International Journal of Research in Medical Sciences
Mohammed M et al. Int J Res Med Sci. 2024 May;12(5):1754-1758
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20241271

Case Report

Analysis of mixed connective disorder: a case report

Muzammil Mohammed[1]*, Riyaz Mohammed[2]

[1]Department of Medicine, Shadan Institute of Medical Sciences, Telangana, India
[2]Department of Medicine, MNR Medical College and Hospital, Telangana, India

Received: 16 March 2024
Revised: 04 April 2024
Accepted: 05 April 2024

***Correspondence:**
Dr. Muzammil Mohammed,
E-mail: muzammilesani@gmail.com

ABSTRACT

Mixed connective tissue disease (MCTD) as an autoimmune disorder with characteristics that resemble systemic sclerosis, systemic lupus erythematosus (SLE), and polymyositis. Due to this overlap, MCTD is often categorized as an overlap disease. As the disease progresses, symptoms may become more indicative of one of the three primary illnesses, accompanied by elevated levels of anti-U1RNP antibody. 30yrs female Patient presented with a classical malar rash as the initial presentation, followed by the development of a painful red lesion on the knuckles over a few weeks. Additionally, the patient observed a hypopigmented large lesion on the forearm resembling vitiligo, with a salt and pepper appearance. Upon clinical evaluation and further extensive investigation, the patient was diagnosed with mixed connective tissue disease (MCTD). On further evaluation the anti-U1RNP antibody, ANA, was positive and patient was treated on lines of MCTD. Patient responded well to the treatment. Our case suggests that mixed connective tissue disease if recognised early with symptoms and signs and workup we can prevent the shift to other connective tissue diseases over a long period; therefore, it is necessary to identify whether patients with mixed connective tissue disease fulfil the diagnostic criteria for other connective tissue diseases when new manifestations appear.

Keywords: Autoantibody, Systemic lupus erythematosus, Mixed connective tissue disease, Malar rash, Salt pepper like appearance

INTRODUCTION

In 1972, Sharp et al. described mixed connective tissue disease (MCTD) as an autoimmune disorder with characteristics that resemble systemic sclerosis, systemic lupus erythematosus (SLE), and polymyositis.[1-2] Due to this overlap, MCTD is often categorized as an overlap disease. Patients typically present with non-specific symptoms such as swollen digits, joint pain, muscle pain or weakness, acid reflux or difficulty swallowing, Raynaud's phenomenon, exertional dyspnoea, general malaise, and fatigue. As the disease progresses, symptoms may become more indicative of one of the three primary illnesses, accompanied by elevated levels of anti-U1RNP antibody.[3-4]

Mixed connective tissue disease is a rare condition, and its exact prevalence remains unknown. According to a population-based study by Ungprasert et al conducted in Olmsted County, Minnesota, the annual incidence of MCTD was found to be 1.9 cases per 100,000 adults.[5] The average age at which individuals were diagnosed with this disease was 48 years, and it predominantly affected females, accounting for 84% of the affected population. Another study Gunnarsson et al, conducted in Norway reported an incidence rate of 2.1 cases per million individuals per year.[6] In this study, the female to male ratio was 3.3 to 1, and the average age at diagnosis was 37.9 years. It is important to note that MCTD affects individuals of all races, and its clinical manifestations are similar across different ethnic groups.

The exact cause of mixed connective tissue disease remains unknown; however, as an autoimmune condition, MCTD has been observed to have a familial tendency and predominantly affects women over men. The lack of a clear causal relationship and the diverse clinical presentation contribute to the challenges associated with diagnosing this rare disorder.

CASE REPORT

30 years' female patient presented with a classical malar rash as the initial presentation, followed by the development of a painful red lesion on the knuckles over a few weeks. Additionally, the patient observed a hypopigmented large lesion on the forearm resembling vitiligo, with a salt and pepper appearance. Upon clinical evaluation and further extensive investigation, the patient was diagnosed with mixed connective tissue disease (MCTD).

History of the patient was: (1) sudden eruption of raised lesions on her knuckles, accompanied by discomfort upon exposure to cold temperatures, (2) intermittent low-grade fever, recurring mouth ulcers, and joint pains were observed, (3) gradual onset of skin tightening over the past two years, accompanied by changes in skin pigmentation on the forearms, (4) presence of a butterfly-shaped rash on the face, worsened by exposure to sunlight, (5) complaints of excessive hair loss and (6) significant weight loss of approximately 10 kilograms was noted.

