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

ABSTRACT

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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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CASE REPORT

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Mixed connective tissue disorder: A case report

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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.

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

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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.

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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 1.2×10^5 mm³. 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/clavulanic 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.

Figure 1: (A, B): Bluish discoloration of fingers on exposure to cold water.

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

Hb	9.8 g/dL
TLC	6500/mm ³
Peripheral blood smear	Normocytic normochromic
MCV	94 fl
MCH	30.7 pg
MCHC	32.7 g/dL
Reticulocyte count	0.5%
Platelet count	120000/mm ³
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
Antimicrobial 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)

Table 2: 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 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 erythema
Leucopenia/thrombocytopenia
B. Scleroderma like
Sclerodactyly
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-mRNP/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

Figure 2: X-ray of chest posterior-anterior view had the following findings. Soft tissues and bony thorax are normal. The trachea is central. Left costophrenic and cardiophrenic angles are clear. Right costophrenic angle appears blunted. Both domes of diaphragm are normal in position and contour. Both the hila are normal in size, shape, position and density. The visualized lung fields are normal. Cardiac shadow is enlarged in size (CT ratio 54%). Impression: Cardiomegaly.

Figure 3: Skin biopsy was suggestive of mild hyperkeratosis of the epidermis (thick arrow). The dermis showing mild increase in the amount of collagen with few congested blood vessels (thin arrow). No evidence of perivascular infiltrates and fibrinoid necrosis.

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.

Figure 4: Barium study. Filled phase showing dilatation of esophagus with barium in thoracic oesophagus, however no peristaltic wave was seen on dynamic study. No evidence of any filling defect was seen. Suggestive of hypomotility disorder of esophagus, likely to be scleroderma.

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 in CPK was seen.

Lung function tests, especially the single breath diffusing 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.

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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