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CASE REPORT

Mixed Connective Tissue Disorder: A Rare Case Report

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Abstract

MCTD is a rare disease with overlapping features of many connective tissue disorder and the presence of positive anti-U1RNP antibodies with anti-ssA (Ro), anti-ssB (La) being negative. We report a case with fever and edema of upper limb and lower limb small joints associated with violaceous discolouration which on further evaluation led to diagnosis of MCTD. A female aged 44 years presented with history of fever of moderate degree with no diurnal variation and subsides on taking medication for 7 days and had also noticed ecchymoses followed by maculopapular rashes (violaceous) associated with tenderness of fingers and toes (more on exposure to cold). On further evaluation led to a diagnosis of MCTD. This case report urges the clinicians to exercise great caution for connective tissue diseases in patient presenting with similar history. This rare case of disease is uncommon in the available literature, especially for this ethnicity or region. This report should be of great interests to all diagnosticians of internal medicine.

Keywords: Mixed connective tissue disorder; Raynaud's phenomenon; sclerodactyly; Anti-U1nRNP antibody; Scleroderma

Introduction

MCTD is an autoimmune disease which was first described in 1972 by Sharp et al. as a disease syndrome with overlapping features of systemic sclerosis, systemic lupus erythematosus (SLE) and polymyositis.[1] Therefore, MCTD is sometimes referred to as an overlap disease. The initial presentation of the patients usually comprises nonspecific signs such as swollen digits, arthralgia, myalgia or muscle weakness, acid reflux or dysphagia, Raynaud's phenomenon,

shortness of breath on activity, a general malaise and fatigue. Over a period the symptoms are dominated by symptoms of either of one of the three illness along with high titers of anti-U1RNP antibody. The etiology of the mixed connective tissue disorder is unknown but being an autoimmune disease MCTD can run within families and is known to affect women more than men, with female to male ratio of 16:1. [(2)] No causal association and the varied presentation, makes the diagnosis of this rare condition difficult.

We encountered one such case with fever, edema of upper limb and lower limb small joints with violaceous discoloration and tenderness as the initial presentation that eventually led to the diagnosis of MCTD with no complications.

Case report

A 44-year-old female, a known hypothyroid and depression on regular treatment for 2 and 9 years respectively was ad mitted with complaints of fever(intermittent) with no diurnal variation and not associated with chills and rigor with violaceous discoloration and tenderness of small joints of upper limb and lower limb for 7 days. The tenderness was increasing every day in intensity and aggravated on exposure to cold/low temperatures. The fever responded to antipyretics.

On inquiring, she gave history of dyspeptic symptoms since two months with no history of dysphagia or difficulty in opening mouth, but on visualization microstomia was noted.

On examination, mild pallor present and temperature recorded 99.8F. She had edema of upper limb and lower limb small joints with violaceous discoloration and multiple ecchymoses and maculopapular rashes over forearm and lower limb. On palpation tenderness was present as explained above restricting her day-to-day activities and difficulty in getting up from sitting position or holding on to any object due to pain and swelling. Facial skin was taut with pinched up nose.

Physical examination Per Abdomen was normal. Cardiovascular examination was within normal limits. Respiratory system and Nervous system examination provided no abnormal findings.

She was on, Tab. Thyroxine 25mcg 1-0-0, Tab. Oxcarbazepine 150mg 1-0-1, Tab. Chlordiazopoxide + Amitryptaline [25mg/10mg] 0-0-1, Tab. Clonazepam 1mg $\frac{1}{2}$ -0-1, Tab. Respirodone + Tri-hexiphenydyl [2mg/2mg] $\frac{1}{2}$ -0-1

The above mentioned drugs doesn't cause any vasculitis.

On investigating laboratory values are as follows

Hb- 9.4gm%, Total count- 12190cells/cumm, Platelet count-1.06lakh cells/cumm

Peripheral smear- Normocytic Normochromic Anaemia with Leucocytosis and Thrombocytopenia, renal function was normal

Others

HIV 1&2- negative, HbsAg-negative, Anti HCV- negative, Dengue serology-negative, Weil-felix test-negative, Mp card test-negative, Serum calcium- 6.5

Pt/INR: P.time-14.3sec; Control-11.9sec; INR-1.2sec; APTT-24.5sec; APTTcontrol-35sec; Tsh-14.5 mcIU/ml; Urine(routine and microscopy)- within normal limits

Sonography (abdomen and pelvis)-grade 1 fatty changes; -no other significant abnormality detected.