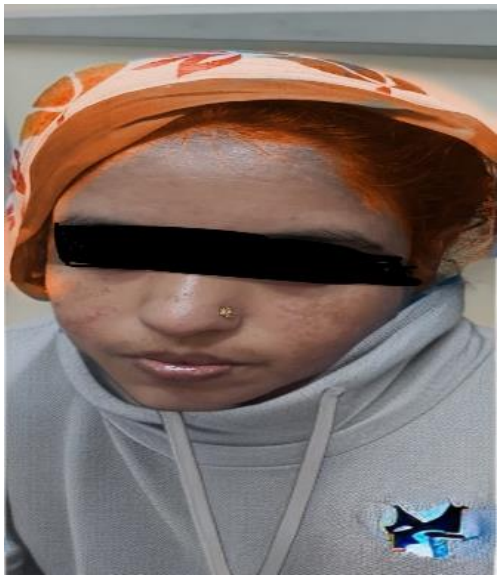

Figure 1: Malar rash, classical feature, non-scarring, hair loss, pinched nose appearance, pursed lips and parotid gland swelling.

Examination of the patient was cutaneous examination, scalp with non-scarring hair loss, eyes with positive ingrams sign, indicating the presence of dryness and irritation, nose with distinctive appearance of a pinched nose, lips with pursed lips with a fish mouth appearance, swelling of the parotid gland was observed, malar rash with increased sensitivity to sunlight, forearms with displayed a salt and pepper appearance due to changes in pigmentation, hands with presence of pitted scars on the fingertips, along with sclerodactyly. Gottrons papules were seen on the knuckles and nails with nail capillaroscopy revealed dilated capillaries.

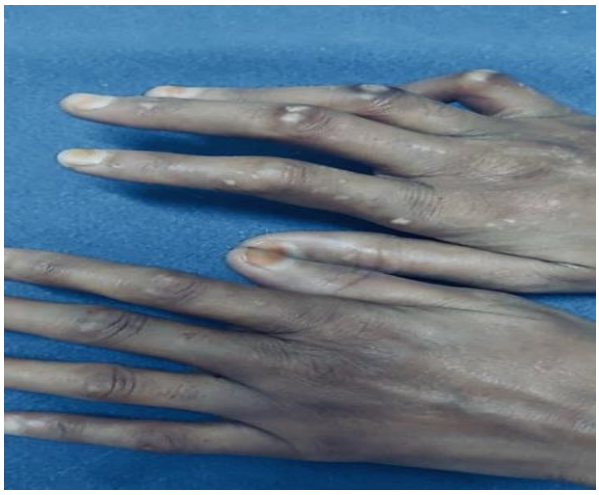

Figure 2: Hands - presence of pitted scars on the fingertips, along with sclerodactyly. Gottrons papules were seen on the knuckles. Nails - Nail capillaroscopy revealed dilated capillaries.

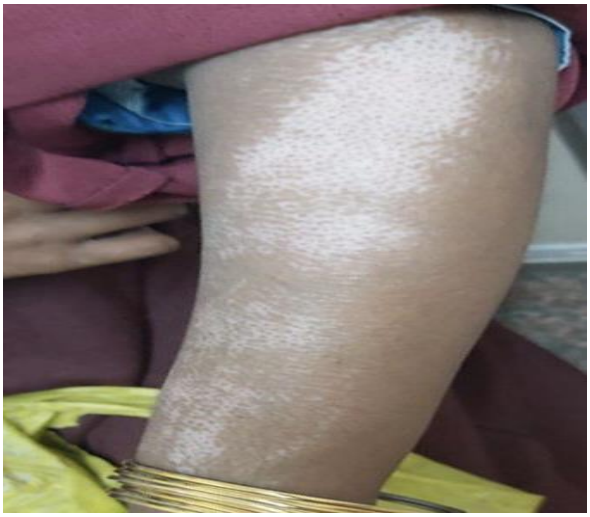

Figure 3: Hypopigmented large lesion on the forearm resembling vitiligo, with a salt and pepper appearance.

