Mixed connective tissue disorder: A case report

Rishi Katewa, Jakhar R. S., Barala G.L.

ABSTRACT

Introduction: Mixed connective tissue disorder is rarely reported in India. It is a disease with overlapping features of many connective tissue disorders and the presence of anti-U1RNP. We present a case with dyspnea and generalized swelling as the initial presentation that led to the diagnosis of mixed connective tissue disorder.

Case Report: A 60-year-old female came with initial complains of progressive dyspnea limiting her daily activities, palpitations, generalized body swelling since 15 days and fever since one week. Detailed history and physical examination revealed bluish discoloration of fingers on exposure to low temperature, dysphagia and difficulty opening the mouth and sclerodactyly. Laboratory workup and radiography concluded the diagnosis of mixed connective tissue disorder. Pulmonary function tests suggested restrictive lung disease and two-dimensional echo showed pulmonary hypertension. Our patient followed both the Alarcon-Segovia’s criteria and Kasukawa diagnostic criteria for mixed connective tissue disease (MCTD).

Conclusion: 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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Introduction: Mixed connective tissue disorder is rarely reported in India. It is a disease with overlapping features of many connective tissue disorders and the presence of anti-U1rNP. We present a case with dyspnea and generalized swelling as the initial presentation that led to the diagnosis of mixed connective tissue disorder. Case report: A 60-year-old female came with initial complains of progressive dyspnea limiting her daily activities, palpitations, generalized body swelling since 15 days and fever since one week. Detailed history and physical examination revealed bluish discoloration of fingers on exposure to low temperature, dysphagia and difficulty opening the mouth and sclerodactyly. Laboratory workup and radiography concluded the diagnosis of mixed connective tissue disorder. Pulmonary function tests suggested restrictive lung disease and two-dimensional echo showed pulmonary hypertension. Our patient followed both the Alarcon-segovia’s criteria and Kasukawa diagnostic criteria for mixed connective tissue disease (MCTD). Conclusion: 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.

Keywords: Mixed connective tissue disorder (MCTD), Raynaud’s phenomenon, Sclerodactyly, Anti-U1RNP antibody, Scleroderma

INTRODUCTION

Mixed connective tissue disease (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 non-specific 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 of time 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. No causal association and the varied presentation, makes the diagnosis of this rare condition difficult.

We encountered one such case with dyspnea and generalized swelling as the initial presentation that eventually led to the diagnosis of MCTD disorder with restrictive lung disease and pulmonary hypertension.
CASE REPORT

A 60-year-old female was admitted with complaints of dyspnea on exertion, intermittent fever without chills since last seven days. Dyspnea was limiting her daily activities and fever was mild, low grade, without chills and rigors, responded to antipyretics. Since 15 days, she also had swelling all over the body and pedal edema used to increase with her daily activities.

On enquiry she gave history of painful bluish discoloration of fingers while washing hands with water or in cold temperature (Figure 1) since last two years, difficulty in opening mouth from last one year and dysphagia with dyspeptic symptoms since two months.

On examination there was mild pallor and temperature of 98.9°F. She had generalized edema with diffuse alopecia. Facial skin was taut with pinched up nose. Mouth orifice was small with difficulty in opening. Fingers showed peripheral cyanosis and sclerodactyly.

Physical examination per abdomen showed hepatomegaly 3 cm below costal margin, non-tender, firm. Cardiovascular examination showed normal heart sounds with soft systolic murmur at apex and pulmonary area with same intensity. However, respiratory and central nervous system examination provided no physical findings.

On investigating hemoglobin was 9.8 g/dL with platelet count 1.2x10^5 mm^3. Urine (routine and microscopic) was normal. Liver function test revealed ALT of 94 IU/L, however, renal function test was normal (Table 1). Serum CPK levels were raised (942 IU/L).

Two-dimensional echo showed moderate to severe pulmonary hypertension and X-ray showed cardiomegaly (Figure 2). Pulmonary function test was suggestive of severe restrictive disease. Esophagogastroduodenoscopy revealed multiple small gastric ulcers with evidence of old hemorrhages in the centre at the antrum suggestive of vasculitic lesion. Antral biopsy was suggestive of a single superficial erosive patch. Skin biopsy showed features of scleroderma with dermis showing mild increase in the amount of collagen with few congested blood vessels (Figure 3). Our patient followed the Alarcon-Segovia diagnostic criteria (Table 2) with positive serology and three of the five clinical criteria’s namely Raynaud’s phenomenon, edema of hands and myositis depicted by high serum CPK value. Our patient also followed the Kasukawa diagnostic criteria (Table 3) with both the common symptoms of Raynaud’s and swollen hands being present associated with positive serology and mixed findings of thrombocytopenia, esophageal dysmotility (Figure 4), sclerodactyly and high CPK values.

