Mixed connective tissue disease presenting as quadriparesis in a female

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ABSTRACT

Mixed connective tissue disease (MCTD), or overlap syndrome, is a multisystem autoimmune disease characterized by a combination of clinical features similar to those of polymyositis, systemic sclerosis, and rheumatoid arthritis. MCTD patients present with a distinct rise (high titers) of anti-U1 ribonucleoprotein antibody in serum. Here, we present the case of a 45-year-old female who presented with subacute onset weakness on all four limbs and later on diagnosed as overlap syndrome with severe myositis.

Key words: *Autoimmune, Mixed connective tissue disease, Overlap syndrome, Polymyositis, Rheumatoid arthritis, Systemic sclerosis*

Mixed connective tissue disease (MCTD), also known as "overlaps syndrome," is an autoimmune disorder with an overlap of rheumatoid arthritis (RA), polymyositis, systemic sclerosis (SSc), and systemic lupus erythematosus (SLE). MCTD has a high titer of a specific antibody anti-U1 ribonucleoprotein (U1RNP) in their serum. It was first described by Sharp *et al*., in 1972 [1]. The prevalence of MCTD is 1.9/100,000 population per year (3.1/100,000 population among females and 0.7/100,000 population among males) [2,3]. Prevalence is high in females than in males and the F: M ratio varies from 3:1 to 16:1 [3]. The onset of MCTD can occur anytime from early childhood to elderly adulthood, but the average age of onset is 37 years [4].

MCTD is quite rarely reported in India. The patients usually present with mixed clinical findings of SLE, RA, polymyositis, and SSc. Definite diagnostic criteria have been put forth. Our case was unique as the patient presented predominantly as weakness in all four limbs and clinical examination revealed features of other disorders.

CASE REPORT

A 45-year-old woman presented to us with weakness in all four limbs for 2 months. She noticed weakness in her proximal lower limbs in the form of difficulty in getting up from squatting position and climbing stairs associated with pain in thighs. After 2 weeks of lower limb involvement, the weakness involved proximal upper limbs in the form of difficulty in combing hair and reaching to the objects above shoulder level while working in the kitchen. There was no history of involvement of the distal muscles, back pain, neck pain, tingling in extremities, paresthesia, bladder bowel involvement, blurring of vision, vomiting, and fever. On asking leading questions, there was a history of arthralgia involving large and small joint for 7 months and morning stiffness lasting >1 h in the hand joints for 4 months along with Raynaud's phenomenon. For these complaints, the patient visited a local practitioner and was treated with intermittent painkillers and calcium supplements.

On clinical examination, vitals were normal (pulse=80/min regular, BP was 110/70 mmHg, and respiratory rate=16 breaths/min). Her oxygen saturation was 99% while breathing ambient air. There were no signs of icterus, clubbing, cyanosis, and lymphadenopathy. The jugular venous pressure was 4 cm of water at 45° and edema was absent. Oral cavity examination revealed multiple oral ulcers.

She had a puckered face (Fig. 1) and pinching of skin was not possible. Musculoskeletal and dermatological examination revealed stiffness in small joint and sclerodactyly (Fig. 2). Neurological examination revealed normal higher functions and cognition, no cranial nerve abnormality. In motor system examination, power was 5/5 in the distal upper and lower limb and 3/5 in proximal muscles of upper and lower limb. There was palpable tenderness in both deltoids, quadriceps, and hamstrings. Deep tendon reflexes were normal and planters were bilateral flexors. Sensory examination was normal. On the background of sclerodactyly and muscle weakness with joint involvement, a possibility of MCTD was kept and she was investigated.

