Case Report

Mixed Connective Tissue Disease- A Rare and Distinct Rheumatological Case Study

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Abstract

In this article we present this 35 year old lady with history of fever, multiple joints pain with swelling and skin conditions such as tightening, glistening and bluish discoloration while exposure to cold. After taking detailed history and clinical examinations, she was found to have features consistent with multiple rheumatological conditions such as systemic lupus erythematosus and systemic sclerosis. With directed and specific investigation she was diagnosed to have Mixed Connective Tissue disorder.

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Case report

Mrs. Beauty Begum, 35 years old housewife, mother of two kids, hailing from Tangail presented with the complaints of intermittent fever, generalized bodyache, multiple joints pain with swelling involving hands, knees and ankles for the 3 months duration. She did not have any morning stiffness, skin nodules or shortness of breathing. She also noticed that her skin of face, forehead, arms and fore-arms has become tightened for 1 month. On further query, she added that she is having pain and numbness of hands while handling water (especially cold). There is change in skin colour and experienced pain under the skin which is not related to the joint pain. She does not give any history of leg swelling, chest pain, dryness of eyes or mouth, difficulty in swallowing or hair loss.

On clinical examination, she had expressionless face, tight and glistening skin of face with loss of wrinkles on forehead. The perioral skin area was tightened and she could not open her mouth fully as she could have previously. The skin of arm, fore-arm was tightened and fingers examination revealed sclerodactyly with superficial ulcers in metacarpophalangeal and interphalangeal joints of both hands. There is pain, swelling and tenderness of joints of hands, ankles and knees but no deformity. There was no cervical spine or joints lower back involved. Her BP was 110/70 mmHg, pulse rate 96, Temp-101^{0}F.

In clinical summary she had fever, polyarthritis, sclerodactyly, Raynaud's phenomenon, sclerosis and calcinosis of skin which are suggestive of combined features of SLE and systemic sclerosis. There was no indication of other rheumatological conditions such as rheumatoid arthritis or dermatomyositis or polymyositis etc. She did not have any shortness of breath, dysphagia, peripheral oedema that could suggest pleuropulmonary, gastroesophageal or renal involvement. The provisional diagnosis was Mixed connective tissue disease. Overlap syndrome of rheumatological diseases and undifferentiated connective tissue disease (UCTD) were included in differential diagnoses.

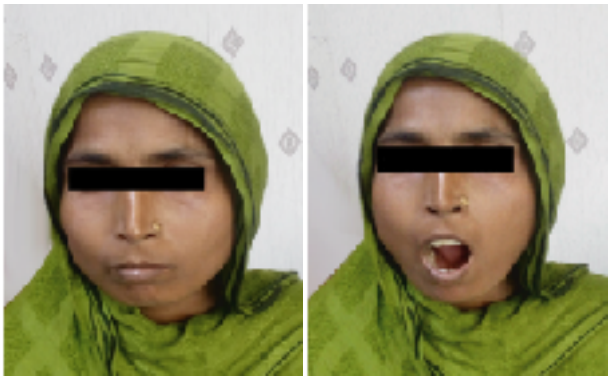

Fig1: Expressionless face, tight and glistening skin

The relevant investigations were done and reports are given below.

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Table - I: Investigation reports

• FBC- Hb 9.1 gm%, MCV 60.9 fl, ESR 90mm in 1st hour, TC & DC within normal limit • PBF- microcytic, hypochromic anaemia • CRP- 24 • Random blood sugar- 5.8 mmol/L • Renal function tests- normal • Liver function test- normal • Urine R/E- normal findings • CXR- normal findings • ECG- within normal limit • Colour doppler Echo- normal • USG of whole abdomen- normal	• X-ray hands- soft tissue swelling, no joint deformity was noted • Autoantibodies: ▪ **ANA- positive** ▪ RF test- negative ▪ Anti CCP- negative ▪ Anti ds-DNA- negative ▪ **Anti SM Ab- positive** ▪ **Anti SSA Ab- positive** ▪ Anti SSB Ab- negative ▪ **Anti U1-RNP- positive** ▪ Anti Scl-70 Ab- negative ▪ Anti Jo-1 Ab- negative

