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Case Report

A case of autoimmune hypothyroidism presented as overlap syndrome of mixed connective tissue disorder

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ABSTRACT

Mixed connective tissue disease is a distinct complex overlap disorder characterised by combination of clinical features of systemic lupus erythematosus, systemic sclerosis, polymyositis and rheumatoid arthritis. Higher levels of anti-U1-ribonucleoprotein (anti-U1RNP) antibody has been found in these patients. 39 year old female, known case of hypothyroidism, came with complaints of multiple joint pains with swelling associated with morning stiffness of fingers since last 2 years. She also had dryness of skin, loss of appetite, constipation, difficulty in swallowing and dyspnea on exertion since last 2 months. Considering the joint pains an antinuclear antibody (ANA) was sent. She turned out to be RNP, Sm, Ro 52, Mi-2 positive. Anti-CCP, rheumatoid factors (RA), Raynaud's phenomenon all were positive. Rheumatologist opinion was taken and she was diagnosed as mixed connective tissue disorder with hypothyroidism. Patient was successfully treated with immunosuppressants and supportive measures and responded well to tablet methotrexate, prednisone, nifedipine and hydroxychloroquine. Our patient had one major and 3 minor criteria: anti RNP antibody positive, Raynaud's phenomenon, swollen fingers and synovitis. Thus, diagnosed as mixed connective tissue disease.

Keywords: Mixed connective tissue disorder, Anti RNP antibody, Raynaud's phenomenon

INTRODUCTION

Mixed connective tissue disease (MCTD) is an autoimmune disorder which is characterized by features of other connective tissue diseases such as systemic sclerosis, systemic lupus, and polymyositis along with higher levels of anti U1 small nuclear ribonucleoprotein particle (snRNP) antibody and antinuclear antibody (ANA) positive with speckled pattern being common.[1] It was more prevalent in women than men and the mean age at diagnosis was 37.9 years. The most common organ systems to be involved were musculoskeletal system, skin and mucosa, gastrointestinal and hepatobiliary systems. Pulmonary artery hypertension (PAH) was found to be major cause of mortality in MCTD and prognosis becomes poor. Early diagnosis and treatment is necessary to prevent pulmonary complications.

CASE REPORT

A 39 year old female presented to medicine outpatient department (OPD) with complaints of multiple joint pains involving both wrist, ankles, phalanges since 2 years. It was associated with joint swelling and morning stiffness of fingers. She also had dryness of skin, loss of appetite, constipation and difficulty in swallowing along with dyspnea on exertion since 2 months. Patient was a k/c/o hypothyroidism since last 6 years on medication. On examination she was afebrile with pulse of 70 beats per minute (bpm) and blood pressure (BP) 110/70 mmHg and saturation of peripheral oxygen (SpO_2) of 98% on room air. There was no signs of respiratory distress seen. On physical examination pallor and bilateral pitting type of oedema in lower limbs were seen. Wrist, small joints of hand and ankle were painful and restricted. The

presentations were initially attributed to hypothyroidism but thyroid function was later found to be under control and patient was reviewed. Patient was found to have positive Raynaud's phenomenon. Systemic examination revealed no abnormality. Routine lab investigations were normal. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and rheumatoid arthritis (RA) was positive. Anti-cyclic citrullinated peptide (anti-CCP) was positive and ANA blot was also positive for ribonucleoprotein (RNP), Smith (Sm), Ro 52, and Mi-2 antibodies. Chest x ray and x ray of hand was normal.

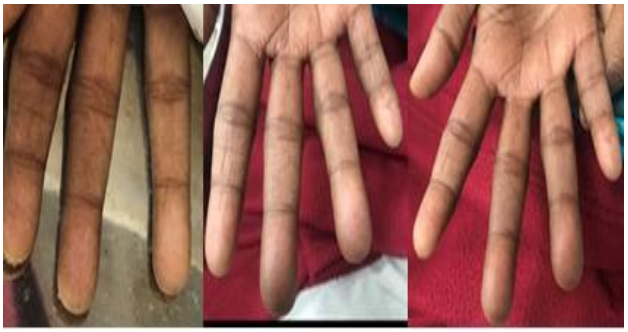

Figure 1: Raynaud's phenomenon.

Figure 2: Swollen joints.

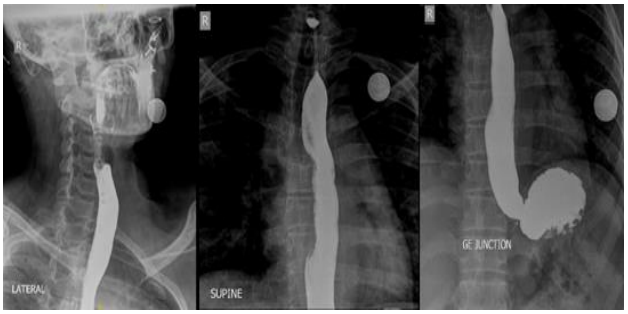

Figure 3: Barium swallow showing minimal persistent dilatation with impaired peristaltic wave seen in thoracic oesophagus.

