CASE STUDY

Overlap syndrome of ankylosing spondylitis and mixed connective tissue disease in female

Nallasivan S[1]*, Rajendran R[2], Mariappan S[3], Palaninathan P[4], Yadav K[5], Sundara S[6]

[1-6]Velammal Speciality Hospital and Research Institute, Anuppanadi, Madurai, Tamilnadu, India

Abstract

Ankylosing spondylitis is a chronic inflammatory disease affecting the young men and less commonly women with a spectrum of manifestations including uveitis, arthritis, sacroiliitis, colitis and psoriasis (spondyloarthropathy). Mixed connective tissue disorder (MCTD) is a complex and heterogenous autoimmune disease that affects women in their childbearing age. It is characterized by circulating autoimmune antibodies that deposit in tissues, resulting in inflammatory response, causing irreparable tissue damage. Overlap and co-existence of these diseases are uncommon, as per literature evidence. The present study has reported the case of a 35-year-old female, who had HLA B27-positive spondyloarthropathy for 10 years and had been receiving sulfasalazine, and had neck swelling for 4 months. Screening conducted for TB in view of fever, weight loss and neck nodes, had reported negative results. She was found to have Reynaud's disease, arthritis, bilateral cervical lymphadenopathy and elevated autoantibody titers including ANA, U1SM/RNP and Coombs-positive hemolysis. The diagnosis was concluded as MCTD and she had responded well to the treatment. As per the available literature, this could be touted as the first case study of a female patient with ankylosing spondylitis and MCTD.

Keywords: ankylosing spondylitis, mixed connective tissue disease, HLA B27, U1RNP, overlap syndrome

Introduction

Ankylosing spondylitis is a chronic inflammatory disease affecting the young men and less commonly women with a spectrum of manifestations including uveitis, arthritis, sacroiliitis, colitis and psoriasis (spondyloarthropathy, SpA). HLA B27 carrier has been found to be the genetic abnormality in many patients with SpA. Patients generally present with inflammatory back pain and peripheral arthritis that forms part of seronegative arthritis. Mixed connective tissue disease (MCTD) is the prototype of an overlap syndrome, since its original description by Sharp and colleagues in 1972, with clinical elements of scleroderma, lupus, polymyositis and anti-U1RNP antibodies.[1] It is characterized by circulating autoimmune antibodies that deposit in tissues, resulting in inflammatory response, and irreparable tissue damage. As per literature evidence, overlap and co-existence of these diseases are uncommon. The present study has reported the case of a 35-year-old female who had SpA for 10 years, and neck swelling for 4 months. She was found to have characteristic features of MCTD.

Case report

A 35-years-old female presented with multiple swelling in neck for 4 months and she was on sulfasalazine treatment for SpA (10 years). The empirical treatment for lymphatic TB for 3 months did not yield much benefit. Her clinical examination showed pallor, lymphadenopathy, and stomatitis with restricted spinal movements due to rigid spine. There was no history of fever or rash, but she had myalgia and fatigue. She did not have contact history with patient who was on anti-TB therapy.

Investigations showed microcytic hypochromic anemia (Hb: 6.2 gm/dl and MCV 68 mmol) with normal platelet (426000 /ul) and creatine kinase, and elevated ESR (61 mm) and LDH (1082 U/L). Direct Coombs test was positive. Peripheral smear showed microcytic hypochromic RBCs with moderate anisopoikilocytosis, target cells and elliptocytes. WBC was normal with few reactive lymphocytes and platelet levels were adequate. Mantoux was negative. Her spine MRI showed evidence of established ankylosed bamboo spine. Since the anesthetist expressed difficulty in

intubation due to cervical spine deformities, bronchoscopy and excision biopsy of lymph node were not done. Fine needle aspiration cytology (FNAC) of submandibular lymph node showed features of reactive lymphoid hyperplasia (Fig 1). Her HLA B27 antigen was positive.

Ultrasound imaging of abdomen was normal. ECHO showed no evidence of pulmonary hypertension or pericardial effusion. HRCT of chest showed multifocal patchy areas of consolidation in bilateral lung fields. There were focal sub pleural ground glass appearances with surrounding tree-in-bud pattern in left upper lobe. (Fig. 2). There was no evidence of pleural effusion or hepatosplenomegaly.

Immunology investigations revealed: positive ANA (1 in 2560) and U1RNP antibodies, and negative anti-Smith antibodies, DsDNA, SARS CoV-2 IgG (0.09 COI), IgM (0.42 COI), and COVID RT-PCR and normal C3 and C4. Based on the clinical and lab investigations, it was inferred that she had long-standing ankylosed spine with features of connective tissue disease (CTD), Coombs positive hemolytic anemia and anti-U1-RNP positivity. The diagnosis was concluded as MCTD.

Specific features considered in the present case were polyarthritis, oral ulcers, weight loss, lymphadenopathy, Raynaud's disease, anti-U1-RNP, and hemolysis. The

