

Rheumatic Diseases and Malignancies

Violeta BOJINCA; Iustina JANTA

Department of Internal Medicine and Rheumatology, "Sfanta Maria" Hospital, Bucharest, Romania

ABSTRACT

There are many studies which demonstrate a higher risk for malignancy in patients with rheumatic diseases. There have been a number of possible explanations for the differences in the risk of certain malignancies in patients with rheumatic disease, compared with general population, but a clear mechanism is difficult to identify.

Rheumatoid syndromes may be associated with malignancy as paraneoplastic conditions, which can antedate the neoplasm diagnosis.

On the other hand, autoimmune rheumatic diseases have a higher risk of malignancy by themselves or because of the immunosuppressant treatments.

Keywords: rheumatic disease, malignancy, paraneoplastic syndromes

BACKGROUND

Rheumatic diseases can be associated with malignancy in a variety of ways. Causes are difficult to define clearly in many situations. The musculoskeletal system may be either directly or indirectly associated with cancer. Rheumatic syndromes have been associated with various malignancies – paraneoplastic syndromes, patients with preexisting connective tissue disease have developed malignancies (ex. the development of lymphoma in patients with Sjögren's syndrome) and treatment for rheumatic disease – immunosuppressants agents – can cause malignancy. Until now little is understood regarding the pathogenesis of connective tissue diseases in association with neoplastic disease. □

PARANEOPLASTIC SYNDROMES

Paraneoplastic syndromes are caused by malignancy but not directly related to invasion by the tumor or its metastases. Occasionally they can be the first manifestation of an underlying malignancy. Approximately 15% of patients with cancer develop paraneoplastic syndromes as a result of tumor-derived biologic mediators like hormones, peptides, antibodies, cytotoxic lymphocytes, autocrine and paracrine mediators. (1)

Hypertrophic osteoarthropathy (HOA)

HOA is a syndrome characterized by abnormal proliferation of the skin and osseous tissue at the distal parts of extremities and includes

Address for correspondence:

Violeta Bojinca, Department of Internal Medicine and Rheumatology, "Sf. Maria" Hospital, 37, Ion Mihalache Blv., Bucharest, Phone number: +40723 924 823.

E-mail: vmbojinca@yahoo.com

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clubbing of fingers and toes, periostitis of the long bones, arthritis (mostly in large joints). There is a primary form – hereditary – and secondary. The secondary form can be localized or generalized – usually associated with lung cancer, pulmonary infections, cystic fibrosis, right-to-left cardiac shunts and other less often disorders.

Pathogenesis is still unclear, but appears that platelet-endothelial activation, high release of von Willebrand factor plays a role. A valid theory proposes that a fibroblast growth factor could be at the base of syndrome. Megakaryocytes emerge from the bone marrow and are fragmented in the lung microvasculature. In cyanotic heart diseases this fragments enter directly in the systemic circulation activating endothelial cells, releasing growth factors for fibroblasts and thus inducing finger clubbing. In cases with diffuse pulmonary fibrosis or lung cancer, a growth factor derived from abnormal tissue enters systemic circulation and induces clubbing. (2,3)

The diagnosis is based on physical findings and radiographs that demonstrate periostitis of the long bones, osteophytosis in the hands and rarely acroosteolysis.

Removal of lung cancer or treatment of the other causes of HOA results in regression in the clinical manifestation.

Carcinomatous polyarthritis

Describe the development of arthritis in association with malignancy, but it is distinct from direct tumor invasion.

Carcinomatous polyarthritis can occur in association with breast, colon, lung and ovarian cancer as well as with lymphoproliferative disorders. The pathogenesis is unclear.

It generally develop in older patients, has an explosive onset and it is mostly a seronegative (absence of rheumatoid factor) asymmetric polyarthritis predominant in lower extremities. The symptoms may improve with successful treatment of the malignancy. (2)

Vasculitis

Vasculitis is rarely associated with malignancy having a reported prevalence of only 8% of patients with cancer. The association is higher with lymphoproliferative and myeloproliferative disorders and commonly predates the identification of malignancy. (2)

Some proposed mechanism for vasculitis as a paraneoplastic syndrome include immune complex formation (the persistent antigen stimulation from the tumor stimulates T cell activation), direct vascular injury by antibodies to endothelial cells and a direct effect of leukemic cells on the endothelium. (2,4)

Case reports have found both antineutrophil cytoplasmic antibody (ANCA) negative and ANCA positive. Histopathologic exam reveals in most cases leukocytoclastic vasculitis. (5)

Vasculitis associated with underlying malignancy is often poorly responsive to conventional therapy directed against the vasculitis or the malignancy.

