PREDAVANJE U SPOMEN DRAGI ČOPU
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OVERALL CHARACTERISTICS AND EARLY DIAGNOSIS OF PATIENTS WITH CONNECTIVE TISSUE DISEASES

SVEUKUPNA OBILJEŽJA I RANA DIJAGNOZA U BOLESNIKA S BOLESTIMA VEZIVNOG TKIVA

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Abstract

The most important issue in regard to systemic autoimmune diseases is early recognition and early, long-term treatment. In certain disorders, including rheumatoid arthritis and systemic sclerosis, the revised new classification criteria help to identify the cases as early as possible. Once the diagnosis has been established, a "treat-to-target" approach is important. Further work is required to improve the currently available activity damage indexes and outcome measures in these particular disorders; in particular, better composite activity indexes seem to be necessary for the future.

Early recognition of the typical symptoms and signs of these particular diseases is crucial. These disorders are usually accompanied by permanent or temporary inflammatory signs, and the inflammation often occurs in waves. The most frequent symptoms of systemic autoimmune disorders include polyarthritis, Raynaud phenomenon, inflammatory and non-inflammatory skin symptoms, sicca syndrome (dry eyes, dry mouth), pulmonary arterial hypertension/lung fibrosis, a variety of central and peripheral nervous system-related symptoms, and symmetric proximal muscle weakness and pain. Furthermore, proteinuria, hematuria, and recurrent pleuritis/pericarditis also belong to the disease spectrum of these disorders. Symptoms representing antiphospholipid syndrome (recurrent thrombo-embolic events, fetal morbidity, and presence of antiphospholipid autoantibodies) can also be typical contributors. There are further rare findings, including persistent peripheral/central nervous system-related symptoms, leukopenia, and pulmonary arterial hypertension. The early recognition of "unusual" associations of organ symptoms is a crucial point.

Keywords: systemic autoimmune disease, systemic lupus erythematosus, systemic sclerosis, classification, treat-to-target

Sažetak

Najvažnije pitanje sustavnih autoimunih bolesti jest rano prepoznavanje i rano dugotrajno liječenje. U nekim bolestima, uključujući reumatoidni artritis i sistemsku sklerozu, novi revidirani kriteriji mogu pomoći identificirati bolest što je prije moguće. Nakon postavljanja dijagnoze važno je „liječenje prema cilju". Potrebni su dodatni napori za poboljšanje zasad dostupnih indeksa aktivnosti/oštećenja i mjera ishoda u ovim bolestima, a napose bolji složeni indeksi aktivnosti koji se čine nužnima u budućnosti.

Ključno je rano prepoznati tipične simptome i znakove bolesti. Ove su bolesti obično praćene stalnim ili povremenim znakovima upale koja često nastupa u valovima. Najčešći simptomi sustavnih autoimunih bolesti uključuju poliartritis, Raynaudov fenomen, upalne i neupalne simptome kože, „sicca" sindrom (suhe oči, suha usta), plućnu hipertenziju / fibrozu pluća, različite simptome središnjega i perifernoga živčanog sustava te simetričnu slabost i bol proksimalne muskulature. Osim toga, u spektar ovih specifičnih poremećaja pripadaju i proteinurija, hematurija te ponavljajući pleuritis/perikarditis. Simptomi tipični za antifosfolipidni sindrom (ponavljajući trombo-embolijski događaji, fetalni morbiditet i prisutnost antifosfolipidnih protutijela) mogu također biti obilježja ovih poremećaja. Rijetki nalazi uključuju stalne simptome središnjega i perifernoga živčanog sustava, leukopeniju i plućnu hipertenziju. Stoga je ključno rano prepoznati „neobične" kombinacije organskih simptoma.

Ključne riječi: sustavne autoimune bolesti, sistemski eritemski lupus, sistemska skleroza, klasifikacija, liječenje prema cilju

Introduction

The early symptoms of systemic autoimmune diseases (Table 1) are usually highly variable, and the clinical presentations during their onset may often be very similar. One of the major hallmarks of these diseases is inflammation. In general, inflammation can be caused by a great variety of infectious diseases, as well as by certain malignancies and autoimmune/auto- inflammatory disorders. It is crucial that the systemic nature of the disease and the autoimmune phenomena should be recognized as early as possible.

Clinical presentation of patients with connective tissue diseases

One of the frequently present symptoms is symmetric polyarthritis affecting the metacarpophalangeal and proximal interphalangeal joint lines, as well as the large joints (predominantly the knees and wrists). Other characteristic symptoms of connective tissue diseases (CTDs) include Raynaud phenomenon, inflammatory and non-inflammatory skin symptoms, sicca syndrome (dry eyes, dry mouth), pulmonary arterial hypertension/lung fibrosis, a variety of central and peripheral nervous system-related symptoms, and symmetric proximal muscle weakness and pain. Furthermore, proteinuria, hematuria, and recurrent pleuritis/pericarditis also belong to the wide disease spectrum of these particular disorders. Symptoms representing antiphospholipid syndrome (recurrent thrombo-embolic events, fetal morbidity, and presence of antiphospholipid autoantibodies) can also be typical contributors to the disease spectrum. There are further rare findings which may also be present, including peripheral/central nervous system-related symptoms, leukopenia, and pulmonary arterial hypertension (Table 2). It is crucial to recognize "unusual" associations of different organ symptoms as early as possible; the larger the number of typical manifestations found, the more likely the diagnosis of a connective tissue disease is going to be.