Lab investigation

Hemogram

Hemoglobin level is 10.8 g/dl, total leukocyte count is 6500/mm, and peripheral blood smear shows normocytic normochromic cells. Mean corpuscular volume (MCV) is 94 fl, mean corpuscular hemoglobin (MCH) is 30.6 pg, and mean corpuscular hemoglobin concentration (MCHC) is

32.5 g/dl. Reticulocyte count is 0.5%, platelet count is 130000/mm,

Liver function test

Total serum bilirubin is 0.9 mg%, direct serum bilirubin is 0.3 mg%, alanine aminotransferase (ALT) level is 34 IU/l, alkaline phosphatase (ALP) level is 42 IU/l.

Renal function test

Urea level is 36 mg/dl, serum creatinine level is 1.0 mg/dl, Uric acid: 4.2 mg/dl.

Electrolytes

Serum sodium level is 132 mmol/l, serum potassium level is 4.1 mmol/l, urine analysis: protein +1, anti-hepatitis C virus (HCV) is negative, human immunodeficiency virus (HIV)/hepatitis B surface antigen (HBsAg) is negative, antimicrosomal antibody level is 31 IU/ml.

Thyroid function test

Triiodothyronine (T3) level is 144.2 ng/dl (normal range: 80-200), thyroxine (T4) level is 8.3 microgram/dl (normal range: 5.1-14.1), and thyroid-stimulating hormone (TSH) level is 4.09 IU/ml (normal range: 0.27-4.2).

Chest X-ray was not showing any abnormalities, echocardiogram: feature of left ventricular hypertrophy, and grade 1 diastolic dysfunction.

Table 1: Lab investigation.

Rheumatoid factor:	Negative
Anti CCP	Negative
ANA	Positive, 1:1100 Coarse granular nucleoplasm with nucleoli
Anti dsDNA:	Negative
Anti Sm	Negative
Anti U1 RNP:	Positive
Anti SSA	Negative
Anti SSB	Negative
Anticentromere	Negative
Anti Scl-70	Negative
APLA	Negative
CRP	15
C3 C4	Normal
ESR	40

The patient was started on the standard treatment protocol for mixed connective tissue disease (MCTD), which included the use of emollients for skin protection. Additionally, the patient was prescribed HCQ 200 mg twice daily for a period of 8 weeks. This treatment regimen resulted in a reduction of arthritis and arthralgia-like symptoms in the patient. Subsequently, the patient was advised to continue taking HCQ at the same dosage for another 8 weeks due to intermittent arthritis-like manifestations. The patient was treated with corticosteroids, specifically prednisolone at a daily dose of 40 mg, antimalarial drugs like hydroxychloroquine at 200 mg three times a day, and calcium channel blockers including nifedipine at 40 mg twice a day. As part of the treatment plan, azathioprine was initiated at a daily dose of 50 mg while concurrently tapering the prednisolone dosage to 10 mg per day over a month. Following the treatment regimen, the patient's condition significantly improved. Subsequent to the initial treatment, the patient underwent a 2-month follow-up period during which maintenance therapy with azathioprine and intermittent use of paracetamol for pain management was continued. Regular monitoring of the patient's hemogram during azathioprine therapy revealed no abnormalities, indicating good tolerance. The patient was instructed to return for a follow-up evaluation after 2 months.

DISCUSSION

Since its initial description in 1972, our understanding of mixed connective tissue disease (MCTD) has significantly advanced. We now recognize MCTD as a distinct condition with its own unique clinical features, response to treatment, and prognosis.[5-6] Recent studies conducted by Reiseter et al have further solidified our understanding of MCTD by establishing the stability of its phenotype.[7-10]

A considerable number of patients initially present with nonspecific symptoms such as fever and fatigue. Unfortunately, the diagnosis of MCTD is often missed at first and only correctly identified as the disease progresses. Arthritis and Raynaud's phenomenon are prevalent among our patient cohort. Additionally, sclerodactyly, interstitial lung disease (ILD), and myositis are also commonly observed. Therefore, when a patient exhibits a combination of arthritis, Raynaud's phenomenon, ILD, sclerodactyly, and myositis, along with constitutional symptoms of fever and fatigue, it is crucial for physicians to consider MCTD as a potential diagnosis.[11-13]

