

Paraneoplastic syndromes in rheumatology

Zespoły paranowotworowe w reumatologii

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Streszczenie

Zespoły paranowotworowe są to objawy lub zespoły objawów towarzyszące chorobie nowotworowej, które często ustępują po skutecznym wyleczeniu nowotworu. Przyczyny zespołów paranowotworowych nie zostały w pełni poznane. Mechanizmy związane są z nieprawidłowym wydzielaniem hormonów lub cytokin, a także z wytwarzaniem przeciwciał skierowanych przeciw nowotworowi. Najczęstsze zespoły paranowotworowe objawiają się pod postacią zespołów neurologicznych, zaburzeń hematologicznych, zmian skórnych. Artykuł przedstawia związek nowotworów złośliwych z autoimmunologicznymi chorobami tkanki łącznej.

Słowa kluczowe: zespoły paranowotworowe, nowotwory złośliwe, choroby tkanki łącznej

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Abbreviations

RA – Rheumatoid arthritis
SLE – Systemic lupus erythematosus
PM – Polymyositis
DM – Dermatomyositis
NHL – Non-Hodgkin lymphomas
HL – Hodgkin's lymphoma

Introduction

Paraneoplastic syndromes are a group of rare disorders related to the presence of cancer, but independent of the tumour's location or size. Due to the fact that cancers are more common in aged populations, paraneoplastic syndromes also typically occur in the elderly.

Symptoms of paraneoplastic syndromes may precede, accompany or coincide with onset of cancer, but they mostly appear during the first 2 years before cancer is diagnosed.

This article presents typical rheumatic entities which may be related to or directly caused by the expansive process ongoing within the body.

The relation between cancer and autoimmune rheumatic diseases is sufficiently understood; it is assumed that progression of the process may occur due to activation of multiple potential mechanisms. Cancer may occur as a consequence of rheumatic diseases due to chronic inflammation in the tumour microenvironment [1, 2], damage caused by the rheumatic process or cytostatic therapy.

Conversely, a rheumatic disease may occur as a consequence of cancer (pure paraneoplastic syndromes), due to a cancer-induced autoimmune response or as a consequence of the immunotherapy or chemotherapy utilized in cancer treatment. For example, administration of bleomycin, vinblastine, vincristine or cisplatin may lead to Raynaud syndrome, while using aromatase inhibitors may contribute towards development of arthritis and myositis.

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Approx. 15% of cancer patients develop paraneoplastic syndromes as a result of action of tumour-derived biologic mediators, such as hormones, peptides, antibodies, cytotoxic lymphocytes, autocrine and paracrine mediators [3, 4].

Patients with paraneoplastic syndromes may develop autoantibodies many years before clinical symptoms [5]. Similarly, autoantibodies in neoplastic sera may be detected many years before cancer is diagnosed [6–8]. The presence of autoantibodies in sera of patients with solid or hematologic tumours has been documented by several studies [9–14]. All data concerning cancer-related autoantigens is collected in databases available at <http://www.cancerimmunity.org/peptide/>.

The presence of antinuclear antibodies is detected in approx. 24% of patients with paraneoplastic syndromes, while in a group of people in whom antinuclear antibodies have been detected by coincidence, cancer incidence was estimated at approx. 2.9% [15, 16].

Various studies demonstrate the relation between antibodies characteristic for rheumatic diseases and cancer incidence. In a report by Zuckerman et al., anticardiolipin antibodies were present in 22% of neoplastic sera, compared to 3% for healthy population in control group [17]. Lossos et al. detected antiphospholipid antibodies in 68% of sera from patients with acute myeloid leukaemia [18].

Meanwhile, Crawford et al. described antibodies against human p53 in 9% of sera from breast cancer patients. These findings were confirmed by Caron de Fromental et al., who found anti-p53 antibodies in 21% of sera from children with B-cell lymphoma [19].

Finally, autoantibodies against c-myc have been described in sera from patients with breast and colorectal cancer, as well as with scleroderma, systemic lupus erythematosus and dermatomyositis [20–22].

These observations prove a significant autoimmune response activation, resulting in production of antibodies which also take part in pathogenesis of autoimmune and rheumatic diseases.

Polyarthritis

Paraneoplastic arthritis is a seronegative arthritis which may occur before cancer diagnosis. Typical symptoms include muscle pains and morning stiffness. Joint pains involve hands, ankles and knees. Characteristic features include reduced prevalence of RF and anti-CCP antibodies, increased concentration of LDH and CRP and visibly accelerated ESR compared to regular arthritis. Other features helpful in differential diagnosis are asymmetric joint involvement, dominance of elderly patients, dominance of male sex and steroid resistance.

