An Interesting Case Series Of Mixed Connective Tissue Disorder With Intricate Features Of Systemic Lupus Erythematous.

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Abstract
Mixed connective tissue disorder (MCTD) is a rare autoimmune clinical entity with features of an overlapping syndrome, including systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, polymyositis, and dermatomyositis. The annual incidence of mixed connective tissue disorder (MCTD) was 1.9 per 10,000 population. In this study we described the progonosis, clinical features, treatment of mixed Connective tissue disorder with systemic lupus erythematous of three patients in a clinical center of Hyderabad. It should be of great interest to internal medicine and rheumatology diagnosticians. A long-term treatment and management plan is crucial for patients with mixed connective tissue disorders (MCTD). Based on our study we concluded that, patient's condition got better by prescribing corticosteroid therapy.

Key words: MCTD, systemic lupus erythematous, corticosteroid

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INTRODUCTION

MCTD was defined in 1972. MCDC is a rare systemic autoimmune disease with an overlapping feature of at least two connective tissue diseases (CTD), including systemic lupus erythematous, systemic sclerosis, polymyositis, dermatomyositis, and rheumatoid arthritis. In addition to the presence of an antibody against U1-ribonucleoprotein (RNP), previously known as ENA antibody, the antibody is unique [1]. The mixed connective disease is most commonly associated with Raynaud's phenomenon, arthralgias, swollen joints, esophageal dysfunction, muscle weakness, sausage-shaped fingers, and the presence of anti-ribonucleoprotein (RNP) antibodies [2]. According to a Norwegian study, living adult MCTD prevalence was 3.8 per 100,000 in 2008. Females are more likely to suffer from MCTD, with a male: female ratio of 6:1[3]. MCTD pathophysiology is unknown, but post-translational modifications of U1-snRNP 70k generate pathogenic neoepitopes. As a result, autoreactive B and T cells (mainly CD41) recognize U1-snRNP 70k and produce auto Abs. The activation of innate immune receptors, such as Toll-like receptors, Fc receptors, and complement receptors, by anti-U1snRNP antibodies and their antigen, leads to vascular disease pathogenesis and tissue injury [4]. Alarcon-Segovia is one of the most commonly used diagnostic criteria for MCTD, which is characterized by a high titer of anti-U1-RNP (over 1 per 1600) and three clinical manifestations, including Raynaud's phenomenon, hand edema, synovitis, and acrosclerosis [5]. The most common SLE occurs in MCTD. SLE is an autoimmune connective tissue disorder that includes renal, cardiac, hematologic, integumentary, gastrointestinal, and even neuropsychiatric manifestations [6]. Systemic lupus erythematosus (SLE) is characterized by discoid rash, serositis, oral ulcer, arthritis, photosensitive rash, blood dyscrasia, and neurological disorder.

This article illustrates three cases of mixed connective tissue disorders with systemic lupus erythematosus.

Case presentation

Case 1:

A 48 year female patient of Indian origin came to the hospital with a chief complaint of bleeding gums, numbness, swelling and burning sensation over the bilateral foot more over the toes for 2 weeks. The patient was taking tablet mycophenolate mofetil 500mg BD due to previous history of mixed connective tissue disorder. Patient having no known history of epistaxis, melena, arthralgias, Raynaud's phenomenon, arthritis, hair loss, and GERD.

On examination, the patient was conscious, coherent, and febrile. Her pulse rate was 90 beats per minute, Bp was 120/80 mmHg. The patient's oxygen level was 90% on room air, CVS was, S_1S_2+ and presence of bilateral pedal edema. On dermatology examination patient had mouth ulcer, skin rashes over the body, butterfly-shaped rash present across the nose and cheeks, joint pain, and swelling present in the bilateral limbs.

The clinical laboratory test revealed that the lower level of hemoglobin was 8.8 g/dl (normal- 13-16 gm/dl), the lower level of mean corpuscular volume was 77.5 fl (normal 80-100 fl), and lactate dehydrogenase was normal as 177 IU/L. Her platelet count was 40,000 /mm3 on the smear. Her liver enzymes revealed an elevated level of alanine aminotransferase (ALT), i.e. 132 IU/L (normal 5–45 IU/L), and aspartate aminotransferase (AST) 68 IU/L (normal 5–45 IU/L**).**

Antinuclear antibodies (ANA) and Direct Coombs Test (DCT) were positive. The prognosis of Mixed connective tissue disorder with systemic lupus erythematosus was made primarily based on the aforementioned clinical and laboratory findings.