Palmar fasciitis

Palmar fasciitis (palmar fibromatosis) is characterized by progressive bilateral contractures of the digits, fibrosis of palmar fascia. Sometimes may be associated with polyarthritis. Biopsy of the palmar fascia reveals nodules or whorls of fibroblasts surrounded by dense connective tissue with fibrous septa. Some have suggested an autoimmune etiology, based on the presence of immunoglobulin deposits in biopsy specimen. (5)

The most frequently reported tumor is ovarian cancer, but other primary sites including the stomach, pancreas, lung and colon have been described. The presence of palmar fasciitis and arthritis portends a poor prognosis because it typically manifests after tumor metastasis. Successful removal of the underlying tumor may result in clinical improvement of the affected extremities. (4)

Reflex-sympathetic dystrophy syndrome (chronic regional pain syndrome II)

Is characterized by regional pain, swelling, vasomotor instability, focal osteoporosis in a limb. The development of reflex-sympathetic dystrophy syndrome has been associated with Pancoast tumor of the lung, other malignancies that infiltrates the stellate ganglion or brachial plexus. The absence of associated antecedents – like stroke, myocardial infarction, and trauma – as well as failure to response to conventional therapy warrants a search for an underlying malignancy.

Erythromelalgia

Erythromelalgia manifests by attacks of severe burning, erythema and warmth of the ex-

tremities, predominantly in the feet, often exacerbated when are placed in a dependent position. Can occur idiopathic (60%) or secondary to myeloproliferative disorders, especially polycythemia vera and essential thrombocytosis. Symptoms of erythromelalgia can precede the onset of a myeloproliferative disease by a median of 2.5 years. Therefore, all patients with erythromelalgia should be monitored with periodic blood cell counts. (6)

The exact cause is unknown but microvascular arteriovenous shunting has been hypothesized. (7)

The most effective therapy seems to be aspirin daily, leading to significant relief of symptoms, so it is believed that cyclooxygenase-1 may play a role in pathogenesis.

Polymyalgia rheumatica (PMR)

PMR is a disorder affecting older adults that manifests with discomfort and stiffness in the shoulder and hip girdle, fatigue, anemia of chronic disease and elevated ESR. This condition responds promptly to moderate doses of prednisone.

The relationship to various malignancies is questionable, as both share similar clinical and biological features. However, atypical manifestations of PMR – like age less than 50 years, asymmetric involvement, ESR less than 40mm/h or greater than 100 mm/h, severe anemia, proteinuria, poor or delayed response to prednisone – suggest the presence of malignancy. Kidney, lung, colon cancer and multiple myeloma are most often found in these patients. (2,4)

Amyloidosis

Amyloidosis is a disease characterized by the deposition of an insoluble proteinaceous material in the extracellular matrix of various organs. 15% of amyloidosis cases occur with malignant diseases, most frequent multiple myeloma, lymphomas and carcinomas. (8)

The clinical spectrum of amyloidosis of malignancy includes peripheral and autonomic neuropathy, weight loss, restrictive cardiomyopathy, carpal tunnel syndrome and arthropathy and cutaneous manifestations like purpura, subcutaneous nodules and “scleroderma-like” skin infiltration.

Digital necrosis – Raynaud’s syndrome

Profound Raynaud’s syndrome and digital necrosis may appear in some infections, in-

flammatory diseases or malignancy. In patients over 50 years, asymmetric Raynaud’s phenomenon or digital necrosis should raise the possibility of paraneoplastic syndrome. These situations are associated with solid tumors (most frequent stomach, lung, ovarian) and lymphoproliferative disorders. The Raynaud’s syndrome may antedate the diagnosis of neoplasm by an average of 7-9 months. (9)

The mechanisms proposed are cryoglobulinemia, immune complex-induced vasospasm, hypercoagulability, emboli and necrotizing vasculitis.

Remitting seronegative symmetric synovitis with pitting edema (RS3PE)

RS3PE is a rare disorder affecting the metacarpophalangeal joints and the wrists with unclear pathogenesis. Has been reported in association with lymphoma, myelodysplastic syndrome, adenocarcinoma. Characteristics suggestive of possible underlying malignancy include the presence of systemic features (fever, weight loss) and a poor response to glucocorticoids. (2)

Multicentric reticulohistiocytosis

Multicentric reticulohistiocytosis is a rare disorder characterized by the insidious onset of polyarthritis, which often evolves into a severe erosive deforming arthritis (50% of cases), firm cutaneous papules and nodules on the skin, often around the hand’s joints and the periungual regions.