Serological examination showed anti-mRNP/Sm and anti-Ro52 positive. However anti-nuclear antibody and ScL-70, Pm-Scl, Jo-1, CENP-B, dsDNA, anti-histone, anti-nucleosome, anti-ribosomal-P protein all were negative (Table 2).

A diagnosis of MCTD was made.

The management of the patient included:

The patient was started on injection amoxicillin/clavulonic acid 1.2 g 1-1-1 (three times a day) and paracetamol SOS for fever. Later the following drugs were added to the management:

- A combination of furosemide 20 mg + spironolactone 40 mg 1-1-0
- Sildenafil citrate 50 mg bid
- Syrup muciane gel 2 tsp 1-1-1 (three times a day) for dyspeptic symptoms.
- Oral steroids. Prednisone 40 mg tapered every five days to 30 mg, 20 mg, 10 mg, 5 mg. 1-0-0.
- Metoprolol 12.5 mg 1-0-0.
- Supplemental oxygen was given for dyspnea.

The patient was discharged after 22nd day of hospitalization and is currently on sildenafil citrate 50 mg bid.

DISCUSSION

The initial history of Raynaud’s phenomenon are generalized swelling and dysphagia. Physical examination findings of sclerodactyly and microstomia guided our
Table 1: Laboratory examination of the patient

| Parameter                  | Value          |
|----------------------------|----------------|
| Hb                         | 9.8 g/dL       |
| TLC                        | 6500/mm³       |
| Peripheral blood smear     | Normocytic normochromic |
| MCV                        | 94 fl          |
| MCH                        | 30.7 pg        |
| MCHC                       | 32.7 g/dL      |
| Reticulocyte count         | 0.5%           |
| Platelet count             | 120000/mm³     |
| Serum bilirubin            |                |
| Total                      | 1.0 mg%        |
| Direct                     | 0.4 mg%        |
| ALT                        | 94 IU/L        |
| ALP                        | 43 IU/L        |
| Urea                       | 35 mg%         |
| Serum Creatinine           | 1.2 mg%        |
| Serum Sodium               | 130 mmol/L     |
| Serum Potassium            | 4.0 mmol/L     |
| Urine albumin              | +1             |
| Total CPK                  | 942 IU/L       |
| Anti HCV                   | negative       |
| HIV/HBsAg                  | negative       |
| Antimicrosomal antibody    | 31 IU/mL (negative-<34 IU/mL) |
| T3                         | 54 ng/dL (60-200) |
| T4                         | 6.3 µg/dL (4.5-12.0) |
| TSH                        | 11.79 uIU/mL (0.30-5.5) |
| Anti HCV negative          | negative       |
| HIV/ HBsAg negative        | negative       |
| Antimicrosomal antibody    | negative       |
| T3                         | 54 ng/dL (60-200) |
| T4                         | 6.3 µg/dL (4.5-12.0) |
| TSH                        | 11.79 uIU/mL (0.30-5.5) |

Table 2: Alarcon-Segovia diagnostic criteria for mixed connective tissue disease

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

Table 3: Kasukawa diagnostic criteria for mixed connective tissue disease

1) Common Symptoms
   - Raynaud’s Phenomenon
   - Swollen fingers or hands
2) Presence of Anti U1 RNP
3) Mixed findings
   A. Systemic lupus erythematosus (SLE) like
      - Polyarthritis
      - Pericarditis/pleuritis
      - Lymphadenopathy
      - Facial erithema
      - Leucopenia/thrombocytopenia
   B. Scleroderma like
      - Sclerodactyl
      - Pulmonary fibrosis
      - Esophageal dysmotility
   C. Polymyositis like
      - Muscle weakness
      - High creatine phosphokinase (CPK)
      - Myopathic 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 4: Serological examination of the patient

| ANTIBODY     | RESULT     |
|--------------|------------|
| ANA          | negative   |
| SS-a         | negative   |
| SS-b         | negative   |
| Scl-70       | negative   |
| Anti U1RNP/Sm| positive   |
| Pm-Scl       | negative   |
| Jo-1         | negative   |
| CENP-B       | negative   |
| Anti-Ro52    | positive   |
| PNCA         | negative   |
| ds-DNA       | negative   |
| Anti-histone | negative   |
| Anti-nucleosome | negative   |
| Anti-ribosomal P Protein | negative |
| AMA-M2       | negative   |
laboratory and radiologic workup and thereafter helped us to reach the diagnosis.