The patient was given Inj methyl prednisolone 1gm in 100 ml NS for 5 days, after 5 days the patient was Inj methyl prednisolone was stopped and converted to tablet prednisolone 60 mg OD for 15 days. The immunosuppressant drug mycophenolate

mofetil 500mg BD was continued during the hospital stay. Tab. Hydroxychloroquine 200 mg BD was given for 7 days. After 15 days of treatment, the patient had improvement in their bleeding gums, numbness burning sensation over the bilateral foot, mouth ulcer, and skin rashes. The medications prescribed during discharge were mycophenolate mofetil 500mg BD, tablet methylprednisolone 10 mg BD and advised the patient to come to our outpatient department for further evaluation.

Case 2

A 35-year female patient came to the hospital due to a chief complaint of blackish discoloration of the left 4th toe and 5th toe for 1-month, oral ulcer, burning micturition, and facial puffiness for 5 days, burning sensation in all fingers and toe for 1 month. No chief complaint of abdominal distention, and decreased in urine output.

On examination, the patient was conscious and febrile. Bp was 130/90 mmHg, pulse rate was 96 beats for minutes. CVS was S_1S_2+. Examination of dermatology confirmed multiple hyperpigmented scaly plaques present over the neck, and upper back, oral ulcer, dry skin, alopecia, facial puffiness, multiple small healing ulcers over the forearm, buttock, and lips, and hair loss were present in the patient.

The clinical laboratory test revealed that elevated the level of WBC was 20.40 × 109/L (normal range- 4.5 to 11.0×109/L), ESR Level was elevated (normal <20 mm/hr), and platelet level was normal. Antistreptolysin o (ASO) level was elevated at 527 IU/ML (normal- 200 IU/ML). C3 and c4 protein tests, Peripheral antineutrophil cytoplasmic antibodies (p-ANCA) test, rheumatoid factor test was found to be positive and Liver function test was found to be abnormal. The erythrocyte sedimentation rate (ESR) level was elevated at 110 mm/hr (normal range - < 20 mm/hr). The antinuclear antibody test was positive by the Elisa method. The prognosis of Mixed connective tissue disorder with systemic lupus erythematosus was made primarily based on the aforementioned clinical and laboratory findings.

The patient was given an Inj. Methylprednisolone 1gm intravenously OD for 10 days. After 10 days Inj. methyl prednisolone was stopped and converted to tablet prednisolone 50 mg OD for 7 days. Inj. ceftriaxone 1gm intravenously BD was given for 7 days. Zytee gel (choline salicylate and Benzalkonium chloride solution) local application was given for mouth ulcers. Biologic medications of Inj. Rituximab 500 mg intravenously OD was given for 4 weeks. Tab. Hydroxychloroquine 100 mg BD was given for 7 days. Mucopain gel local application was given to the patient for sore throat and skin irritation. Liquid paraffin was given to the patient for dry skin. Sunscreen local application was given to the patient. After 15 days of treatment, the patient's mouth ulcer was found to be cured, skin rashes, hair loss, subsided multiple hyperpigmented scaly plaques present over the neck, and upper back, oral ulcer, dry skin, alopecia, facial puffiness, subsided multiple small healing ulcers over forearm, buttock, and lips. The medications prescribed during discharge were tablet methylprednisolone 10 mg BD, protein diet, Zytee gel for local application, and advised the patient to come to our outpatient department for further evaluation.

Fig.1: The figure represents the hyperpigmentated scaly plaques on her upper back.

Fig.2: The figure represents the swelling of palm.

Case -3

A 63-year female patient came to the hospital due to a chief complaint of oral ulcer, burning micturition, and facial puffiness, low-grade fever, pain, and swelling in bilateral lower limbs, difficulty in lifting the hand above the head, mouth ulcer, rash on the neck and face and had weight loss since 30 days.

On examination, the patient was conscious and febrile. Her BP was 130/90 mmHg, pulse rate was 96bpm. CVS was S_1S_2+. The clinical laboratory test revealed that elevated the level of WBC was 26.40 × 109/L (normal range- 4.5 to 11.0×109/L), ESR Level was elevated 67 mm/hr (normal <20 mm/hr), and platelet level was normal. Antistreptolysin o (ASO) level was elevated at 427 IU/ML (normal- 200 IU/ML). C3 and c4 protein tests, Peripheral antineutrophil cytoplasmic antibodies (p-ANCA) test, rheumatoid factor test, and Liver function test was normal. The erythrocyte sedimentation rate (ESR) level was elevated at 210 mm/hr (normal range - < 20 mm/hr). The antinuclear antibody test was positive by the Elisa method. The prognosis of Mixed connective tissue disorder with systemic lupus erythematosus was made primarily based on the aforementioned clinical and laboratory findings.