Thus, the patient was diagnosed to have Mixed Connective tissue disorder (MCTD) having features of systemic lupus erythematosus, systemic sclerosis and Raynaud's phenomenon. The diagnoses excluded are rheumatoid arthritis, limited systemic sclerosis, dermatomyocitis and sjogren's syndrome. Apart from the clinical suggestions the patient has positive ANA, rheumatoid factor and positive anti U1-RNP antibody which is characteristic feature for MCTD. The patient is being treated with collaboration with Medicine and Physical medicine consultants. She is put on Methotrexate, Hydroxychloroquine, NSAIDs with proton pump inhibitors and pulse steroid (oral prednisolone) whenever needed. She is doing well and disease activity is under control. She is under close follow up regarding complications of management and disease diversity.

Introduction

MCTD was first described by Sharp[1] as a distinct syndrome in which the combination of features similar to those of systemic lupus erythematosus (SLE), systemic sclerosis (SSC), rheumatoid arthritis (RA) and dermatomyositis/polymyositis and The disease was considered unique as it was associated with autoantibodies to a Ribonuclease - sensitive component of extractable nuclear antigen (ENA) now known as RNP[2]. It is a separate entity other than UCTD and overlap syndromes[3].

MCTD is now recognized to occur throughout the world. It is predominantly a disease of females, with female to male ratio of 16:1[4] . The disease is seen among all age groups range from 4 - 80 years; the mean age of onset in adult is 35 years. There is both T-cell & B cell response with less immune complex formation. The characteristic lesions in the involved organs are intensive obliterative, proliferative vascular lesions in large, medium and small vessels with less inflammatory infiltrates.

In the early phases of the MCTD many patients complain of easy fatigability poorly defined myalgias, arthralgias and Raynaud's phenomenon; systemic involvements are as follows-

- Fever of unknown origin may be the presenting feature of MCTD[5]. The most common skin change is the Raynaud's phenomenon, others are malar rash, generalized erythematous rash.
- Raynaud's phenomenon is seen in 75%-100% of patients. Approximately 60 percent of patients develop an obvious arthritis. Myalgias and myositis can be seen in 30%-50% of patients.
- The gastrointestinal symptoms may range from heartburn, dysphagia, diarrhea and symptoms of malabsorption. Disordered motility in the upper gastrointestinal tract is the commonest problem[6].
- Pleuropulmonary involvement is common, it may be asymptomatic or the patient may present with pleurisy and effusion, interstitial lung disease, pulmonary arterial hypertension (PAH)[7].
- All three layers of the heart may be involved in MCTD with abnormal ECG findings[8].
- Neurological manifestations are less common, presenting as aseptic meningitis, trigeminal neuralgia, demyelination, transverse myelitis and peripheral neuropathy.
- The absence of severe renal disease is a hallmark of MCTD; it is possible that high titers of anti-RNP antibodies, which are characteristic of MCTD, may protect against the development of diffuse proliferative glomerulonephritis. But patients may have glomerulonephritis, nephritic syndrome or renal crisis of scleroderma.

Discussion

Diagnosis is clinical along with supporting laboratory investigations. There criteria are-

A. Serological criteria: positive Anti RNP antibody.

B. Clinical Criteria: (1) Swollen hands (2) Synovitis (3) Myositi (4) Raynaud's phenomenon (5) Acrosclerosis. MCTD is present if A is associated with three or more clinical criteria.