In the presence of a combination of the most frequently observed phenomena, including Raynaud syndrome, polyarthritis, sicca syndrome, and skin symptoms, it is mandatory to think about the likelihood of a connective tissue disease. There are several characteristic findings which may help in the evaluation of the patients (Table 3).

Table 1 Systemic autoimmune diseases

Systemic autoimmune diseases
• systemic lupus erythematosus
• systemic sclerosis
• inflammatory myopathies
• Sjögren syndrome
• systemic vasculitides
• antiphospholipid syndrome
• mixed connective tissue disease
• overlap syndromes
• undifferentiated connective tissue disease

Table 2 The clinical spectrum of connective tissue diseases

The clinical spectrum of connective tissue diseases
• fever/inflammation of unknown origin
• polyarthritis
• skin symptoms
• Raynaud phenomenon
• recurrent serositis (pleuritis, pericarditis)
• proteinuria, hematuria, cylindruria
• leukopenia
• "unusual" association of organ symptoms
• sicca symptoms
• symmetric proximal muscle pain/weakness of extremities
• "unexplained" polyneuritis, neuropathy
• symptoms of antiphospholipid syndrome (recurrent arterial/venous thrombosis, miscarriages, etc.)
• lung fibrosis or pulmonary arterial hypertension

Table 3 Characteristic findings during physical examination in connective tissue diseases

Lacrimal, salivary gland enlargement	SS
Dry eyes, dry mouth	SS
Lymphadenopathy	SLE
Synovitis	RA, other CTDs
Tendon friction rubs (fibrous tenosynovitis)	diffuse cutaneous SSc
Lack of peripheral arterial pulse	Takayasu arteritis, APS, systemic vasculitis
Painful temporal arterial branch	Temporal arteritis
Postthrombotic syndrome	APS
Leg ulcers	APS, necrotizing vasculitis, SSc
Proximal symmetric muscle weakness/pain	DM-PM
Deformed (impressed) nose	Granulomatosis with polyangiitis, polychondritis
Hypo/hyperpigmentation	SSc
Teleangiectasia	SSc
Cutaneous vasculitis	SLE, SS, MCTD, systemic vasculitides, DM, Henoch-Schönlein disease, etc.
Inflammatory skin symptoms	SLE, DM
Livedo reticularis	APS, lupus
Digital ulcers, gangrenes	SSc, APS, systemic vasculitis, cryoglobulinemia
Digital pad atrophy	SSc
Sclerodactyly	SSc
Digital skin thickening	SSc, MCTD
Subcutaneous nodule on extensor surface	RA
Subcutaneous calcinosis	SSc, myositis calcificans
Raynaud phenomenon	SSc, MCTD, SLE, DM-PM, etc.
Alopecia	SLE
Oral ulcers	SLE, Behcet disease

Abbreviations used: SS - Sjögren syndrome, SSc - systemic sclerosis, DM-PM - dermato-polymyositis, RA - rheumatoid arthritis, SLE - systemic lupus erythematosus, aPS - antihpospholipid syndrome

Clinical/laboratory signs of inflammation

In the discussed disorders inflammation often occurs in waves, and there are periods when no signs of inflammation can be observed. Apart from some rare cases, systemic inflammation is generally caused by a large variety of infections, certain malignancies, and systemic autoimmune diseases. In many SLE cases an increased ESR without an acute phase reaction (i.e., increased CRP) may be present, while in infections and tumors both ESR and CRP are elevated. It is therefore crucial to consider that connective tissue disease may be one of the important background causes of the inflammation. An extended search for the presence of an infectious/malignant disease without taking immediate basic differential diagnostic steps for the presence of a CTD can cause a significant delay in the treatment. In fact, there is a brief "window of opportunity" in the early phase of CTDs when the therapy usually efficiently stops the disease progression.

Polyarthritis

A symmetric polyarthritis affecting the metacarpophalangeal and proximal interphalangeal lines as well as the large joints (predominantly knees and wrists) is often present in these disorders. Conversely, the distal interphalangeal (DIP) joints are not affected. In the differential diagnosis, infection-related arthritides, psoriatic arthritis, osteoarthritis, and chronic gout are especially important.