An MCTD is a rare disease with unknown etiology, but few cases have been reported after occupation of vinyl chloride [2], and even after breast augmentation surgeries [3]. 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 [4]. Mean age of onset was 31.9 years and more than three quarters of patients were females [5]. 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 3 gives the Alarcon-Segovia’s criteria and Table 4 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 [6]. Our patient showed the Alarcon-Segovia diagnostic criteria with positive serology and three of the five clinical criteria’s namely Raynaud’s phenomenon, edema of hands and myositis depicted by Serum CPK value of 942 IU/L.

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, esophageal dysmotility, sclerodactyly and high CPK values.

Myositis clinically presenting as muscle weakness is more common than laboratory increase in muscle enzymes but in our patient a frank increase is CPK was seen.

Lung function tests, especially the single breath diffusion capacity may be abnormal in many patients but only a small fraction of those are symptomatic,
meanwhile our patient had dyspnea as the presenting complaint. Pulmonary artery hypertension is not common in early MCTD [7]. Pulmonary hypertension, occurring secondary to interstitial lung disease is an increasingly recognized complication and our patient was suffering from pulmonary hypertension as diagnosed by two-dimensional echo.

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 [8]. Our patient had +1 hematuria on urine examination.

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 are used for Raynaud’s phenomenon. TNF blockers etanercept and TNF antibodies infliximab, adalimumab are used in inflammatory arthritis in some cases. So two people with the same disease but different presentations would require an altogether different management [9].

The use of therapeutic antibodies like rituximab, a CD20 receptor blocker in MCTD have shown benefit in cases of refractory polymyositis and lower CPK [10].

CONCLUSION

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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Author Contributions
Rishi Katewa – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Jakhar R.S. – Substantial contributions to conception and design, Analysis and interpretation of data, Drafting the article, Final approval of the version to be published
Barala G.L. – Substantial contributions to conception and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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REFERENCES
1. Sharp GC, Irvin WS, Tan EM, Gould RG, Holman HR. Mixed connective tissue disease—an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). Am J Med 1972 Feb;52(2):148–59.
2. Kahn MF, Bourgeois P, Aeschlimann A, de Truchis P. Mixed connective tissue disease after exposure to polyvinyl chloride. J Rheumatol 1989;16(4):533–5.
3. Kumagai Y, Shiokawa Y, Medsger TA Jr, Rodnan GP. Clinical spectrum of connective tissue disease after cosmetic surgery. Observations on eighteen patients and a review of the Japanese literature. Arthritis Rheum 1984;27(1):1–12.
4. Gunnarsson R, Molberg O, Gilboe IM, Gran JT. The prevalence and incidence of mixed connective tissue disease: A national multicentre survey of Norwegian patients. Ann Rheum Dis 2011 Jun;70(6):1047–51.
5. Hench PK, Edington TS, Tam EM. The Evolving clinical spectrum of mixed connective tissue disease. Arthritis Rheum 1975;18:404–8.
6. Alarcon-Segovia D, Cardiel MH. Comparison between 3 diagnostic criteria for mixed connective tissue disease. Study of 593 patients. J Rheumatol 1989 Mar;16(3):328–4.
7. Haroon N, Nisha RS, Chandran V, Bharadwaj A. Pulmonary hypertension not a major feature of early mixed connective tissue disease: A prospective clinicorheological study. J Postgrad Med 2005 Apr-Jun;51(2):104–7.
8. Maldonado ME, Perez M, Pignac-Kobinger J, et al. Clinical and immunologic manifestations of mixed connective tissue disease in a Miami population compared to a Midwestern US Caucasian population. J Rheumatol 2008 Mar;35(3):429–37.
9. Ortega-Hernandez OD, Shoenfeld Y. Mixed connective tissue disease: An overview of clinical manifestations, diagnosis and treatment. Best Pract Res Clin Rheumatol 2012 Feb;26(1):61–72.
10. Mok CC, Ho LY, To CH. Rituximab for refractory polymyositis: An open-label prospective study. J Rheumatol 2007 Sep;34(9):1864–8.
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