Barium swallow was done suggestive of minimal persistent dilatation with impaired peristaltic wave seen in thoracic oesophagus. High resolution computed tomography (HRCT) thorax showed multiple prominent pre tracheal, para tracheal, pre vascular and subcarinal lymph nodes largest measuring 17×14 mm, multiple prominent bilateral axillary lymph nodes (LN) largest measuring 22×18 mm. Rheumatologist opinion was taken and patient diagnosed as a case of MCTD. The patient was treated with tablet methotrexate 15 mg, Tablet folic acid 5 mg, tablet prednisone 5 mg, tablet nifedipine 10 mg, tablet etoricoxib 90 mg and tablet hydroxychloroquine 200 mg and was discharged with regular follow up.

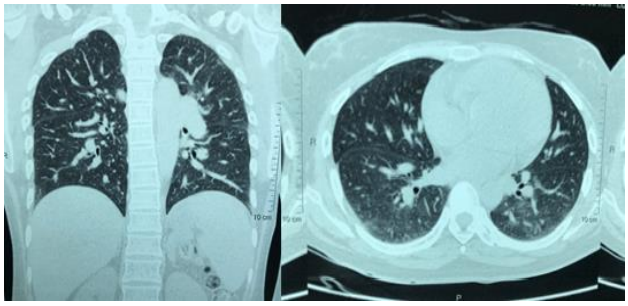

Figure 4: HRCT thorax showed multiple prominent pre tracheal, para tracheal, pre vascular and subcarinal lymph nodes largest measuring 17×14 mm, multiple prominent bilateral axillary LN largest measuring 22×18 mm.

DISCUSSION

MCTD was initially described by Sharp et al.[2] It was explained as a chronic immune-mediated disorder which had overlapping features of systemic lupus erythematosus (SLE), scleroderma, and polymyositis.[3] Cutaneous manifestations of MCTD may be the presentation of the disease. MCTD is now considered as a separate entity the characteristic feature of which is the presence of higher levels of antibodies against U1 RNP complex.[4] The U1 snRNP is a target of autoreactive B and T cells in MCTD.[5] Patients with MCTD have been found to have a higher incidence of Raynaud's phenomenon and pulmonary hypertension with less severe involvement of kidney's which include membranous or mesangioproliferative glomerulonephritis and have a better overall prognosis.[4,6-8] Individuals who express human leukocyte antigen (HLAs), HLA-DR4 or HLA-DQB1, are genetically predisposed.[9] Specific nature of HLA associations that occur in relationship with MCTD differ with the ethnicity of populations studied and it may account in part to the variability of cutaneous features.[10] MCTD more common among woman. The most common symptoms were arthritis and Raynaud's phenomenon.

Raynaud's phenomenon involves intermittent blanching followed by cyanosis and rubor on exposure to cold and often characterizes as earliest manifestations of MCTD.[11] Nedumaran et al documented all patients of MCTD suffering from this phenomenon in their study.[12]

Patients with MCTD can have other cutaneous features such as photosensitivity, livedoid vasculitis and

calcinosis.[13] Arthritis in MCTD may be associated with RF and anti-CCP.[14] Anti-U1RNP can be a predictor of more aggressive erosive arthritis.[15] 85% of cases have lung involvement in the form of ILD. HRCT is the sensitive tool to diagnose it. PAH is the most common cause of death in MCTD. PAH may be due to coexistent of antiphospholipid antibodies. 70% of patients had GI involvement in the form of oesophageal dysmotility, gastro esophageal reflux, lower esophageal sphincter laxity.[16] Up to two-thirds of MCTD patients have overt myositis which ranges from mild to severe.[15] Pericarditis was the most common cardiac involvement in MCTD patients seen in 10-30% of cases. Anemia due to chronic inflammation is seen in 75% of cases. Diagnosis of MCTD is clinicoserolgic. The clinical and serological markers of MCTD take time to develop.[17] Four criterias for MCTD have been published: Sharp's, Kasukawa et al's, Alarcon-Segovia's and Kahn's.[16,18,20] Kahn and Alarcon-Segovia are considered to be more sensitive. Based on Alarcon-Segovia classification, MCTD is established if criteria A along with 3 or more clinical criteria. Criteria A is high titre of anti-RNP, clinical criteria include swollen hands, synovitis, myositis, Raynaud's phenomenon, acrosclerosis.[21]

Our patient had criteria A and 3 of the clinical criteria. The overall 10-year survival rate of the disease is about 80%.[22] Prognosis is worse for people with features of systemic sclerosis and/or polymyositis. Pulmonary hypertension is the most common MCTD-associated cause of death.[21] Sharp's original paper had stated that MCTD responded well to steroids. Lundberg reported that one third patients improved with immunosuppressive therapies.[23]

In the study by Furst et al administration of HCQ was associated with best clinical response. Our patient responded well with prednisolone, methotrexate and hydroxychloroquine.

CONCLUSION

We diagnosed MCTD in patient with pre-existing hypothyroidism on the basis of 1 major and 3 minor criteria of presence of anti RNP antibody, synovitis, Raynaud's phenomenon and swollen hands respectively. Patient responded to methotrexate, prednisolone and hydroxychloroquine and is on regular follow up.

Recommendations

MCTD has to be looked up in patients with multi-systemic involvement along with rheumatological diseases where clinical features may overlap. Every patients with hypothyroidism always have a look for other autoimmune associations. Though MCTD is rare autoimmune disorder delayed diagnosis may be lead to pulmonary complications such as pulmonary artery hypertension.

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