As expected, in our case, patient had elevated levels of anti-U-1 RNP antibody, and patients tested positive for antinuclear antibodies (ANA). The most common pattern observed in ANA testing was the speckled pattern. However, it is important to note that anti-U-1 RNP antibodies may also be positive in other connective tissue diseases. In various studies, it was shown that antibodies were found to be positive in 20-40% of patients with systemic lupus erythematosus (SLE), 2-14% of patients with systemic sclerosis, and 6-9% of patients with myositis and direct Coombs test positive haemolytic anemia. The prevalence of other antibodies such as anti-dsDNA, rheumatoid factor, anti-Ro/SS-A, and anti-La/SS-B was much lower. It is worth mentioning that anti-dsDNA and anti-Smith antibodies are only transiently positive in MCTD.[13-17]

To aid in the diagnosis of MCTD, various criteria such as the Sharp Criteria, Kasukawa criteria, Segovia criteria, or Khan criteria can be utilized to confirm the presence of the disease.

Sharp major criteria minor criteria diagnosis[18]

Major criteria are myositis, pulmonary involvement (diffusion capacity <70% of normal values, pulmonary hypertension and proliferative vascular lesions on lung biopsy), phenomenon or oesophageal hypomotility, swollen hands and anti-ENA Ab>1:10,000 and anti-U1 RNP Ab positive and anti-Sm negative.

Minor criteria are alopecia, leukopenia, anemia, pleuritic, pericarditis, arthritis, trigeminal neuropathy, malar rash, thrombocytopenia, mild myositis and history of swollen hands.

At least 4 major criteria plus anti-U1-RNP Ab titer of at least 1: 4000 or two major criteria from among criteria 1, 2, and 3 plus 2 minor criteria plus anti-U1-RNP Ab titer of at least 1: 1000, exclusion criteria are positivity for anti-Sm Ab.

Diagnosis

Serological criteria combined with a minimum of 3 clinical criteria, with either synovitis or myositis being present.

Differential diagnosis

Due to the presence of nonspecific symptoms and different organ involvement, MCTD mimics several other conditions, especially CTD. Few differential diagnoses are: (i) systemic lupus erythematosus, (ii) rheumatoid arthritis, (iii) polymyositis, (iv) dermatomyositis, (v) scleroderma, (vi) bacterial infections, (vii) idiopathic pulmonary arterial hypertension and (viii) primary Raynaud disease.

Treatment / management

To date, there have been no randomized controlled trials conducted to provide guidance on the treatment of mixed connective tissue disease. The primary objective of therapy is to effectively manage symptoms, which is determined based on the clinical manifestations and the extent of organ involvement. Medication can help manage the signs and symptoms. The type of medication prescribed depends on the severity of your disease and the symptoms.

General measures: Sun protection and Emollients.

Medication

Corticosteroids drugs, such as prednisolone (40 mg o.d.) tapering of dose has to be slowly, antibiotics such as amoxicillin and clavulanic acid, antimalarial drugs such as hydroxychloroquine (200 mg t.i.d), calcium channel blockers-Nifedipine (400 mg b.d.), other immunomodulator: while tapering the dose of prednisolone over a period of one month to 10 mg per day azathioprine 50 mg per day was added.

CONCLUSION

We have effectively managed disease activity by adjusting the treatment approach, and it is possible for mixed connective tissue disease (MCTD) to transition to another connective tissue disease (CTD) over time. It is crucial to verify if new clinical findings align with other diagnostic criteria. Numerous uncertainties persist regarding MCTD, particularly concerning its long-term clinical trajectory and the factors that predict its transformation into a different CTD. MCTD, once perceived as a mild and treatable condition, can pose a significant risk to life. Approximately one-third of MCTD patients experience complete remission, while another third may encounter life-threatening complications. The prognosis hinges on the affected organ, the extent of inflammation, and the disease's progression rate. Mortality rates range from 8% to 36%. A Hungarian study revealed a 98% survival rate at 5 years and 96% at 10 years post-diagnosis. Pulmonary hypertension stands as the primary cause of death, with interstitial lung disease, infections, cardiovascular issues, and malignancies also contributing. The presence of IgG anticardiolipin antibodies could indicate severe disease. Enhanced understanding of the precise clinical course of MCTD could lead to more tailored treatment approaches. We anticipate further research endeavours to shed light on the pathogenesis of MCTD.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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;52(2):148-59.
2. Bennett RM, O'Connell DJ. Mixed connective tissue disease: a clinicopathologic study of 20 cases. Semin Arthritis Rheum. 1980;10(1):25-51.
3. Alarcón-Segovia D, Cardiel MH. Comparison between 3 diagnostic criteria for mixed connective tissue disease. Study of 593 patients. J Rheumatol. 1989;16(3):328-34.
4. Tanaka Y, Kuwana M, Fujii T, Kameda H, Muro Y, Fujio K, et al. 2019 Diagnostic criteria for mixed connective tissue disease (MCTD): From the Japan research committee of the ministry of health, labor, and welfare for systemic autoimmune diseases. Mod Rheumatol. 2021;31(1):29-33.
5. Ungprasert P, Crowson CS, Chowdhary VR, Ernste FC, Moder KG, Matteson EL. Epidemiology of