The period between diagnosis of paraneoplastic arthritis and diagnosis of malignant neoplasm is shorter than

a year. Although nearly all cancers may involve development of arthritis, most data concerns lymphomas, both NHL and HL, as well as breast cancer in women and lung cancer in men.

As mentioned in the introduction, anti-cancer therapies may lead to arthritis. The main culprits are cyclophosphamide, 5-fluorouracil, tamoxifen, methotrexate and cisplatin. Aromatase inhibitors are related to joint pains and loss of bone mineral density. Studies indicate that 47% of arthritis symptoms develop 2–3 months after administration of aromatase inhibitors has started.

Hypertrophic osteoarthropathy

It is characterized by clubbed fingers, synovitis of neighbouring joints, periosteal reaction visible on X-ray images, tibia and femur pains and joint pains. This syndrome occurs in respiratory system cancers.

Palmar fasciitis and polyarthritis

This syndrome is characterized by bilateral contracture of distal phalanges, fasciitis, fibrosis and polyarthritis. It occurs in ovarian cancer, endometrial cancer, stomach cancer, pancreatic cancer, prostate cancer, cervical cancer and in Hodgkin disease.

Inflammatory myopathies

Polymyositis (PM) is an idiopathic inflammatory myopathy involving striated muscle tissue. The second syndrome from this group – Dermatomyositis (DM) – is an idiopathic inflammatory myopathy with skin manifestations. Both are characterized by acute or subacute onset, symmetric proximal muscle weakness, infiltration of mononuclear cells into muscle tissue and increased activity of muscle enzymes. Risk factors for DM/PM patients include: age > 45 years, male sex, skin necrosis, dysphagia, duration of disease < 4 months, ESR > 40 mm/h, high CRP concentration and high phosphocreatine kinase activity, presence of anti-p155 antibodies. Studies indicate that the risk of a malignant neoplasm is significantly reduced in PM/DM patients with concomitant interstitial lung disease, arthralgia, Raynaud syndrome.

Several studies proved that cancer may occur before, at the same time as or after diagnosis of myositis. Cancer risk is much higher within the first 3 years of diagnosis [23]. Polymyositis is most common in tracheal cancer, lung cancer and non-Hodgkin lymphoma. On the other hand, dermatomyositis is related to stomach cancer, colorectal cancer, pancreatic cancer, prostate cancer, breast cancer and ovarian cancer, as well as tracheal/lung cancer and NHL.

Vasculitis

The term cutaneous vasculitis encompasses a wide and heterogeneous range of syndromes, clinically characterised by inflammatory process involving vessels of various calibres and consequential skin damage, wherein usually a typical histopathological picture is established [24]. Vasculitis may be related to malignant neoplasms and may behave like a paraneoplastic syndrome. Palpable purpura is the most common skin manifestation. Patients with paraneoplastic vasculitis are usually elderly and the syndrome more frequently involves significant areas of the skin; on the other hand, gastrointestinal tract and kidney involvement is observed less frequently compared to typical vasculitis cases. Furthermore, these patients more often suffer from anaemia, accelerated ESR and cytopenia. Paraneoplastic cutaneous vasculitis is related to the presence of a solid tumour. Lung cancer (non-small cell), prostate cancer, colon cancer, kidney cancer, breast cancer, head and neck cancer (squamous cell) and endometrial cancer are the most common non-hematologic cancer types associated with cutaneous vasculitis [25].

Erythromelalgia

Erythromelalgia, that is painful erythema of the extremities, is a vasomotor disorder involving paroxysmal redness and warming of the distal parts of extremities, usually toes rather than fingers, accompanied by intense, burning pain. As a paraneoplastic syndrome, it is related to myeloproliferative disorders and thrombocythaemia in the course of systemic connective tissue diseases and chronic myeloid leukaemia.

RS3PE syndrome (remitting seronegative symmetrical synovitis with pitting oedema).

This syndrome is characterised by symmetrical synovitis of the hands and ankles with oedema, high concentration of acute-phase proteins, negative RF and no features of structural joint damage in radiographic examination. There is considerable oedema on the dorsal part of the palm, which makes grabbing difficult; it is caused mainly by extensor tenosynovitis.

Several cases of cancer involving RS3PE have been described thus far. The most commonly named types include Hodgkin's lymphoma, leukaemias, myelodysplastic syndromes, T-cell lymphocytic leukaemia, prostate cancer, lung cancer, breast cancer, ovarian cancer, bladder cancer, endometrial cancer and malignant fibrous histiocytoma.

Prognosis for patients with RS3PE without concomitant cancer is excellent. Patients with RS3PE and cancer are characterised by weak response to glucocorticoid treatment and more dramatic systemic symptoms.

