Una afección cardíaca poco común en la enfermedad mixta del tejido conjuntivo

An unusual cardiac involvement in mixed connective tissue disease

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ABSTRACT

Mixed connective tissue disease is an autoimmune disorder with overlapping features of systemic lupus erythematosus, systemic sclerosis and polymyositis. Cardiac involvement is common, being pericarditis the most frequent manifestation, as also pulmonary hypertension.

The authors present a case of a woman with one year of symptoms of polyarthritis and myalgia with gradual muscle weakness and weight loss, with severe impaired mobility in the last months. The initial evaluation showed an inflammatory systemic condition with an infiltrative pattern in echocardiogram, with pulmonary hypertension, that was confirmed by cardiac magnetic resonance.

After an extensive study, where infiltrative cardiomyopathies were a differential diagnosis, the patient meet criteria to mixed connective disease with signs of pulmonary hypertension and an atypical cardiac involvement. Immunosuppressive treatment and rehabilitation were initiated and one year after the patient remains asymptomatic without any limitations.

Keywords: Mixed connective tissue disease, amyloidosis, restrictive cardiomyopathy, infiltrative cardiac disease, pulmonary hypertension.

RESUMEN

La enfermedad mixta del tejido conectivo es un trastorno autoinmune con características superpuestas de lupus eritematoso sistémico, esclerosis sistémica y polimiositis. La afectación cardiaca es común, siendo la pericarditis la manifestación más frecuente, al igual que la hipertensión pulmonar.

Los autores presentan el caso de una mujer con un año de síntomas de poliartritis y mialgia con debilidad muscular gradual y pérdida de peso, con grave deterioro de la movilidad en los últimos meses. La evaluación inicial mostró un cuadro inflamatorio sistémico con patrón infiltrativo en ecocardiograma, con hipertensión pulmonar, que se confirmó por resonancia magnética cardiaca.

Tras un amplio estudio, en el que las miocardiopatías infiltrativas constituyeron un diagnóstico diferencial, la paciente cumplía criterios de conectivopatía mixta con signos de hipertensión pulmonar y una afectación cardiaca atípica. Se inició tratamiento inmunosupresor y rehabilitación y un año después la paciente permanece asintomática sin limitaciones.

Palabras clave: Enfermedad mixta del tejido conjuntivo, amiloidosis, cardiopatía restrictiva, enfermedad cardíaca infiltrativa, hipertensión pulmonar.

INTRODUCTION

In 1972, Sharp and colleagues described as a disease characterised by overlapping clinical features of systemic lupus erythematosus (SLE), systemic sclerosis, and polymyositis with high titers of serum anti-U1 ribonucleoprotein (U1-RNP) antibody. Definition and classification criteria of mixed connective tissue disease (MCTD) have been changed in the last decades. Since the initial description, the definition as an independent clinical entity has been discussed and currently there are no guidelines for the evaluation of these patients, as well as international consensus for their diagnosis. Four different sets of classification criteria are available: Sharp's, Kasukawa's, Alarcón-Segovia's and Kahn's criteria. Previous literature concluded that those of Alarcón-Segovia criteria and Kasukawa criteria had the highest sensitivity and specificity[1,2] (Table 1). The suspicion of MCTD should be considered in the presence of clinical signs such as high anti-U1-RNP titers, Raynaud's phenomenon, puffy hands and at least two of the following: arthritis, myositis, leukopenia, oesophageal dysmotility, pleuritis, pericarditis, interstitial lung disease or pulmonary hypertension (PH). There aren't specific clinical features of MCTD and it may present a wide spectrum of manifestations, although cardiac involvement is common among patients with MCTD this is often a subclinical manifestation[2,3,4]. In studies, it is described cardiac involvement that could vary from 18% to 85%, dependent of patient's selection and the method used to detect cardiac disease, and symptomatic cardiac disease from 24 to 63%[2,3]. Pericarditis is the most frequent manifestation, 30-43% of patients, followed by mitral valve prolapse, conduction disturbances and impaired diastolic function[2,3,4]. PH is the most significant cardiovascular problem, associated with an increased mortality, and it's described in studies in a range from 2% to 24%[1,2,5]. The myocardial lesions frequently found in cardiac magnetic resonance (CMR) include myocardial infarction, inflammation, diffuse subendocardial fibrosis and diffuse perfusion defects.[6,7]

CLINICAL CASE

A 60-year-old female presented to the emergency department with symptoms of severe asthenia, myalgia, muscle weakness with functional limitation and weight loss (20kg in one year). The symptoms started one year before, with additive and symmetrical polyarthritis (wrists, metacarpal (MCJ) and proximal interphalangeal joints (PIJ), knees and ankles), associated with progressive worsening myalgia, proximal muscle weakness and paraesthesia, that result in significant functional limitations in the daily routine. She also referred xerostomia. Several analgesics and anti-inflammatory drugs were prescribed during this period with worsening symptoms (losing the ability to walk without support). There was no history of malar rash, photosen-

