SAS Journal of Medicine
Abbreviated Key Title: SAS J Med
ISSN 2454-5112
Journal homepage: https://saspublishers.com

OPEN ACCESS

Mixed Connective Tissue Disease (MCTD) or SHARP Syndrome: A Case Report with Review of the Literature

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DOI: 10.36347/sasjm.2021.v07i06.003 | **Received:** 17.04.2021 | **Accepted:** 02.06.2021 | **Published:** 08.06.2021

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Abstract **Case Report**

Mixed Connective Tissue Disease or SHARP Syndrome was originally described by Gordon. C. Sharp as a syndrome combining clinical signs of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), scleroderma, polymyositis/dermatomyositis (PM/DM), associated with an elevated level of ribonuclease-sensitive antinuclear antibodies. These antibodies were later defined as anti-U1-RNP antibodies. In routine practice, the clinical and immunological distinction between mixed and overlapping connectivitis or a particular form of differentiated connectivitis is sometimes difficult and has little therapeutic consequence. Nevertheless, this can be an ease of approach for the therapist and an ease of understanding for the patient. We report a case of Sharp's syndrome diagnosed in a 37-year-old female patient at the CHU Aristide LeDantec in Dakar, Senegal.

Keywords: Mixed Connective Tissue Disease or SHARP Syndrome; Senegal.

INTRODUCTION

Sharp's syndrome or mixed connectivitis was originally described by Gordon. C. Sharp [1] as a syndrome combining clinical signs of rheumatoid arthritis, systemic lupus erythematosus, scleroderma, polymyositis/dermatomyositis, associated with an elevated level of ribonuclease-sensitive antinuclear antibodies. These antibodies were later defined as anti-U1-RNP antibodies [1]. It is a rare disease, with an estimated prevalence of 0.21 to 10 per 100,000 inhabitants in different parts of the world. This prevalence remains uncertain in the world because of the divergence of the criteria for classification of the disease and the frequent confusion between mixed connectivitis, overlapping syndrome and undifferentiated connectivitis. This confusion is due to the imperfect translation of the term MCTD (Mixed Connective Tissue Disease) used in the literature. There is a female predominance [2, 3]. The disease seems to start most frequently around the age of 30 years but can occur at any age. The pathophysiology of the disease is partially known at present. We report a case of Sharp's syndrome diagnosed in a 37-year-old female patient at the Aristide LeDantec University Hospital in Dakar, Senegal.

OBSERVATION OF THE PATIENT

A female patient born in 1979 (37 years old in 2016), black, Senegalese, who had been suffering from inflammatory pain (waking up at night and waking up in the morning for more than an hour) of severe intensity in the distal extremities of both hands and feet for about 5 years. Then, about 4 months ago, we noted the occurrence of skin coloration disorders in the fingers (bluish coloration) of both hands, aggravated in cold periods (Raynaud's phenomenon). This motivated the consultation in the rheumatology department at the Aristide LeDantec Hospital (HALD).

The general examination revealed an altered general condition with physical asthenia and grade 2 underweight (BMI 16.32 kg/m2). The other parameters were normal. On clinical examination, the peripheral joints were unremarkable and there was no deformity. Examination of the mucocutaneous system revealed erythematous lesions on the palmoplantar area, associated with digital necrosis on the 2nd and 3rd fingers of the upper limbs and the 1st, 2nd, 3rd and 4th fingers of the lower limbs. Sclerodactyly and scars from old digital ulcerations were also noted. Examination of the pleuropulmonary system revealed discrete crepitus rales at the base of both lung fields. The hypotheses evoked, taking into account the age of our patient (37

years), the female sex, the symptoms and her clinical examination were systemic lupus erythematosus, systemic scleroderma and Mixed Connective Tissue Disease or SHARP Syndrome.

The biology showed an inflammatory syndrome with a blood pressure of 28 mm at the first hour, hyperalpha2globulinemia at 12.1 g/l and hypergammaglobulinemia at 21.5 g/l. Immunology showed antinuclear antibodies greater than 1/160, with a homogeneous and mottled appearance. Their typing showed the presence of anti-U1-RNP antibody. The search for anti-SSA, anti-SSB, anti-Scl70, anti-Sm and ANCA antibodies was negative. The other analyses, in particular the red blood cells and leukocytes per minute (HLM) and the 24-hour proteinuria were normal ; the bacilloscopy and the quantiferon test were negative. On imaging, the pulmonary CT scan showed an interstitial syndrome ; the ECG, cardiac Doppler and venous Doppler of the limbs were normal ; the arterial Doppler of the four limbs showed a stenosis of less than 50% of the dorsal digital arteries of the upper limbs and a stenosis of less than 50% of the intermetatarsal arteries of the lower limbs.