Multicentric reticulohistiocytosis has been reported in association with hyperlipidemia, autoimmune disease and malignancies – carcinoma of the lung, stomach, breast, cervix, colon and ovary. Malignancies have been associated in 25-31% of cases. (10)

Panniculitis

Panniculitis can mimic RA, juvenile RA or erythema nodosum. This can be idiopathic and have a benign course or it can be secondary to infections, vascular or traumatic etiologies. In a small number of cases it is associated with hematologic malignancies or pancreatic cancer. Is more frequent in females and is refractory to prednisone. Occasionally it will regress with treatment of the underlying malignancy. (2)

Lupus-like syndromes

Lupus-like syndrome is rarely associated with cancers. Case reports have been described

association with ovarian carcinoma, hairy-cell leukemia and breast carcinoma. (2) Clinical features include pleural effusions, pneumonitis, pericarditis, no deforming polyarthritis with or without positive antinuclear antibodies. (11)

Scleroderma-like syndrome

Is associated with adenocarcinoma and carcinoid tumor and is more frequent in woman. Skin changes resembling scleroderma may also occur in patients with osteosclerotic myeloma (POEMS syndrome) as the early manifestation of cancer. Although all patients have cutaneous manifestations of scleroderma, fewer than half have proven systemic sclerosis. □

INFLAMMATORY MYOPATHIES

The relationship between myositis and malignancy is unclear and reports in the literature are conflicting. Dermatomyositis (DM) has classically been associated with occult malignancies, whereas the association between polymyositis (PM) and inclusion body myositis are less clear.

It is debatable as well is whether the inflammatory myopathy predates the malignancy and can be considered a primary rheumatic disease with known risks of developing malignancy or whether it simply represents a manifestation of a paraneoplastic process.

DM has been associated with breast, ovarian, lung and gastric tumors in European population and nasopharyngeal malignancies in Asian population. In PM the relative risk for development internal malignancies appears to be lower than for DM. The pathogenesis is unknown.

Malignancies associated with inflammatory myopathies have been known to develop many years after diagnosis of muscle disease, so continued vigilance and repeated screening for malignancy is warranted. Nevertheless, most cases of DM and malignancy seem to occur within a year of each other. (12)

The risk of malignancy may be higher in patients with clinical active DM but normal creatine kinase level and the prognosis is poorer in these cases. (13,14) Patients with myositis-associated autoantibody may be at less risk for the development of malignancy. (14)

The patients with paraneoplastic DM may have more severe muscular symptoms, with diaphragmatic involvement and with poorer res-

ponse to glucocorticoids. Removal of the malignancy may result in improvement if the myopathic process (15). □

RISKS OF DEVELOPING MALIGNANCIES IN RHEUMATIC DISEASES

During the past 30 years there have been many attempts to determine more precisely the link between cancer and rheumatic disease (RD).

The explanation of this association remains unclear. The association may be due to chance alone. However, the development of RD shortly after a diagnosis of cancer is in fact a paraneoplastic syndrome. Alternatively, the malignancy might be a consequence of immunosuppressive therapy used in the treatment of patients with RD.

Several factors, including autoimmune disease itself, common etiology between the RD and malignancy, including genetics factors, viruses (EBV) and smoking have been implicated in the pathogenesis of tumor development (16). However, it is difficult to separate disease-related mechanism from the potential oncogenic properties of immunosuppressive drugs used in RD.

Sjögren's syndrome

Sjögren's syndrome is characterized by a benign lymphocytic infiltrate of salivary and lacrimal glands. The development of lymphoproliferative disorders in the setting of Sjögren's syndrome is perhaps the prototypic example of chronic autoimmune disease and an increased risk of malignancy.

The majority of lymphoproliferative disorders are non-Hodgkin's lymphoma and lymphoma of mucosal-associated lymphoid tissue (MALT); Waldenström's macroglobulinemia, chronic lymphocytic leukemia and multiple myeloma are more rarely reported. (2,16) The incidence of other malignancies is not increased in patients with Sjögren's syndrome. (17)

It is believed that chronic B cell stimulation may lead to the malignant transformation of clonal lines characteristic of Sjögren's syndrome. The presence of a viral trigger, like EBV, accounting for malignant transformation is one possible theory. There also have been reports of chromosomal translocation (proto-oncogene bcl-2) being present in patients with Sjögren's syndrome who developed lymphoma. (2)

The development of lymphoma seems to be a late manifestation of Sjögren's syndrome, often after 6.5 years. Features associated with development of lymphoma include palpable purpura, cutaneous ulcerations, cryoglobulinemia, low C4, monoclonal gammopathies, cytopenias, splenomegaly and adenopathies. (2)

Rheumatoid arthritis (RA)