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Table 1. Proposed classification criteria for mixed connective tissue disease.[1,2]

ALARCON-SEGOVIA (1987)	
Serological criteria	Anti-RNP Ab titer N 1:1000
Clinical criteria	1. Edema in hands 2. Synovitis 3. Myositis, 4. Raynaud's phenomenon 5. Acrosclerosis
Diagnosis	Serological criteria plus at least 3 clinical criteria included either synovitis or myositis
KASUKAWA (1987)	
Common symptoms	1. Raynaud's phenomenon 2. Swollen fingers or hands Anti-RNP Ab positive
Mixed symptoms	1. SLE-like symptoms: a. Polyarthritis b. Lymphadenopathy c. Facial erythema d. Pericarditis or pleuritis e. Leukopenia or thrombocytopenia. 2. SSc-like findings: a. Sclerodactyly b. Pulmonary fibrosis, restrictive changes of lung, or reduced diffusion capacity c. Hypomotility or dilatation of esophagus. 3. PM-like findings: a. Muscle weakness b. Elevated serum levels of muscle enzymes (CPK) c. Myogenic pattern on EMG
Diagnosis	At least one of common symptoms plus positivity for anti-RNP Ab plus one or more signs/symptoms of the mixed symptoms in at least two of the three disease categories

Abbreviation:
RNP = ribonucleoprotein.
SLE = systemic lupus erythematosus.
SSc = systemic sclerosis.
PM = polymyositis.
CPK = creatine phosphokinase.
EMG = electromyography.

sitivity, oral or genital ulcers, xerophthalmia, alopecia, dysphagia, fever, or other symptoms.

She had history of essential hypertension and diabetes, both well controlled with antihypertensive drugs and oral antidiabetics. On physical examination she had puffy hands with signs of slight sclerodactyly with a biphasic Raynaud's phenomenon (Figure 1). Face and neckline did not present skin thickening or other changes. She presented wrists, MCJ, IFJ, knees, and metatarsophalangeal joints arthritis. Tetraparesis with proximal predominance was present, with a strength of 4+/5 on the Medical Research Council (MRC) Scale for Muscle Strength in the upper limbs, and 3+/5 on MRC in lower limbs. Manual Muscle Testing (MMT8) of 42/80 points. Reflexes were normal.

The initial study revealed a haemoglobin of 12.9 g/dL without leucocytosis, C3 and C4 in normal values, increased levels of erythrocyte sedimentation rate (ESR) (73mm/1 hour) and rhabdomyolyses (creatine phosphokinase (CK) 994 U/L and myoglobin 438ng/mL). She had non-nephrotic proteinuria of 1.8g/24 hours with normal glomerular filtration rate, monoclonal protein wasn't present in serum or urine immunofixation and serum angiotensin converting enzyme was normal. Autoimmunity revealed positive anti-nuclear antibodies (1/1280 titer) with nuclear large/coarse speckled pattern (AC-5), anti-Ro52 and anti-U1-RNP anti-bodies were also positive.

Electrocardiogram presented sinus rhythm with deep R waves of V1-V4 suggesting infiltrative pathology. The echocardiogram showed systolic pulmonary artery pressure of 59 mmHg and a thickened atrial septum suggestive of infiltrative cardiomyopathy. CMR revealed moderate hypertrophy of the septal midbasal segments, slight compromise of systolic function with shortening of myocardial inversion time and late enhancement pattern, compatible with infiltrative cardiomyopathy (Figure 2).

Nail capillaroscopy showed rarefaction of capillary density, tortuous capillaries and megacapillaries. Electromyography showed a pattern of severe myopathic/ myositis process which was confirmed by muscle biopsy that showed inflammatory myopathy. No amyloid deposits were found in subcutaneous fat tissue, transbronchial and muscle biopsies. Myelogram was normal. High-resolution lung computed tomography revealed extensive area of pulmonary fibrosis and ground-glass opacities. Right heart catheterization measured a mean pulmonary arterial pressure of 27mmHg.

Figure 1. Patient's hands with signs of sclerodactyly.