Systemic lupus erythematosus and systemic scleroderma are ruled out because they do not meet the ACR (1997) classification criteria for systemic lupus erythematosus (2 points/11) and the new ACR/EULAR criteria for systemic scleroderma (5 points/32) respectively. The diagnosis of Mixed Connective Tissue Disease or SHARP Syndrome was retained based on the diagnostic criteria:

- Kasukawa's Criteria: one common symptom (Raynaud's phenomenon), the presence of anti-U1-RNP antibodies and two mixed symptoms (polyarthritis, sclerodactyly and pulmonary fibrosis).
- Sharp's Criteria: two major criteria (Raynaud's phenomenon and sclerodactyly), one minor criterion (arthritis) and the presence of anti-U1-RNP antibodies.

The treatment instituted in our patient was a corticosteroid therapy (40 mg per day) at a decreasing dose, azathioprine 100 mg per day, hydroxychloroquine 400 mg per day, lovenox® (enoxaparin) 1.2 IU per day subcutaneously for 5 days and sintrom® (Acenocoumarol) 4 mg per day at a progressive dose with monitoring of the INR up to the effective dose.

After 2 weeks of treatment, the capillary recoloration time is less than 1 second, whereas it was 4 to 6 seconds before the beginning of the treatment.

REVIEW OF THE LITERATURE

From an epidemiological perspective

The incidence of mixed connective tissue disease in the Caucasian population is not known. In Japan it is estimated at 2.7 per 100,000 inhabitants. Mixed connective tissue disease predominantly affects women (sex ratio female/male 16-7911) [2, 3]. The majority of cases occur between the second and third decade of life.

Diagnostically

Several studies have compared the specificity and sensitivity of the criteria. In the study by Amigues et al [4], the Alarcon-Segovia, Sharp and Kasukawa criteria showed a sensitivity of 62.5%, 100% and 56.2% respectively and a specificity of 86.2%, 38% and 65.5% respectively. Based on these results, the use of the Alarcon-Segovia criteria is recommended. A gain in sensitivity seems to be obtainable by replacing the term "myositis" with "myalgia", with sensitivity increasing from 62.5% to 81.3%. Previous publications have used mainly the Alarcon-Segovia criteria because of their simplicity in differentiating mixed connectivitis from other connectivities. The Kasukawa criteria were more specifically used to study the symptoms of mixed connectivity [5].

Therapeutic aspect

- Raynaud's syndrome is the most frequent problem. Preventive measures should be implemented : prevention of sun exposure, sun cream [1, 6]. It is also recommended to discontinue estrogen-progestin contraception. Mild forms of exanthema, photosensitivity and ulceration respond to dermocorticoids, cortisone and hydroxychloroquine [1, 7]. Severe forms require treatment with systemic corticosteroids, immunosuppressants (azathioprine). Intravenous immunoglobulin is an alternative in resistant forms [8]. Prophylactic measures are useful. Exposure to cold should be avoided, extremities should be protected against microtrauma, smoking and vasoconstrictive treatments should be stopped.
- In the case of non or slightly destructive joint damage, a first line of treatment combining NSAIDs and hydroxychloroquine should be considered [1]. If the symptomatology persists, a trial with small doses of corticosteroids (10mg/day) may be useful. In case of refractory or erosive involvement similar to that observed in rheumatoid arthritis, methotrexate is used in the absence of contraindication [9].

Evolution

Several longitudinal studies have followed up clinically patients with mixed connectivitis. One of the most recent studies provides a follow-up of 47 patients over a period of 3 to 29 years (15±8years) [7]. The initial clinical picture includes Raynaud's phenomenon (74%), polyarthralgia and arthritis (68%), hand swelling (45%), skin rash (13%), pleurisy/pericarditis (19% of patients). It is completed during the course of the disease and at the last evaluation includes Raynaud's phenomenon and polyarthritis in 96% of cases, swelling of the hands, esophageal hypomotility, pulmonary

involvement in 66%, myositis in 51% of cases. PAH affected 23% of patients, skin rash 53%, sclerodactyly 49%, central nervous system involvement 17%, renal involvement Il%. In total, the initial picture marked by Raynaud's phenomenon, arthralgia and the pudgy appearance of the fingers is completed with time by muscular, pulmonary, pleuropericardial and sometimes renal involvement.

In the most recent follow-up study of patients with mixed connectivity [7], the mortality rate reached 23% after an average of 15 years of follow-up. Other older studies with shorter follow-up times show a mortality rate of 12-13%.

The two main causes of death in mixed connective tissue disease are Pulmonary Arterial Hypertension (PAH) related complications and infectious complications [7, 10].

CONCLUSION

Mixed connective tissue disease or SHARP syndrome is relatively rare and the vast majority of people with the disease are women. The disease seems to begin most frequently around the age of 30 but can occur at any age. It is usually diagnosed on the basis of the patient's medical history, a physical examination revealing the presence of some connective tissue disease and a positive U1-RNP antibody screen. This antibody may be present in other connective tissue diseases, such as scleroderma and SLE, but is almost always present in mixed connectivitis. In this study, we report a case diagnosed in a 37-year-old female patient at the CHU Aristide LeDantec in Dakar, Senegal.

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