Investigations revealed hemoglobin - 8.9 g% and normocytic normochromic RBC. Total and differential leukocyte counts were within normal limits. Erythrocyte sedimentation rate was 68 mm in the 1st h. A spot urine albumin-to-creatinine ratio was 68 mg albumin per gram creatinine (20–200 mg/g). Rheumatoid factor (RA) was positive, antinuclear antibody (ANA) was positive (122.92 IU/ml) with speckled pattern, and U1RNP antibody was strongly positive, 1217.36 units by ELISA (>80 strongly positive). The hemagglutination titer of U1RNP was

1:1732 (>1:1600). Creatinine phosphokinase (CPK) was raised at 4614 IU (21–192 IU). Electromyography (EMG) showed myopathic potentials. X-rays of the hands showed periarticular osteopenia and synovitis (Fig. 3). A muscle biopsy was obtained from the quadriceps muscle, and histopathologic slide was made which shows the features of degenerating fibers, necrotic fibers, and internalization of nuclei, suggestive of polymyositis (Fig. 4). Her barium swallow, upper gastrointestinal endoscopy, and gastrointestinal endoscopy were normal. All the clinical and laboratory findings of our patient were shown in Table 1.

A final diagnosis of subacute onset, gradually progressive lower motor neuron quadriparesis due to polymyositis was made. Most likely, overlap syndrome was kept and the diagnosis was confirmed using diagnostic criteria of MTCD.

The patient was started on pulse methylprednisolone therapy at a dose of 1000 mg per day for 3 days and started on tablet prednisolone 40 mg/day from the 4th day. Tablet methotrexate was added at a dose of 15 mg/week as add-on immunosuppressant and tablet amlodipine 5 mg per day was added for Raynaud's phenomenon. After 2 weeks, CPK levels decreased, pain in muscle decreased, and the power of the muscle increased to 4/5. The dose of corticosteroids was tapered over next 3 weeks to a maintenance dose of 10 mg/day, and tablet methotrexate was continued with folic acid supplement. The patient is awaiting subsequent follow-up.

Figure 1: Puckered face

Figure 2: Stiffness in small joint and sclerodactyly

DISCUSSION

MCTD is a rare autoimmune condition affecting almost all organs of the body with a majority of the patients being female [3]. This condition presents with overlapping features of other connective tissue diseases such as SLE, polymyositis, sclerosis, and RA. The major diagnostic criterion for MCTD is raised titer of ANA (anti-U1RNP antibody). The term overlap syndrome has been described for the patients who have signs of two or more connective tissue disease simultaneously.

The immunopathology of the development of MCTD is complex as both the innate and adaptive immune system play role. Structural modifications of antigens occur during apoptosis and subtle immunogenic alterations drive the self-antigens to become immunogenic. There is also an overproduction of immunoglobulin-G autoantibodies which are directed against select components of the spliceosome. Evidence also prove that B-lymphocyte activation, and CD4 and CD8 T-lymphocyte participation occur in the process. B-lymphocyte

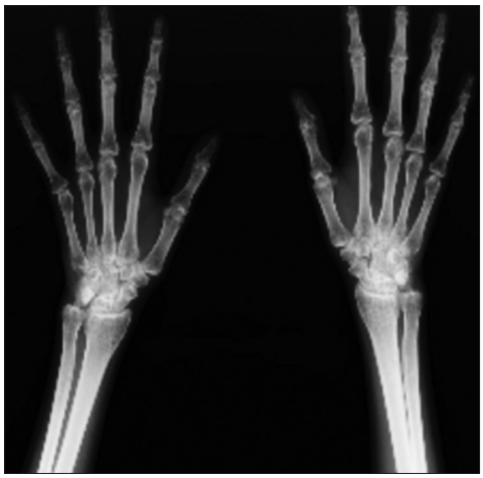

Figure 3: Periarticular osteopenia with synovitis

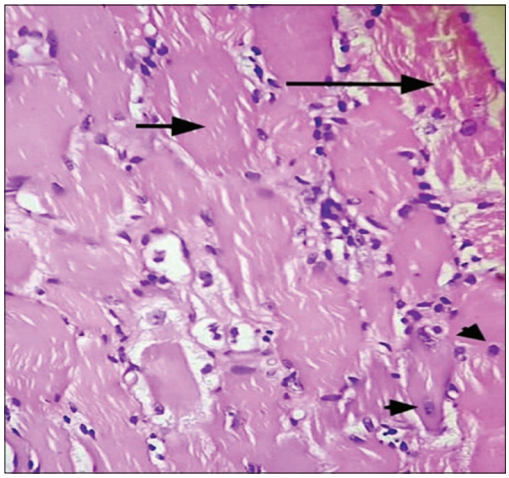

Figure 4: Histopathologic slide showing degenerating fibers (short arrow), necrotic fibers (long arrow), and internalization of nuclei features suggestive of polymyositis (arrow tip)