The data from several studies are consistent that in patients with RA the risk for lymphoproliferative disorders is about two or three-fold increased compared to the general population. The determinants of this association are unknown, but the mechanism proposed include persistent immunologic stimulation, which may lead to clonal selection and malignant transformation of CD5+ B cells; proliferation of latent infection with EBV; direct oncogenic action; decreased apoptosis of infected B cells; decreased natural killer (NK) cell activity. All of these may be potentiated by the use of immunomodulating therapies. (2) The association has been highlighted with widespread use of tumor necrosis factor (TNF- α). In general, lymphomas in patients with RA do not seem to be different with respect to grade, histology or immunophenotype from the lymphomas seen in general population. (18) Most studies have suggested that the risk for the development of lymphoma is related to the degree of inflammation. (19) Patients with Felty's syndrome were found to have a 12-fold increased risk of non-Hodgkin's lymphoma. (20) In one study, lymphoma patients with underlying RA seemed to have a lower risk of progression, relapse or death for lymphoma. (21)

As for solid tumors it seems that there is an increased risk only for the lung cancer (probably related to smoking). (22) On the other hand, several studies demonstrate that there was decreased risk for colon cancer. The use of non-steroidal anti-inflammatory drugs may protect against the development of large bowel cancers. (23)

Systemic lupus erythematosus (SLE)

The results from several studies concerning the development of malignancy in association with SLE are conflicting. Some of them did not find an increased risk of overall malignancies in patients with SLE (24) but have shown an increased risk for lymphoproliferative disorders.

(25) Other studies have raised concerns about an increased risk of gynecologic malignancies. Women with SLE have been shown to have less exposure to oral contraceptives and greater prevalence of nulliparity, obesity and tobacco use, all of which may mitigate the number of hormonal malignancies. Those have also an age-appropriate screening for gynecologic malignancies less frequent than do healthy women. (26)

Systemic sclerosis

Most evidence suggests that individuals with systemic sclerosis seem to have an increased risk of developing malignancies. The malignancies occur mostly in the organs affected by inflammation and fibrosis, like lung, breast, esophagus and skin. (27) Older age at the time of diagnosis of systemic sclerosis seems to be a risk factor for the development of cancer. Cases of non-Hodgkin's lymphoma seem to be more likely to occur in the first year of the diagnosis of systemic sclerosis. (28) Localized scleroderma does not seem to have an increased risk of malignancies.

Vasculitis

There are three types of cryoglobulins: type I – monoclonal immunoglobulin, either IgG or IgM, associated with lymphoproliferative disorders; type II – monoclonal IgM directed against polyclonal IgG, associated with non-Hodgkin's lymphoma; type III – mixed polyclonal IgG and IgM, in association with connective tissue diseases. Symptoms are usually represented by fatigue, arthralgia or arthritis, cutaneous vasculitis or purpura, neuropathy, digital ischemia and visceral organ involvement (renal or pulmonary).

Wegener's granulomatosis (more recently named granulomatosis with polyangiitis - GPA), has likewise been associated with the development of several types of malignancies, including lymphoproliferative disorders, bladder cancer and renal cell carcinoma. (29)

Spondyloarthritis

The malignancy risk in patients with spondyloarthritis seems to be similar to that in the general population. Moreover, the risk of hematopoietic malignancies is not increased. (30) An explanation could be that patients with spondyloarthritis don't have such an important

inflammatory syndrome, since only half of these patients demonstrate elevated levels of acute phase reactants. (31) However, there are some studies that raise the possibility of an increased risk of malignancy in patients with psoriatic arthritis, but this need more investigations. (32)

Paget's disease of bone

Paget's disease of bone can be rarely (under 1% of patients) associated with the development of osteosarcoma (malignant tumor of bone). When there is a sudden onset or worsening of pain, sarcoma should be considered.

Soluble tumor antigens in rheumatic disease

Several tumor-associated antigens (TAA) are present not only on the tumor cells, but also on activated leukocytes. Elevated serum levels of several TAA have been reported in some autoimmune diseases, like RA, SLE and systemic sclerosis. In RA are found increased levels of CEA and CA 19-9 and in SLE and systemic sclerosis an elevated level of CA 125, CA 15-3 and CA 19-9 were reported. Some authors also correlate ATT with rheumatic disease activity and organ-specific manifestation. In systemic sclerosis elevated levels of CEA, CA 15-3 and CA 19-9 seemed to correlate with renal involvement. In SLE, CA 72-4 correlates with central nervous system involvement and CA 125 with SLEDAI disease activity index. The presence of elevated levels of CA 15-3 correlates with articular manifestations and the presence of antinuclear antibody (1,33,34). □

RISKS OF DEVELOPING MALIGNANCIES IN ASSOCIATION WITH IMMUNOMODULATORY AGENTS

Many of the medication used to treat the rheumatic disease are modulators of the immune system. An agent may confer the risk of malignancy through direct mutagenesis of DNA, through generalized immunosuppression with the risk of development an EBV-associated lymphoproliferative disorder or through direct injury to an organ, such as bladder with the use of cyclophosphamide. Longer duration of treatment has been associated with an increased risk of malignancies. (35) However, it is difficult to differentiate the individual risk of an agent, particularly in the background of an autoimmune disease.

