailed clinical management recommendations.

Abbreviations

anti-TNF-alpha: anti-tumour necrosis factor alpha

CI: confidence interval

IIMs: idiopathic inflammatory myopathies

SIR: standardised incidence risk

SLE: systemic lupus erythematosus

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The author declares that he has no conflicts of interest.

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