Raynaud phenomenon

Raynaud phenomenon is an episodic digital vasospasm following an exposure to cold. Emotional stress may also be a provoking factor in some patients. Primary Raynaud phenomenon is a common disease, in which no other organ manifestations, such as nailfold capillaroscopy changes or antinuclear antibodies, are present (1). Sometimes the patients may not notice the characteristic color changes (white-blue-red), and they complain about digital pain following exposure to cold. In case of secondary Raynaud syndrome, there is an underlying disease, as can often be observed in patients with connective tissue disease. Important basic differential diagnostic steps to be performed are nailfold capillary microscopy and antinuclear antibody screening test. As almost all SSc patients have Raynaud phenomenon, it is a very important indicator in early cases, especially if the patient in question also has puffy fingers (2, 3, 4).

Sicca syndrome

Sicca syndrome is characterized by xerostomia and keratoconjunctivitis. Dryness of the mouth often causes difficulties in swallowing dry food, an inability to speak continuously, and a burning sensation. Ocular dryness causes a sandy or gritty feeling under the eyelids, burning, decreased tear production, redness, and itching. Dryness can result from many other causes, including diabetes mellitus and certain drugs with an anticholinergic effect (antidepressants, diuretics, anticholinergic agents, etc.). Infections such as hepatitis C and HIV and autonomic neuropathy may also cause sicca symptoms. Dehydration or the use of diuretics are also possible background causes of xerostomia.

Symmetric muscle pain/weakness of the proximal extremities

One of the typical complaints is pain while climbing stairs or combing one's hair. Secondary causes can be due to drugs, infections, neurological disorders, and malignancy.

Skin symptoms

Exposure to UV light (from sunshine or the use of tanning boots) which provokes dermatitis is a frequent sign in SLE and dermatomyositis patients. Livedo reticularis is typical of primary/secondary antiphospholipid syndrome. In the latter case, the skin changes are stable. Palpable purpura (cutaneous vasculitis), gangrenes, sclerodactyly, and puffy fingers are also important signs of CTDs. Many other signs, including telangiectasia, skin pigmentary changes, or deep necrotic vasculitic lesions, may also be present.

Proteinuria, hematuria

The kidney involvement does not cause complaints, therefore an early detection is exclusively based on the urinalysis. Signs of proteinuria, hematuria, and cylindruria can be important findings, especially in patients with SLE or ANCA-associated vasculitic syndromes.

Signs of antiphospholipid syndrome (APS)

The clinical manifestations of APS include recurrent artiral-venous thromboses and thromboembolic events, recurrent miscarriages, and obstetric events. Many other manifestations, including decreased platelet count, valvulopathy, livedo reticularis, or pulmonary hypertension, can also be present.

Basic investigations for diagnosis verification

Besides the antinuclear antibody (ANA) screening test, other investigations, including rheumatoid factor, ANCA, and antiphospholipid antibody tests (anticardiolipin IgG and IgM, lupus anticoagulant, and anti-beta2 glycoprotein I), may also be necessary. The other basic screening test is nailfold capillaroscopy, which is a crucial investigation in cases presenting with Raynaud phenomenon (2, 3). Giant capillaries, capillary dropout, and hemorrhages are important signs, predominantly present in cases with SSc, MCTD, and, less frequently, in inflammatory myopathies and UCTD. The presence of Raynaud syndrome and scleroderma capillary pattern may be an important indicator of a potential CTD, mainly in the scleroderma disease spectrum.

Early diagnosis is crucial because of the window of opportunity in the early phase of the disease when the treatment seems to be most efficient. This fact prompted the experts in the field to revise several classification criteria, including SSc to involve patients with very early disease manifestations (5, 6, 7). Furthermore, a definition of the very early phase of the disease helps to identify the cases as early as possible (6, 7).

Classification criteria and "treat-to-target" approach

Once the diagnosis of a CTD has been established, the "treat-to-target" approach is the important next step in the management of a particular patient. The treatment strategy for several chronic diseases has been profoundly changed in the last two decades, and the predominantly

symptom-based management has been successfully changed to a target-based approach. This first happened with the management of hypertension and diabetes. In rheumatology, the management of rheumatoid arthritis (RA) has also changed remarkably, based on the results of several randomized clinical trials showing that the targeted therapy approach using composite disease activity scores yielded more favorable outcomes with regard to the extent of joint damage and function (8, 9). Recently, a "treat-to-target" recommendation has been developed and widely used in the treatment of patients with RA as well as gout (10, 11). In systemic autoimmune diseases the measurement of outcome based on composite disease activity scores seems to be difficult. Further work is required to improve the currently available activity damage indexes in these particular disorders; in particular, better composite activity indexes seem to be necessary for the future. Furthermore, systemic autoimmune diseases, especially SLE, show a slowly progressive accumulation of irreversible organ damage, and the presence of damage is a predictor of further damage accrual (12). Based on these facts, it is reasonable to formulate a treat-to-target recommendation like the one established for SLE, as well as to define some new treatment targets beside prevention of damage accrual or flare up, which have been recognized as important treatment goals (13, 14).

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