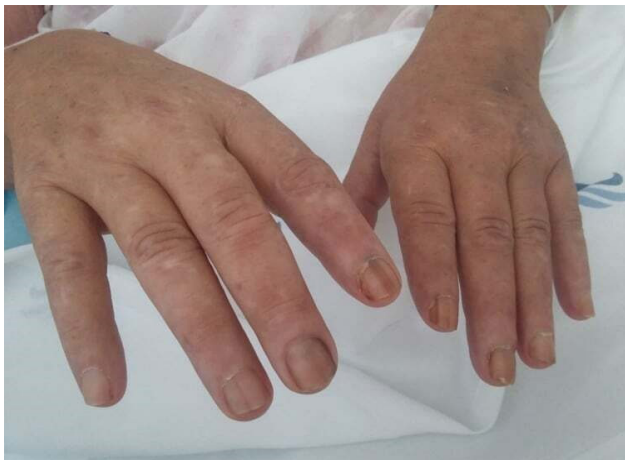
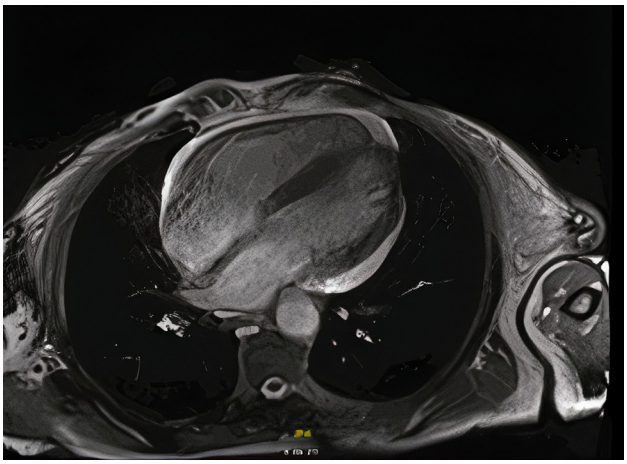


Figure 2. CMR: moderate hypertrophy of the septal midbasal segments, compatible with infiltrative cardiomyopathy (long axis, 4 chamber view).



Attending to these findings the diagnosis of MCTD was confirmed and the patient started 1g of methylprednisolone for three days, followed by a dual immunomodulation therapy consisting of high dose oral prednisolone (1 mg/kg/day) and cyclophosphamide (500mg/m^2 body surface area, administered every four weeks).

One year after the diagnosis, the patient was asymptomatic, with 60/80 points on MMT8 Score. ESR diminished to 13mm/1 hour, CK to 62U/L and proteinuria was in normal range. A second CMR showed late diffuse myocardium enhancement, suggestive of ventricle overload due to right overload pressure, and normal left ventricle ejection fraction. Right heart catheterization was repeated, that confirmed increased pulmonary artery hypertension (pulmonary systolic arterial pressure of 45mmHg and a transpulmonary pressure gradient of 26mmHg, suggesting precapillary pulmonary hypertension). Was referenced to a pulmonary hypertension centre, where started tadalafil 20mg/day. Attending to the evolution, the hypothesis of infiltrative cardiomyopathy was excluded, and the cardiac features were assumed as PH consequence. Currently, the patient is medicated with 5mg prednisolone/day and 150mg azathioprine/day, remaining asymptomatic.

DISCUSSION

MCTD is a systemic autoimmune disorder that can affect any organ/system. The diagnosis of MCTD is difficult, symptoms are often non-specific and overlapping features occur sequentially over several years. In our case, the presence of positive anti–U1-RNP antibodies associated with Raynaud's phenomenon, puffy hands, myositis and synovitis led to the diagnostic suspicion of MCTD. She presented an unusual cardiac involvement resembling an infiltrative cardiomyopathy, with shortening of myocardial inversion time and late enhancement pattern. Attending to these findings, a systemic autoimmune disease was suspected, with an infiltrative cardiomyopathy associated (like amyloidosis or sarcoidosis) and the initial investigation was developed in that direction. Through the investigation, the hypothesis of MCTD with an initial atypical cardiac involvement was suspected, because none of the complementary exams support the presence of infiltrative cardiomyopathies[8] and the cardiac images executed after initiation of treatment already revealed a different pattern, that could be justified by the presence of right overload pressure. The treatment of MCTD is guided by the organ involvement and is similar to other connective tissue diseases[2,5,9,10]. We started treatment with corticosteroids and added cyclophosphamide attending to interstitial lung and kidney involvement, PH and myositis. Due to its role as the main cause of mortality in MCTD, early recognition of PH has gained relevance and is associated to a better prognostic[2,5,9]. In cases of MCTD with PH, there is an association with global failure of the right ventricle.[10]

CONCLUSION

In conclusion, we can state that cardiac involvement initially leaded us to other differential diagnostic besides MCTD, however, after an extensive complementary study with exclusion of other diseases, MCTD was diagnosed. The early recognition of the different organ involvement is an important point, specially in the presence of PH. PH is the main cause of mortality among these patients, making early treatment very relevant for a better prognostic.[1,2,4,5,7,9]

Future research on MCTD based on large scale sample sizes is needed for better characterization of clinical features of the disease and consequently an earlier recognition and prompt treatment, which is directly related to the patient morbimortality.[1]

CONFLICT OF INTEREST
The authors declare that there is no conflict of interest in this work.

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This research had no funding sources.

ETHICAL ASPECTS
All participants submitted a consent form to be included in this study.

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