The laboratory findings are anemia, leucopenia, elevated erythrocyte sedimentation rate, hypergammaglobulinemia (100%), positive combs test, and Rheumatoid factor positive in 50 to 70% of patients[9]. Antinuclear antibody positivity is seen in 100% of patients in high titre with coarse speckled pattern. Anti U1RNP antibodies by haemagglutination test is highly characteristic feature of MCTD. Many patients also make antibodies directed against hnRNP-A2, fibrillin-1, and nucleosomes, but not to RNA polymerases[10]. The absence of anti-Sm antibodies and anti-DNA antibodies in a seropositive for anti U1RNP is an important discriminating finding for MCTD from SLE[13]. Also scleroderma-specific antibodies, including anticentromere and anti-Scl-70 (topoisomerase) are absent[13]. Antiphospholipid antibodies occur, but are less common than in those with SLE[11].

No controlled trials have been performed to guide therapy. Instead, the management of patients with MCTD generally rests upon the effectiveness of specific therapies for similar problems seen in SLE, scleroderma, or polymyositis. By comparison, scleroderma-like features (eg, Raynaud phenomenon, pulmonary hypertension) are usually less responsive to therapy. NSAIDs are given for pain, calcium channel blockers for PAH, Immunosuppression (steroid and other agents) is particularly required in cases with severe arthritis, pulmonary hypertension and serositis involving pericardium or pleura.

MCTD has relatively good prognosis in view of low prevalence of serious renal disease and life-threatening neurologic problems. Morbidity is quite high in patients with MCTD due to multiple factors including recurrent musculoskeletal pain, fibromyalgia, gastroesophageal acid reflux etc. Mortality associated with MCTD ranges, in different studies, from 16 to 28 percent at 10 to 12 years[12]. Those patients with more features of scleroderma and polymyositis had a worse prognosis. The major causes of death include progressive pulmonary hypertension and its cardiac complications.

References

1. Sharp GC;Anderson PC, Current concepts in the classification of connective tissue diseases. Overlap syndromes and mixed connective tissue disease (MCTD). J Am Acad Dermatol 1980 Apr;2(4):269-79.
2. Farhey Y; Hess EV, Mixed connective tissue disease., Arthritis Care Res 1997 Oct;10(5):333-42
3. Ellman MH; Pachman L; Medof ME, Raynaud's phenomenon and initially seronegative mixed connective tissue disease, J Rheumatol 1981 JulAug;8(4):632-4.
4. Nakae, K, Furusawa, F, Kasukawa, R, et al. A nationwide epidemiological survey on diffuse collagen diseases: Estimation of prevalence rate in Japan.
5. Alarcon-Segovia D, Mixed connective tissue disease and overlap syn dromes. Clin Dermatol 1994 Apr-Jun;12(2):309-16
6. Kotajima L, et al , Clinical features of patients with mixed connective tissue disease: analysis of data collected in nationwide collaborative study in Japan, J Rheumatol. 1996 Jun;23(6):1088-94
7. Bennett RM; Bong DM; Spargo BH, Neuropsychiatric problems in mixed connective tissue disease. Am J Med 1978 Dec;65(6):955-62
8. Kumar MS; Smith M; Pischel KD, Case report and review of cardiac tamponade in mixed connective tissue disease, Arthritis Rheum. 2006 Oct 15;55(5):826-30
9. Ramos-Niembro F; Alarcon-Segovia D; Hernandez-Ortiz J , Articular manifestations of mixed connective tissue disease., Arthritis Rheum 1979 Jan;22(1):43-51
10. Hoffman M; Gray RG, Ibuprofen-induced meningitis in mixed connective tissue disease. Clin Rheumatol 1982 Jun;1(2):128-30.
11. Ueda N et al., Mixed connective tissue disease with fatal pulmonary hypertension and a review of literature. Virchows Arch A Pathol Anat Histopathol 1984;404(4):335-40
12. Gendi NS et al, HLA type as a predictor of mixed connective tissue disease differentiation. Ten-year clinical and immunogenetic followup of 46 patients, Arthritis Rheum 1995 Feb;38(2):259-66.
13. Mixed Connective Tissue Disease and Anti-nuclear Antibodies, Kasukawa, R, Sharp, G (Eds), Excerpta Medica, Amsterdam, 1987. p.9