Cyclophosphamide

The use of cyclophosphamide results in an increased risk of development of bladder cancer, skin cancer and hematologic malignancies. Risk factors for the development of neoplasia include higher total dosage, longer duration of therapy and tobacco use. The increased risk for bladder cancer continues many years after cyclophosphamide therapy. The overall risks of bladder cancer may be less with pulsed, intravenous, treatment. (36)

Methotrexate (MTX)

There has been no strong evidence to suggest that MTX increase risk of solid tumors. However, there have been reports of increased risk of lymphomas. Studies have been published regarding the possible association of MTX and the development of lymphoproliferative disorders related to EBV infection. (2)

Azathioprine

The use of azathioprine is associated with an increased risk of malignancy in general. It can increase the risk of lymphoproliferative disorders up to 10-fold compared to general population. It has been seen a correlation between the cumulative dose of azathioprine and the incidence of cancer. (2)

Cyclosporine

There has been an increased risk for development of malignancy, especially lymphoproliferative disorders, in patients with solid organ transplantation. As for rheumatic disease there has not been sufficient number of patients followed for sufficient time to determine the risk for malignancies.

Leflunomide

The use of leflunomide doesn't increase the risk of malignancies. However, long-term safety studies are necessary.

Tumor necrosis factor inhibitors

Until now there are five molecules against tumor necrosis factor approved by Food and Drug Administration for the treatment of rheumatic diseases: infliximab (IFX), adalimumab (ADA), etanercept, golimumab, certolizumab pegol.

An initial report of U.S. Food and Drug Administration of 26 cases of lymphoma in patients treated with IFX for RA and Crohn's disease raises the concerns regarding the increase risk for hematologic malignancy of this therapy. (37)

A meta-analysis of nine randomized clinical trials of IFX and ADA has found an odds ratio of developing any malignancy of 3.3 for patients receiving IFX and ADA compared to placebo. (38) A Swedish study of patients with RA receiving tumor necrosis factor inhibitors found an increased risk for lymphoma comparative with TNF-native RA patients. (39) There are other studies that tried to demonstrate the relationship between anti-TNF therapy and malignancies. In almost all cases they found an increased risk of lymphoma but only some of them demonstrate the higher risk on nonmelanoma skin cancer. (40,41,43)

Several factors make possible these associations: patients with RA already seem to be at an increased risk for the development of a lymphoproliferative disorder, patients with a highest disease activity may be at the highest risk and these patients are also more likely to have received previous immunomodulatory agents.

Others biological therapies

There are others biological therapies approved in treatment of rheumatic disease. One of them is rituximab – a chimeric monoclonal antibody against CD20, primarily found on the surface of B cells. In a long-term safety study the risk of malignancy was similar to that found in general population. (44) Tocilizumab – a hu-

manized anti-IL6 receptor antibody was approved for the treatment of rheumatoid arthritis. The impact of this treatment on the development of malignancies is not known, but as an immunosuppressant treatment the risk of malignancies must be study further (45).



CONCLUSIONS

Recognizing that a relationship exists between malignancy and rheumatic diseases is important to our future understanding of the pathogenesis of the two entities.

When musculoskeletal symptoms appear, the paraneoplastic syndromes must play a part in differential diagnostic. A special attention must be given to atypical symptoms.

The most frequent cancer associated with RD is non-Hodgkin's lymphoma. Chronic inflammation is a major risk factor for the development of neoplasm in patients with rheumatoid diseases. For patients with Sjögren's syndrome, systemic sclerosis or dermatomyositis/polymyositis, there is a documented association with an increased risk of malignant disease. Patients with rheumatoid arthritis may also have an increased risk of cancer. It is still controversial whether systemic lupus erythematosus is associated with an increased risk of developing malignancy.

The treatment of RD can increase the risk of cancer. Cyclophosphamide is associated with increase risk of bladder cancer. Patients in treatment with tumor necrosis factor inhibitors must be supervised for neoplasm (especially lymphomas and non-melanoma skin cancer).

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