The patient was given an Inj. Methylprednisolone 1gm intravenously OD for 10 days. After 10 days the patient was stop Inj methyl prednisolone and converted to tablet prednisolone 50 mg OD for 5 days. Inj. ceftriaxone 1gm intravenously BD was given for 5 days. Zytee gel (choline salicylate and Benzalkonium chloride solution) local application was given for mouth ulcers. Biologic medications of Inj. Rituximab 500 mg intravenously OD was given for 4 weeks. Tab. Hydroxychloroquine 200 mg OD was given for 7 days. . Mucopain gel local application was given to the patient for sore throat and skin irritation. Liquid paraffin was given to the patient for dry skin. sunscreen local application was given to the patient. After 10 days of treatment, the patient has improved in their mouth ulcer, skin rashes, facial puffiness, and swelling in bilateral lower limbs. The discharge medication was prescribed as tablet methylprednisolone 10 mg BD, protein diet, Zytee gel for local application, and advised the patient to come to our outpatient department for further evaluation.

DISCUSSION:

The clinical cases that were presented were from Hyderabad's urban and rural districts. Both of them are females, and they were between the ages of 48yrs, 35yrs & 63yrs at the time of diagnosis, which is in line with the analysis of epidemiological research and the predominance of the female sex [7].

Regarding the initial clinical presentation, we noticed a variety of signs and symptoms in the patients we looked at, despite the fact that the literature typically lists Raynaud's phenomenon, hand swelling, and arthralgia as the most common initial symptoms. In our case report, we discovered constitutional symptoms like fever and asthenia in both the cases, which were then followed by multiple hyperpigmented scaly plaques, bleeding gums, oral ulcers, and edema. MCTD patients who first displayed with severe myositis. Subclinical myopathy is seen in nearly 60% of patients with inflammatory myositis [8].

Few instances in Sharp's study required the use of more than 10 mg/day of prednisone, and a favorable response to the use of steroids was seen with a gradual reduction and symptom control strategy. In our cases the patients, who needed steroids took more than 10 mg of prednisone per day [9].

The patient initially had a lot of weakness and complained of discomfort in many parts of her body. Her AST/SGOT, LDH, and CPK levels were quite high, raising the suspicion that myositis was present. Electromyogram and nerve conduction investigations confirmed this with results that are consistent with inflammatory myopathy. The extensor side of the metacarpophalangeal and interphalangeal joints on both hands displayed Gottron's papules, a defining feature of dermatomyositis (DM) [10,11].

Generalized malaise, arthralgia, myalgia, and low-grade fevers are a few of the non-specific clinical signs and symptoms of MCTD that resemble those of SLE. Another typical overlap symptom is upper gastrointestinal tract involvement, which affects 60–80% of MCTD patients. Raynaud phenomenon, absence of renal and CNS illness, pulmonary hypertension, and anti-U1 RNP are four characteristics that strongly suggest a diagnosis of MCTD [12].

In the above reported cases, in 1st case the ANA test was found to be positive, in the 2nd case the rheumatoid factor test and Peripheral antineutrophil cytoplasmic antibodies (p-ANCA) test was found to be positive and in 3rd case antinuclear antibody test was found to be positive. By which the cases were diagnosed as Mixed Connective Tissue Disorder with Systemic Lupus Erythematous.

Both the innate and adaptive immune systems are involved in the development of MCTD, the immunopathology is complicated. Apoptosis causes structural changes to antigens, and minute immunogenic changes cause self-antigens to develop an immune response. Immunoglobulin-G autoantibodies that are directed against particular spliceosome components are also overproduced. Research also supports the involvement of CD4 and CD8 T lymphocytes as well as B cell activation. Anti-U1RNP and anti-U1-70 kd autoantibodies are present in high amounts as a result of B-lymphocyte hyperactivity the same was observed in the above reported cases. Anti-U1-70 kd - reactive T cells are created during T lymphocyte activation. Human leukocyte antigen (HLA)-DRB1 * 04/*15 major histocompatibility genes have also been linked to a genetic relationship [13].

CONCLUSION:

Despite the fact that MCTD is incurable, medications are used to control the symptoms and pathology of the disease to enhance quality of life. But it is always necessary to diagnose early in order to decrease morbidity and disease related complication. Nonsteroidal anti-inflammatory medicines (NSAIDs) are frequently used to treat it, along with corticosteroids to reduce inflammation and disease-modifying antirheumatic therapies such hydroxychloroquine, methotrexate, and cyclophosphamide. Pulse methylprednisolone therapy was applied in our case due to the myositis and myopathy present. Long term usage of corticosteroids can result in decreased bone density. Hence, calcium and vitamin D3 should be prescribed along with steroid therapy.

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