Oesophago gastro duedenoscopy- Features consistent with chronic gastritis.

Psychiatry opinion was taken i/v/o of depression and was opined as Severe depressive episode with psychotic feature and was advised the following, Tab. Sertaraline 25mg 1-0-0; Tab. Zolpidem 5mg 0-0-1; Tab. Clonazepam 0.25mg sos

Dermatology opinion was taken i/v/o skin biopsy, opined as no significant thickening of skin noted[sclerodactyly] or active lesions of disease present at the time of examination for obtaining skin biopsy

X-ray of chest (Posterior-anterior view): within normal limits

2D-echo cardiogram:withn normal limits

Our patient followed the Alarcon-Segovia diagnostic criteria (Table 1) with positive serology and three of five clinical criteria namely Raynaud's phenomenon, edema of hand, synovitis, myositis. Our patient also followed the Kasukawa diagnostic criteria (Table 2) with both the common symptoms of Raynaud's and swollen hands being present associated with positive serology and mixed findings of thrombocytopenia, muscle weakness.

Serological examination showed antibody to U1-nRNP/Sm positive. However other antinuclear antibody was negative (Table 3).

Diagnosis of MCTD was made

The management of the patient included, antibiotics, antipyretics, and medications for hypothyroidism were continued. Later the following were added to the management:

Tab. Shelcal 500mg 1-0-1; Inj. Dexamethasone 4mg I.V. 1-1-1 x 6days; Tab. Prednisolone 40mg 1-0-0; Tab. Nifedipine 10mg 1-0-0

The patient was discharged after 9days of hospitalization and is currently on tapering doses of steroids (every five days to 30mg, 20mg,10mg, 5mg) with continuation of Thyroxine and medications as advised by psychiatrist.

Table 1. Alarcon-Segovia diagnostic criteria for mixed connective tissue disease

Serologic Criteria	Positive anti-U1RNP at hemagglutination titer >1:1600
Clinical Criteria	Edema of hands Synovitis Myositis Raynaud's Acrosclerosis

Table 2. Kasukawa diagnostic criteria for mixed connective tissue disease

1) Common Symptoms Raynaud´s Phenomenon Swollen fingers or hands 2) Presence of Anti U1-nRNP 3) Mixed findings A. Systemic lupus erythematosus (SLE) like Polyarthritis Pericarditis/pleuritis Lymphadenopathy Facial erythema Leucopenia/thrombocytopenia B. Scleroderma like Sclerodactyly Pulmonary fibrosis Esophageal dysmotility C. Polymyositis like Muscle weakness High creatine phosphokinase (CPK) Myophatic electromyogram (EMG) Requirement for diagnosis: At least one common symptom, with positive U1RNP antibodies and one or more findings in at least two of the three categories A, B, and C.

Table 3. Immunopathology Autoantibody/ENA profile(IgG)

Test name	Test result
Jo-1 antibody	negative
Antibody to Scl-70	negative
Antibody to sm(smith)	negative
Antibody to ss-A(Ro)	negative
Antibody to ss-B(La)	negative
Antibody to Rib.Po	negative
Antibody to U1-nRNP	**Positive +++**
Antibody to CENP B	negative
Antibody to dsDNA	negative
Antibody to Histones	negative
Anitbody to Nucleosomes	negative
Antibody to PM-Sd	negative
Antibody to RO-52	negative
Antibodies to PCNA(proliferative cell nuclear antigen)	negative
Anti mitochondrial antibody-M2	negative
DFS70	**Positive ++**

