

A RARE CASE OF SYSTEMIC AUTOIMMUNE DISEASE WITH INTRICATE FEATURES OF SYSTEMIC SCLEROSIS, LUPUS, POLYMYOSITIS AND RHEUMATOID ARTHRITIS. OVERLAP SYNDROME OR MIXED CONNECTIVE TISSUE DISEASE?

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Abstract

We report an unusual case of connective tissue disease characterized by the coexistence of signs, symptoms and immunological features of 4 defined autoimmune diseases: systemic lupus erythematosus (SLE), systemic sclerosis (SSc), polymyositis (PM) and rheumatoid arthritis (RA). A 53-year-old female was admitted in our clinic with massive polyserositis (pretamponade) as well as skin, joint, muscular lesions and altered general status. The problem we found was the difficulty of including this case in a known clinical entity; SSc/SLE/PM/RA overlap syndrome and mixed connective tissue disease were the two most plausible diagnoses. We discuss the particularities of these clinical and immunological associations and the appropriate therapeutic options used in this kind of patients.

Keywords: Overlap Syndrome; Systemic Lupus Erythematosus; Systemic Sclerosis; Raynaud's Syndrome; Classification Criteria.

Resumo

Descrevemos um caso de doença do tecido conjuntivo em que coexistem sinais, sintomas e alterações imunológicas características de 4 doenças autoimunes definidas: lúpus eritematoso sistémico (LES), esclerose sistémica (ES), polimiosite (PM) e artrite reumatóide (AR). Uma mulher de 53 anos foi

admitida no nosso serviço por polisserosite maciça (pré-tamponamento), associada a manifestações cutâneas, articulares, musculares e alteração do estado geral. Deparamo-nos com o problema de incluir este caso numa entidade clínica conhecida; síndrome de sobreposição ES/LES/PM/AR e doença mista do tecido conjuntivo são os dois diagnósticos mais plausíveis. Discutimos as particularidades destas associações clínicas e imunológicas, bem como as opções terapêuticas apropriadas para este tipo de doentes.

Palavras-Chave: Síndrome de Sobreposição; Lúpus Eritematoso Sistémico; Esclerose Sistémica; Síndrome de Raynaud; Critérios de Classificação.

Introduction

The term "connective tissue disease" (CTD) includes a large group of conditions characterized by considerable clinical diversity, heterogeneity and complexity. It refers to a group of autoimmune disorders classified among the systemic rheumatic diseases that includes systemic lupus erythematosus (SLE), systemic sclerosis (SSc), polymyositis-dermatomyositis (PM-DM), primary Sjögren's syndrome (pSS), primary antiphospholipid syndrome (APS), and rheumatoid arthritis (RA). The etiology of autoimmune connective tissue diseases is unknown and its diagnosis depends on patterns of symptoms and signs. CTDs share a number of epidemiological, immunological and pathological features that suggest a common pathogenetic pathway.¹ For example, autoimmune disorders are associated with the production of autoantibodies and/or self-reactive mononuclear cell populations, many have high levels of immune complexes or defects in cell-mediated immunity.² Sharing of im-

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Figure 1. Patient's face suggestive of systemic sclerosis.

munogenetic markers may lead to the development of common clinical features, which frequently makes the differential diagnosis of a specific rheumatic disease difficult. Since the majority of CTD features are neither frequent nor pathognomonic for a single disease, the most common way to identify a CTD is to look for a cluster of clinical and laboratory results. This is also the main reason why internationally accepted criteria have been developed for CTDs, which frequently incorporate the detection of specific autoantibodies as unique diagnostic markers.^{3,4}

Case report

A 53-year-old female was admitted to our clinic due to drowsiness, fatigue, malaise, dizziness, diaphoresis, anorexia, severe weight loss (approximately 50 kg in 2 months), and intense muscle weakness. She also complained of progressive shortness of



Figure 2. Patient's palm and fingers.

