

Case Report

Mixed Connective Tissue Disease- Physician's Dilemma: A case report

Abu Saleh Shimon¹, *Mahjuba Umme Salam², Monharul Islam Bhuiyan³, Mashuq Ahmad Jumma⁴, Imran Hussain⁵, Farzana Ahmed Bristy⁶, Rehana Parvin⁷

Abstract

Mixed connective tissue disease is an entity of autoimmune disease with overlapping features of systemic lupus erythematosus, scleroderma, rheumatoid arthritis, dermatomyositis and with positive anti-U1 RNP antibody. We report here a 52 year old non-diabetic, normotensive woman presenting with new onset dysphagia for two months with variable features of multiple types of connective tissue diseases for two years. Clinical features and type specific serological tests for different connective tissue diseases showed puzzling results. However, finally a high titer of anti-U1RNP antibody led to the diagnosis of mixed connective tissue disease.

Keywords: Mixed connective tissue disease, anti-U1 RNP, systemic sclerosis, dermatomyositis, polymyositis, systemic lupus erythematosus, MCTD.

DOI: <https://doi.org/10.47648/jswmc2021v11-08>

JSWMC 2021 [11(01)] P: 59-64

Introduction

Connective tissue diseases (CTD) are a group of auto-immune diseases that are of five specific types, each one with definite diagnostic criteria - Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), Scleroderma, Polymyositis, and Sjogren's syndrome.¹ Some patients present with obscure features suggestive of an autoimmune disease like Raynaud's phenomenon, arthralgia, arthritis, skin rash, myalgia and a positive anti-nuclear antibody

(ANA) but they do not fall in the category of a definite CTD type. They are described as undifferentiated CTD.² Some patients show partial features of two or more specific connective tissue diseases but do not fulfil criteria for diagnosis and they are named as overlap syndromes. Patients of this category having a positive anti-U1 RNP antibody are classified as Mixed Connective Tissue Disease (MCTD). Some of the rheumatologists consider it to be the rarest form of CTDs and a strong HLA linkage has been suggested.³ The point prevalence of adult-onset MCTD was 3.8 per 100,000 in a Norwegian epidemiological study.⁴ Though the peak incidence is at 40 years, 7-23 percent of reported MCTD cases have juvenile onset.⁵ Gordon C. Sharp et al first described MCTD as a separate rheumatologic disease entity in 1972.⁶ High titers of anti-U1 RNP antibody in presence of mixed features of SLE, RA, polymyositis and scleroderma are the essentials for diagnosis of MCTD. Whether or not,

1. Indoor Medical Officer, Department of Medicine, SWMC.

2. Professor of Medicine, Department of Medicine, SWMC.

3. Assistant Professor, Department of Medicine, SWMC.

4. Assistant Registrar, Department of Medicine, SWMC.

5. Honorary Medical Officer, Department of Medicine, SOMC.

6. Indoor Medical Officer, Department of Medicine, SWMC.

7. Indoor Medical Officer, Department of Obs and Gynae, SWMC.

Corresponding Author: Mahjuba Umme Salam

Professor of Medicine, Department of Medicine, SWMC.
email-mahjubasalam@yahoo.com

MCTD is a separate disease entity has been an issue of debate over the last 4 decades.⁷ Moreover, a consensus international guideline for diagnosis of this disease is missing till today and variable treatment and outcome reports have left this entity with an undetermined prognosis.⁴ Four different sets of criteria- the Sharp, Kasukawa, Alarcón-Segovia and Khan criteria, are used for diagnosis of MCTD, though they vary in sensitivity and specificity.^{8,9} Though anti-U1 RNP antibody is an important diagnostic marker, at present, 70 kDa anti-U1-RNP or anti-Sm-D are considered as more specific serological markers for diagnosis.¹⁰ Esophageal dysmotility is a common feature. Other gastrointestinal problems like ascites, intestinal ileus and cachexia are less encountered features.¹¹ Lung involvement in the form of interstitial lung disease and pulmonary hypertension complicates half of MCTD patients and accounts for most of the mortality and morbidity.^{12,13,14} As the disease manifests with features of not only multiple CTD entities but also multiple organ-system involvement, it often leaves the physician in a state of dilemma about where to reach. The case being reported here, presented with esophageal, musculoskeletal and respiratory symptoms and on further exploring, results came out with a diagnosis of MCTD.

Case Report

A 52-year-old non diabetic normotensive lady presented with difficulty in swallowing both solid and liquid food for 2 months. Of late, she developed thigh muscle pain with proximal weakness and mild breathlessness on exertion. She gave history of multiple joint pain and recurrent oral ulcer for 2 years. Joint pain was associated with swelling and morning stiffness. The involved joints were, initially inter phalangeal joints of both hands and then knees and elbows. Raynaud's

phenomenon was present on exposure to cold and on examination she had tight swollen digits (Fig 1). She received analgesics and steroids on multiple occasions over the past 2 years which gave her only temporary relief. There were no history of skin rash, photosensitivity, genital ulcer or seizures. On physical examination she was anemic and had difficulty in opening her mouth. She had swollen and tender wrists and proximal interphalangeal joints. She had mild tenderness over thigh muscles. Her pulse was 88 beats/min and blood pressure was 120/80 mmHg. She had difficulty in rising from a squat but there was no neurological deficit with normal reflexes. Her breath sound was vesicular but a few crepitation were diffusely audible over the lung fields.