Table 1: All the clinical and laboratory findings of our patient (laboratory values mentioned in text)

SLE-like symptoms	Polyarthritis, thrombocytopenia, ANA positive, oral ulcers, and proteinuria
Polymyositis-like findings	Proximal muscle weakness, myogenic pattern on EMG, elevated levels of muscles enzymes (CPK), and histopathologic evidence
Rheumatoid arthritis like findings	Morning stiffness, arthralgia, rheumatoid factor positive, and X-ray hands; osteopenia and synovitis
Scleroderma-like findings	Sclerodactyly, pulmonary function test shows restrictive pattern

EMG: Electromyography, SLE: Systemic lupus erythematosus, CPK: Creatinine phosphokinase, ANA: Antinuclear antibody

hyperactivity results in high levels of anti-U1RNP and anti-U1-70 kd autoantibodies. T-lymphocyte activation produces anti-U1-70 kd - reactive T-lymphocytes. A genetic association has also been confirmed to be associated with major histocompatibility genes human leukocyte antigen (HLA)-DRB1*04/*15 [5,6].

The differential diagnosis of MCTD is SLE, RA, scleroderma/SSc, polymyositis and dermatomyositis, idiopathic pulmonary arterial hypertension, and Raynaud's phenomena. Different diagnostic criteria have been laid down for MCTD. These are by Sharp, Alarcón-Segovia, Kasukawa, and Kahn. A comparative study among all these criteria showed that the Alarcón-Segovia criteria, which have 62.5% sensitivity and 86.2% specificity, more accurately diagnose MCTD. The Kahn criteria also have a better diagnostic accuracy [7].

The Alarcon-Segovia diagnostic criteria consist of a positive anti-U1RNP titer (>1:1600) and at least three of the following five clinical findings: Hand edema, synovitis, biologically or histologically proven myositis, Raynaud phenomenon, and acrosclerosis with or without proximal SSc [7,8]. Our patient satisfies the following Alarcon-Segovia diagnostic criteria (positive anti-U1RNP, myositis in histopathology examination, Raynaud phenomena, and SSc). The Khan criteria [7,8] were as follows: Serologic - high titer of anti-U1RNP corresponding to a speckled ANA of >1:1200 titer and clinical - swollen fingers, synovitis, myositis, and Raynaud's phenomena. The final diagnosis is based on serologic criteria, Raynaud's phenomena, and any two of the remaining three clinical criteria. Our patient also satisfied Kahn criteria (serologic+Raynaud phenomena, synovitis, and myositis).

Although MCTD is incurable, drugs are given to control the signs and symptoms and modify the disease pathology to improve the quality of life. It is usually treated with nonsteroidal anti-inflammatory drugs for pain relief, corticosteroids for the reduction of inflammation, and disease-modifying antirheumatic agents such as hydroxychloroquine, methotrexate, and cyclophosphamide are used. Pulmonary hypertension is treated with Bosentan, Raynaud's phenomenon is treated with calcium channel blockers like amlodipine [9-11]. Our case had myositis and myopathy so pulse methylprednisolone therapy was given.

CONCLUSION

MCTD is a rare form of an autoimmune disease which involves each organ system and overlaps between four different autoimmune diseases. Different diagnostic criteria have been published. Among all, Alarcon-Segovia and Kahn's criteria are widely used. Treatment is usually done for the symptoms, and disease-modifying drugs are used to quiescent the immunopathologic progression.

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