breath on exertion but also at rest, reduced exercise capacity, muscle pain in the lower limbs at effort, abdominal pain, nausea, transient bilateral knee pain and swelling and progressive stiffening of both hands, predominantly in the morning with functional impairment. The physical examination revealed an underweight patient (body mass index = 16 kg/m²) with low-grade fever (37.8°C), characteristic facial expression suggestive of SSc (Figure 1), erythematous lesions on the palms and digits of both hands associated with areas of necrotic lesions, epidermal atrophy, induration, loss of mobility and retraction with immobilization of the fingers in a semi flexed position (Figure 2). Photosensitivity was absent. Other findings included reduced muscle mass and strength, inter-osseous atrophy, symmetrical pain, stiffness and swelling of the metacarpophalangeal and proximal interphalangeal joints, wrists and knees, mild ulnar deviation and bilateral Raynaud's phenomenon of the extremities. Dispersed raised red scaling plaques with central atrophy on the extremities, some of them having resolved causing hyper-pigmentation, atrophy and scarring, friable nails, brittle hair and patchy alopecia were also noticed. Firm, mobile, non-tender cervical, axillary and inguinal lymph nodes were identified. The assessment of the cardiovascular system revealed an increased area of cardiac dullness, tachycardia (heart rate = 120/min), hypertension (150/100 mm Hg), faint rhythmic heart sounds and pericardial friction rub. The liver was enlarged (5 cm below the right costal margin) and tender.

The laboratory results revealed hemoglobin 11.3g/dL (12.5-16g/dL), hematocrite 34% (38-



Figure 3. Chest X-ray: globally enlarged cardiac silhouette with a pleural effusion in the left costophrenic sinus.



Figure 5. Echocardiography: medium/large pericardial effusion (exudative pericarditis).

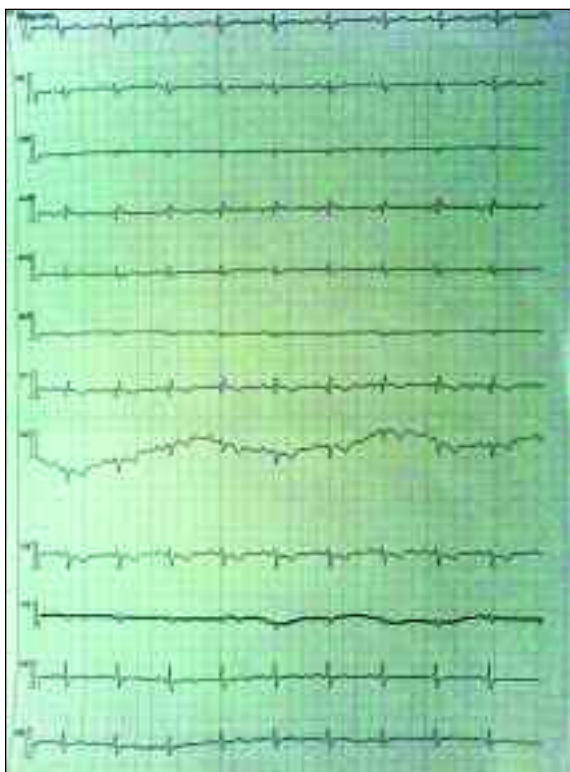


Figure 4. Electrocardiogram: low QRS voltage in all leads.

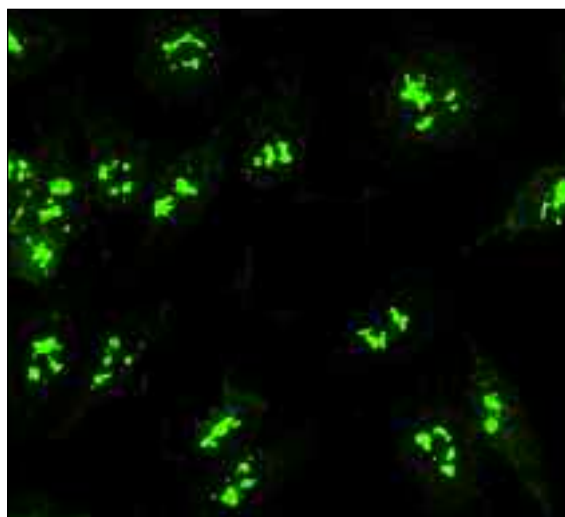


Figure 6. Immunofluorescence: ANA speckled pattern.

-53%), red blood cells $3.82 \times 10^6/\text{mm}^3$; erythrocyte sedimentation rate 80 mm/hour, C reactive protein 3.7 UI/mL (< 0.1 UI/mL); aspartate aminotransferase 198 U/L (< 46 U/L), alanine aminotransferase 78 U/L (< 49 U/L), alkaline phosphatase 372 U/L (98-279 U/L), γ glutamyl transferase 181 U/L (7-30 U/L), creatine kinase 428 U/L (22-198 U/L), 24-hour proteinuria 0.85g, hypoproteinemia 5.4g/

/dL (6-8.2g/dL), with hypoalbuminemia 3.1g/dL (3.5-5.4g/dL), polyclonal hypergammaglobulinemia (Ig G = 4064 mg/dL, Ig M = 180 mg/dL, Ig A = 205 mg/dL) and decreased serum complement fractions C3 and C4. The microbiological exams disclosed urinary tract infection (Enterobacter), oral candidosis and sterile blood cultures. HIV 1 and 2 test results were negative both by ELISA and PCR.