Mixed Connective Tissue Disease, 1985-2014: A Population-Based Study. Arthritis Care Res (Hoboken). 2016;68(12):1843-8.
6. Gunnarsson R, Molberg O, Gilboe IM, Gran JT, PAHNOR1 Study Group. The prevalence and incidence of mixed connective tissue disease: a national multicentre survey of Norwegian patients. Ann Rheum Dis. 2011;70(6):1047-51.
7. Hajas A, Szodoray P, Nakken B, Gaal J, Zöld E, Laczik R, et al. Clinical course, prognosis, and causes of death in mixed connective tissue disease. J Rheumatol. 2013;40(7):1134–42.
8. Reiseter S, Gunnarsson R, Corander J, Haydon J, Lund MB, Aaløkken TM, et al. Disease evolution in mixed connective tissue disease: results from a long-term nationwide prospective cohort study. Arthritis Res Therapy. 2017;19(1):284.
9. Cappelli S, Bellando Randone S., Martinović D., et al. "To Be or Not To Be," Ten Years After: Evidence for Mixed Connective Tissue Disease as a Distinct Entity. Seminars in Arthritis and Rheumatism. 2012;41(4):589–98.
10. Mimura Y, Ihn H, Jinnin M, Asano Y, Yamane K, Tamaki K. Rheumatoid factor isotypes in mixed connective tissue disease. Clinical Rheumatology. 2006;25(4):572–4.
11. Venables PJ. Mixed connective tissue disease. Lupus. 2006;15(3):132–7.
12. Gunnarsson R, Andreassen AK, Molberg Ø, Lexberg ÅS, Time K, Dhainaut AS, et al. Prevalence of pulmonary hypertension in an unselected, mixed connective tissue disease cohort: results of a nationwide, Norwegian cross-sectional multicentre study and review of current literature. Rheumatology. 2013;52(7):1208–13.
13. Vegh J, Szodoray P, Kappelmayer J, Csipo I, Udvardy M, Lakos G, et al. Clinical and immunoserological characteristics of mixed connective tissue disease associated with pulmonary arterial hypertension. Scand Journal Immunol. 2006;64(1):69–76.
14. Reiseter S, Gunnarsson R, Mogens Aaløkken T, Lund MB, Mynarek G, Corander J, et al. Progression and mortality of interstitial lung disease in mixed connective tissue disease: a long-term observational nationwide cohort study. Rheumatology. 2018;57(2):255–62.
15. Fagundes MN, Caleiro MTC, Navarro-Rodriguez T, Baldi BG, Kavakama J, Salge JM, et al. Esophageal involvement and interstitial lung disease in mixed connective tissue disease. Respiratory Medicine. 2009;103(6):854–60.
16. Pepmueller PH. Undifferentiated connective tissue disease, mixed connective tissue disease, and overlap syndromes in rheumatology. Missouri Medicine. 2016;113(2):136-40.
17. Amigues JM, Cantagrel A, Abbal M, Mazieres B. Comparative study of 4 diagnosis criteria sets for mixed connective tissue disease in patients with anti-RNP antibodies. Autoimmunity Group of the Hospitals of Toulouse. J Rheumatol. 1996;23(12):2055–62.
18. Sharp GC. Mixed connective tissue disease and antinuclear antibodies. Diagnostic criteria for classification of MCTD. Amsterdam: Elsevier; 1987: 23-32.

Cite this article as: Mohammed M, Mohammed R. Analysis of mixed connective disorder: a case report. Int J Res Med Sci 2024;12:1754-8.