Lupus-like syndrome

This syndrome is characterised by skin lesions, arthritis, serositis, Raynaud's phenomenon; other visceral complications are rare. Antinuclear antibodies may be present (usually in low titres), as can antiphospholipid antibodies; occasionally, leukopenia, thrombocytopenia or anaemia are also identified.

A metaanalysis of five prospective cohort studies published between 2002 and 2013 showed an increased risk of cancer of the haematopoietic system in patients with SLE [26]. This relation is particularly strong in case of non-Hodgkin lymphomas. Diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL in SLE. Epidemiologic studies were also able to identify increased risk of lung, liver and pancreatic cancer, but a decreased risk of breast and prostate cancer [27].

In addition, immunotherapy using interferon alpha and interferon gamma may also lead to development of a lupus-like syndrome.

Scleroderma-like syndrome

Scleroderma-like syndrome is one of the most common paraneoplastic syndromes. It is characterised by Raynaud's phenomenon, thickening of the skin and pulmonary fibrosis. It typically develops in people over the age of 50; the onset of Raynaud's phenomenon is sudden, skin lesions (on neck and torso, among others) progress quickly and sclerodactyly is present. Infrequently, high titres of antinuclear antibodies and anti-topoisomerase I antibodies are also detected [28]. A study involving 23 patients with scleroderma and a concomitant cancer diagnosis from the cohort of the Johns Hopkins Scleroderma Centre showed that patients with autoantibodies against RNA polymerase III were more at risk of cancer progression, while no time dependency was found in patients with anti-centromere antibodies or anti-topoisomerase I antibodies. Patients were characterised by an enhanced expression of RNA polymerase III in cancerous tissues, suggesting a relation between tumour autoantigen expression and scleroderma-specific immune response [29].

Advanced age at the moment of scleroderma diagnosis was a strong predictor of shorter interval between cancer and scleroderma. For people in whom scleroderma developed at a young age, development of a tumour is a consequence of immunosuppressive therapies, damage caused by the disease itself or environmental exposure rather than occurrence of pure paraneoplastic syndrome mechanisms. Cancer risk in this population was higher within the first 12 months of cutaneous scleroderma diagnosis, gradually decreasing with the duration of the disease [30].

Given the nearly universal occurrence of Raynaud's phenomenon in patients with scleroderma, one should not forget adverse effects of certain cytostatic drugs, such as bleomycin, vinblastine, vincristine or cisplatin, which may lead to Raynaud syndrome [31]. Such clinical situations should be interpreted critically, as they are not examples of onset of a rheumatic disease in a patient undergoing chemotherapy, but constitute an instance of adverse effect of a drug. Occurrence of symptoms of scleroderma, or, more frequently, of a scleroderma-like syndrome, is typically linked with lung cancer; such relation is also encountered less frequently with stomach cancer, breast cancer, ovarian cancer, melanoma and multiple myeloma [32].

Sjögren syndrome

Sjögren syndrome is a systemic connective tissue disease, characterised by damage to the exocrine glands caused by inflammatory process. Immunologically, the basis of the disease is B-cell activation; this means that patients are particularly vulnerable to development of lymphomas.

Non-Hodgkin lymphomas are dominant cancer forms in Sjögren syndrome, and their incidence increases with time,

encompassing approx. 10% of patients after the disease has continued for 30 years [33].

Lymphoma-related risk factors in Sjögren syndrome patients are well-known: persistent glandular itching, low C3 and C4 levels, cryoglobulinaemia, splenomegaly, leukopenia, positive SSA/SSB.

Conclusions

Paraneoplastic syndromes constitute a considerable problem in terms of diagnosis and therapy. In many cases they may represent the first symptom of a disease. In case of patients with a freshly diagnosed systemic connective tissue disease which resists standard treatment, with an unspecific course and atypical clinical picture, it is recommended to extend diagnosis to confirm or exclude a neoplastic background. Procedure in described syndromes does not differ from generally accepted principles applied in rheumatology, with simultaneous antineoplastic therapy. However, the possibility of withdrawal of rheumatic disease symptoms as the underlying neoplastic process is treated should be kept in mind.

Abstract

Paraneoplastic syndromes are symptoms or sets of symptoms accompanying cancer which often pass after said cancer is effectively treated. Causes of paraneoplastic syndromes are not fully understood. Mechanisms are related to abnormal hormone or cytokine secretion, as well as production of antibodies directed against the neoplasm. The most common paraneoplastic syndromes take the form of neurological syndromes, haematological disorders and skin lesions. The article presents the relation between malignant neoplasms and autoimmune connective tissue diseases.

Key words: paraneoplastic syndromes, malignant neoplasms, connective tissue diseases

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