The chest X-ray (Figure 3) revealed a globally enlarged cardiac silhouette with a large pleural effusion in the left costophrenic sinus. The electrocardiogram showed a low QRS voltage (Figure 4) and the echocardiography confirmed large pericardial effusion with tendency for diastolic collapse of the right ventricle and right atrium (pretamponade) (Figure 5). The tricuspid gradient as well

as the pulmonary artery pressure were elevated. The abdominal ultrasound showed liver enlargement, with diffuse increased hepatic ecogenicity and ascites in moderate quantity. The Barium X-ray exam documented gastric and esophageal dysmotility and hypotonia with mildly diminished peristaltic movements and stasis.

The immunological profile revealed positive ANA (titer 1/1280) with speckled pattern (Figure 6) and also the presence of anti-Sm, anti-Ro/SSA, anti-La/SSB, anti-Jo1 and Rheumatoid Factor (85 U -Nephelometry test normal <43 U). Anti-centromere, anti-Scl-70 and anti-U1-RNP antibody were negative. The anti ds-DNA antibodies, ANCA (anti-neutrophil cytoplasm antibodies), SMA (smooth muscle antibody), AMA (antimitochondrial antibody), were also absent. When we repeated the immunological examination after 3 months, we found the same results except for a positive anti-U1-RNP antibody confirmed by double immunodiffusion.

The skin biopsy (from the finger lesions) and the deltoid muscle biopsy revealed typical aspects of vasculitis and characteristic lesions of myositis. The axillary lymph node biopsy ruled out the diagnosis of lymphoma. Percutaneous liver biopsy was also performed and was consistent with congestive hepatopathy. We intended to perform a kidney biopsy as well, to elucidate the renal dysfunction, but the patient refused the intervention.

The treatment consisted of corticotherapy (Methylprednisolone 32 mg/day), antibiotic treatment (for the urinary tract infection), local oral antimycotic and antihypertensive treatment (ACE inhibitor + beta blocker + diuretic). After approximately 1 month the evolution was excellent: remission of subjective clinical complaints, improved general status, apyrexia, regression of hepatomegaly, ascites and pleurisy and improvement of laboratory parameters but pericardial effusion persisted. The patient was prescribed long-term treatment with oral corticosteroids and immunosuppressant drugs (Azathioprine).

The long-term prognosis is uncertain due to the multi-organic dysfunction and the persistence of the pericardial effusion. A close follow-up of the patient's evolution and accurate therapeutic adjustments are necessary.

Discussion

Although CTDs can generally be clinically and serologically defined as distinct and separate entities, many patients diagnosed with autoimmune rheumatic disease cannot be categorized easily into one of the established conditions. Several diseases share similar genetic backgrounds, as reflected by study of loci within the major histocompatibility complex² and some genetic defects can predispose patients to more than one autoimmune disease.¹ The existence of patients with signs, symptoms and certain laboratory test results suggestive of a systemic autoimmune disease but fulfilling more than one classification criteria for well-defined CTDs is a more and more common experience in clinical practice. As opposed to some early stages of CTDs that might be undefined, unclassifiable or perhaps incomplete, with clinical elements and laboratory results suggestive of a systemic disease but not fulfilling criteria for well-defined CTDs, overlap syndromes define patients exhibiting enough features to meet the diagnosis of several CTDs at the same time. Thus, they "overlap" two or more diseases. Any CTD can be a partner in an overlap disorder.⁵ For example, patients can have a combination of RA and SLE («rhumus»), or SSc and PM.⁶ Overall, any CTD can appear in conjunction with features of another connective tissue diseases and thus, it does no longer fit in the traditional classification. The problem is even more complex by the tendency for one disease to merge with another, resulting in a continuous spectrum, with the traditionally accepted entities such as SLE or SSc occupying only part of the continuum with the overlap syndromes lying between. It is not only a co-association, but also a confluence and union of autoimmune disorders. Therefore, to identify an overlap syndrome it is essentially necessary to identify a constellation of distinctive features that constitute a true syndrome.