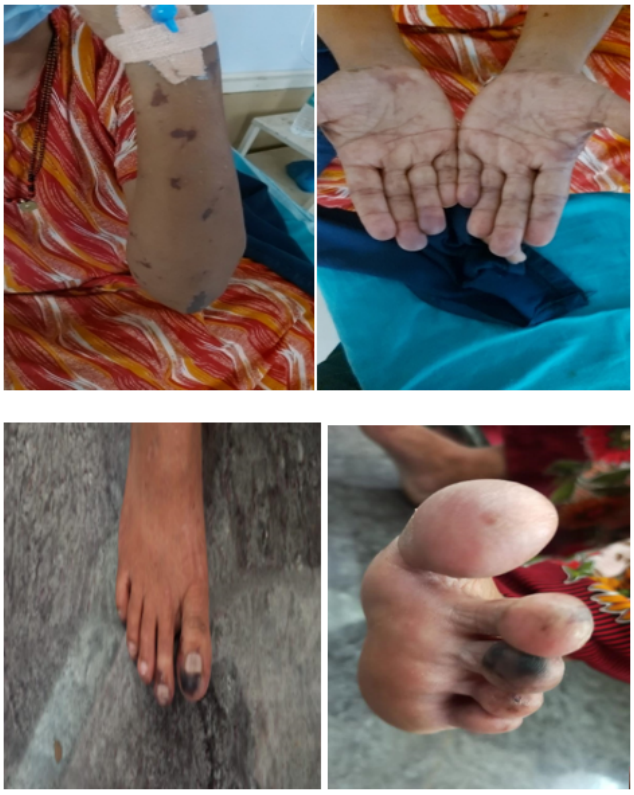

Fig 1. depicting edema of upper limb and lower limb small joints with violaceousdiscolouration

Discussion

The initial history of Raynaud's phenomenon generalized swelling. Physical examination findings microstomia guided our laboratory and radiologic workup and thereafter helped us to reach the diagnosis.

MCTD is a rare disease with unknown etiology, but few cases have been reported after occupation of vinyl chloride,[3] and even after breast augmentation surgeries.[4] There are familial cases of MCTD with increased instance of HLADR4 compared with controls.

A 2011 Norwegian study showed a 3.8 per 100,000 prevalence of MCTD among adults, with an incidence of 2.1 per million per year.[5] Mean age of onset was 31.9 years and more than three quarters of patients were females.[6] This confirms the rarity of the disease and a predilection for female sex.

MCTD should be kept as a differential diagnosis when overlapping signs of autoimmune diseases are present such as swollen digits, arthralgia, myalgia or muscle weakness, acid reflux or dysphagia, Raynaud's phenomenon, shortness of breath on activity, a general malaise and fatigue. Many criteria have been described to classify MCTD. Table 1 gives the Alarcon-Segovia's criteria and Table 2 gives the

Kasukawa diagnostic criteria for mixed connective tissue disease. Alarcon-Segovia's criteria are simple and comprises five clinical manifestations in addition to the serological status.[7]

Our patient also followed the Kasukawa diagnostic criteria with both the common symptoms of Raynaud's and swollen hands being present associated with positive serology and mixed findings of thrombocytopenia.

Myositis clinically presenting as muscle weakness is more common than laboratory increase in muscle enzymes.

Lung function tests, especially the single breath diffusing capacity may be abnormal in many patients but only a small fraction of those are symptomatic. Pulmonary artery hypertension is not common in early MCTD.[8] Pulmonary hypertension, occurring secondary to interstitial lung disease is an increasingly recognized complication.

Membranous glomerulopathy and mesangial proliferative glomerulonephritis are the main renal manifestations. Less common renal manifestations include diffuse proliferative glomerulonephritis, vascular or glomerular sclerosis. It is clinically manifested mainly with proteinuria, rarely with hematuria.[9] Our patient urine examination was within normal limits.

The therapy for MCTD would combine a cocktail of drugs to suppress inflammation including NSAIDS like naproxen, COX-2 inhibitors like celecoxib, steroids such as prednisone, antimalarials (hydroxychloroquine) and immunosuppressants like azathioprine. Nifedipine, nitroglycerin, losartan is used for Raynaud's phenomenon. TNF blockers etanercept and TNF antibodies infliximab, adalimumab is used in inflammatory arthritis in some cases. So, two people with the same disease but different presentations would require an altogether different management.[10]

The use of therapeutic antibodies like rituximab, a CD20 receptor blocker in MCTD have shown benefit in cases of refractory polymyositis and lower CPK.[11]

Conclusion

Systemic rheumatologic disease can hide behind rather non-specific and unrelated symptoms and signs. We therefore recommend holding a high degree of suspicion in the susceptible individuals, and always consider the possibility of presence of any autoimmune pathology where needed, because these diseases, as evident from the discussion before, can present with uncommon features and mimic some other trivial conditions initially. But it is always necessary to diagnose early in order to decrease morbidity, and disease related complications. Patient once diagnosed needs to be monitored on regular basis as pulmonary hypertension presents late in the illness when other clinical signs are easily recognizable and should be treated aggressively as most deaths in mixed connective tissue disorders are due to heart failure caused by pulmonary arterial hypertension

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