Fig. 1: FNAC lymph node with reactive lymhpoid cells

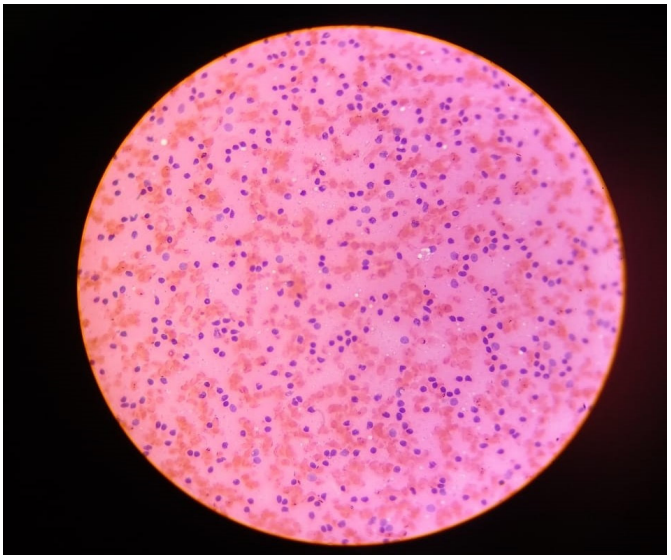


Fig. 2: CT of chest with tree-in-bud appearance

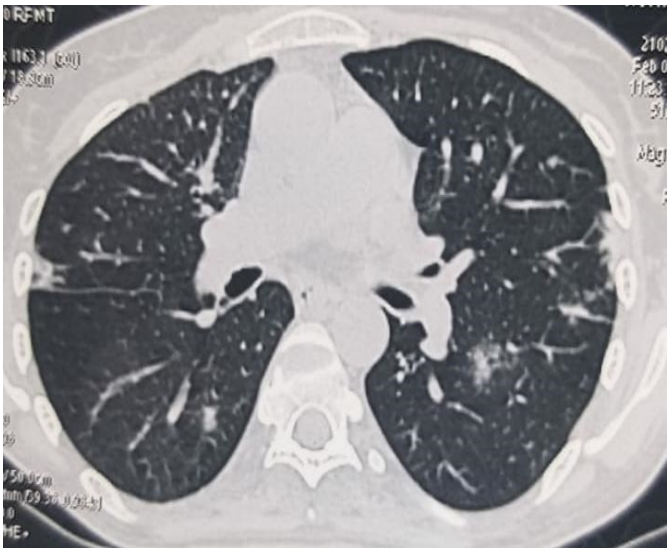
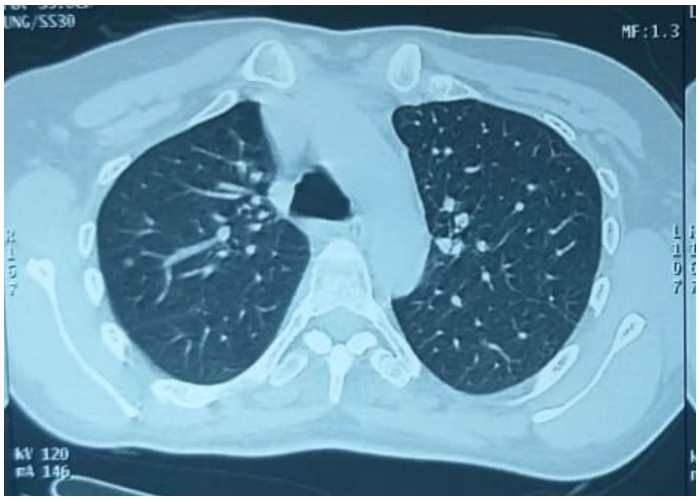


Fig 3. CT chest showing resolution of changes after treatment



differential diagnoses considered were tuberculosis, COVID infection, SLE, and lymphoma. The patient was treated with antibiotics for lung consolidation and subsequently with steroids.

Follow-up conducted after 6 weeks showed near total resolution of lung consolidation (Fig. 3), and normal weight gain and inflammatory markers. She was subsequently prescribed with azathioprine, prednisolone and calcium.

Discussion

SpA and CTD are clinically distinct entities. However, a link between the two has been suggested by certain case studies either due to altered immunological behavior or due to drugs like sulfasalazine and biologics like TNF inhibitors. Sulfasalazine has been reported to induce antinuclear antibodies (ANA) and systemic lupus erythematosus (SLE)-like syndromes such as drug-induced lupus. Lee *et al*. in (1999) and Pham *et al.* in (1999) have described earlier case reports of CTD in patients with ankylosing spondylitis.[2, 3] Brandt and colleagues have reported (2002), the development of Sjogren's syndrome along with MCTD in a patient with ankylosing spondylitis, while Dharmapaliah *et al.* (2018) have reported pulmonary hypertension in a patient with ankylosing spondylitis and CTD.[4,5] All the aforementioned case reports were described in male patients and had HLA-B27. Yongpeng and colleagues have reported manifestations of idiopathic inflammatory myopathy and ankylosing spondylitis.[6] Chandrasekara *et al.* have described overlap syndrome of ankylosing spondylitis with SLE and dermatomyositis.[7]

The current case was reported in a female and she had HLA-B27 positivity with ankylosed spine. Earlier treatment with sulfasalazine had managed the disease reasonably well. Fever, weight loss and fatigue prompted further evaluation. Microcytic anemia, positive Coombs test, and negative COVID RTPCR and Mantoux test assisted in concluding the disease as CTD.

She did not manifest typical features described by Tanaka *et al.* such as hand edema, myositis, and mechanic hands; however she had synovitis, fever, oral ulcers, Raynaud's disease, and lymphadenopathy and lung infiltration with immunology showing anti-U1RNP antibodies, suggestive of MCTD.[8]

The patient promptly responded to steroids. To the best of our knowledge, this is the first case report of a female with SpA developing MCTD.

Take-home message

- Although unusual, ankylosing spondylitis and HLA B27 can happen in females, and development of fever, lymph nodes and weight loss should prompt evaluation for infection and CTD.
- High index of suspicion with clinical features of CTD is essential to diagnose complex autoimmune diseases.
- Sulfasalazine may induce the development of CTD.
- Corona infection screen always precedes infection screen during this pandemic times.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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*Correspondence: Dr. Subramanian Nallasivan, Velammal Medical College Hospital and Research Institute, Madurai, India
drsubramanian14@gmail.com

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