Mixed connective tissue disease (MCTD) is the prototype of an overlap syndrome. Since its original description by Sharp and collaborators⁷ in 1972, as an apparently unique syndrome combining clinical elements of SSc, SLE and PM, associated with antibodies to RNase sensitive extractable nuclear antigen, many clinical, serologic, and genetic studies have analyzed the different aspects of this entity. The relevance of defining MCTD as a separate disease entity has been challenged, some authors considering it just a subset of SLE.⁸ Over the past 30 years there has been a continuing debate as to whether MCTD constitutes a "distinct cli-

nical entity” and it still remains a controversial diagnosis.⁹ Follow-up studies showed that many patients originally diagnosed with MCTD have a tendency to develop a definite CTD, particularly scleroderma or SLE, within a few years.¹⁰ Initial observations of MCTD suggested infrequent renal disease, a good response to corticosteroids and favorable prognosis.¹¹ The early misconception that it has a relatively good prognosis has not proved to be correct, as pulmonary arterial hypertension and scleroderma renal crisis are two important causes of death.¹² The most important aspect of MCTD as a separate entity is its association with antibodies to U1-RNP. Recent studies have suggested that the production of anti-U1-RNP is an antigen-driven process, but the nature of the trigger for its production has not been yet elucidated. Levels of anti-U1-RNP antibodies seem to be concordant with disease activity in MCTD patients.¹³ Most authors agree that MCTD is a distinctive entity rather than a haphazard association of clinical and serological features and that the presence of high titres of autoantibodies to UIRNP influences the expression of connective tissue disease in ways that are relevant to prognosis and treatment.¹⁴ Long-term clinical studies showed that the clinical phenotype of MCTD is robust and can be defined by classification criteria that show reasonable sensitivity and specificity.¹⁴ In addition, the association of MCTD with particular HLA phenotypes (HLA-DR4) distinguishes it from SLE and SSc, and speaks to its being a disease entity, rather than a mixture of yet undifferentiated collagen vascular diseases.¹⁵ As indicated by many authors, MCTD remains a useful concept in daily practice and constitutes a disease entity of its own, helping to predict and diagnose organ problems and to educate the patient accordingly.¹⁵

In our patient, the data obtained did not permit us to include this case in one of the typical, well-established CTDs. The patient exhibited massive polyserositis and multisystemic dysfunction (cardiac, hepatic, renal impairment). Autoimmune hepatitis was initially suspected due to the significantly enlarged liver and very high titer of serum IgG, but the liver biopsy infirmed it. Cardiac and hepatic dysfunctions were probably secondary to the large pericardial effusion. The patient fulfilled most of the SSc criteria, but the presence of other intricate clinical and laboratory findings determined us to bear in mind and consider other entities that might account for the great complexity and

diversity of this case. Therefore, after carefully reviewing our findings, we concluded that we were faced with an SSc overlap. In a study on 118 patients, Caramaschi and collaborators evaluated the coexistence of additional autoimmune disease in a population of patients suffering from SSc. Their findings showed that approximately one third of patients affected by SSc developed one or more additional autoimmune diseases.¹⁶ Therefore SSc patients must be carefully evaluated both at onset and during the follow-up for the possible coexistence of other autoimmune disorders. Besides SSc, our patient presented features of SLE, polymyositis and RA, which lead us towards a diagnosis of complex SSc/SLE/PM/RA overlap syndrome. In order to better differentiate and obtain a confirmation, we considered useful to obtain a second immunological profile after 3 months, which confirmed the existence of anti-U1-RNP antibody, although the first determination was negative. We intend to undergo a close follow-up of the patient's clinical status and to monitor repeatedly, the titers of the autoantibodies in order to obtain an overview of their dynamics.

In practice, the exact immunologic diagnosis makes a big difference because the detection of an autoantibody may help the clinician to anticipate particular complications and to evaluate the outcome of the patient. The identification of overlapping features in a given patient is also important because treatment needs to be directed specifically at some of these features.

Overall, the picture of overlap syndromes with respect to CTDs is complex and heterogeneous. Observer bias might play a role in disease classification, so the presence of specific autoantibody profiles is certainly a useful tool in the diagnosis evaluation of such patients.⁵ Further multi-center analysis is necessary to better define overlap syndromes, to clarify prognosis and facilitate disease management.¹⁷

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