All her routine laboratory investigations (blood counts, serum creatinine, serum ALT, urine routine examination,) showed normal values. But she had raised levels of serum C-reactive protein (34.4 mg/L), lactate dehydrogenase (786 U/L), creatine phosphokinase (1174 U/L), aldolase 11.9 U/L and thyroid stimulating hormone (7.19 mIU/L). She had a normal chest X-ray. Serology for connective tissue diseases revealed inconclusive results (Table 1). She had a high serum titer of anti-nuclear antibody (ANA) but a negative specific test (anti-ds DNA antibody) for SLE. Serological markers for Rheumatoid Arthritis (rheumatoid factor, anti-cyclic citrullinated peptide antibody), scleroderma (anti-scl 70 antibody, anti-centromere antibody) were negative. Anti-Jo antibody and anti-Smith antibody were in low titers. Thigh muscle histopathology was unremarkable and EMG showed neuropathic pattern (Fig 2). Histopathology of skin from hand showed hyperkeratotic epidermis, thickened collagen bundles in dermis which were bound to the adnexal structures and atrophic changes in sweat

glands were noted. Nailfold capillaroscopy showed scleroderma pattern consisting of giant capillaries, avascular areas, capillary loss and neovascularization with bushy capillaries. She had a seven fold raised titers of Anti-U1RNP. Hence, a diagnosis of MCTD and hypothyroidism was made and patient was further evaluated for degree of systemic involvement by connective tissue disease. She had restrictive lung function but high resolution CT scan of chest showed bilateral chronic inflammatory changes but no evidence of diffuse parenchymal lung disease was found (Fig 3). Endoscopy of upper gastrointestinal tract, Barium swallow (Fig 4), Ultrasound of abdomen, Schirmer test, ECG and Echocardiography were normal. Tumor markers like CA 19-9 (19.6U/ml) and CA 125 (5.45 U/ml) were within normal ranges.

Patient initially received a three day course of injectable methylprednisolone and then was prescribed with low daily dose of oral prednisolone with disease modifying agents- methotrexate and chloroquin. Symptomatic improvement occurred in six months.

Fig 1: Tight digits



Fig 2: Neuropathic pattern in EMG

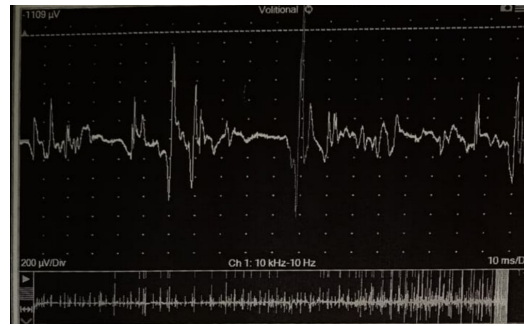


Fig 3: High resolution CT chest

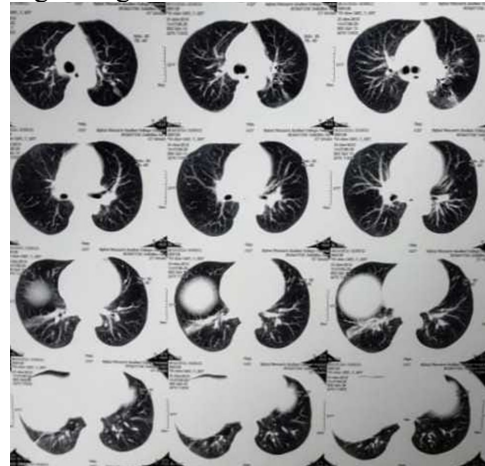


Fig 4: Barium swallow

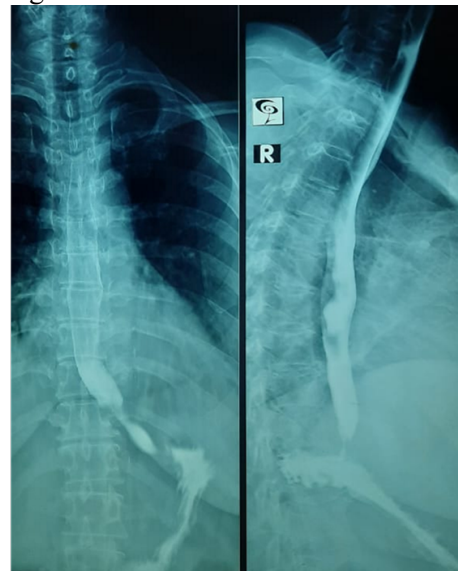


Table 1: Summary of serum serology and other biochemical parameters

Test (serum)	Value	Remarks
ANA	325.7 AU/ml (<40 Au/ml)	strongly positive
Anti-ds DNA antibody	5.23 IU/ml (< 20 IU/ml)	negative
Anti-scl 70 antibody	5.8 U/ml (< 12 U/ml)	negative
Anti-centromere antibody	4.2 U/ml (<12 U/ml)	negative
Rheumatoid factor	8.6 IU/ml (< 20 IU/ml)	negative
Anti-CCP antibody	15 IU/ml (0-30 IU/ml)	negative
Anti-U1 RNP antibody	141.22 units (<20 units)	raised
Aldolase	11.9 U/L (<7.6 U/L)	raised
Anti-Jo-1 antibody	3.6 U/L (<20 U/L)	normal
Anti-Smith antibody	2.6 U/ml (<7 U/ml)	normal
S. CPK	1174 U/L(30-135 U/L)	raised
S. LDH	786 U/L (140-280 U/L)	raised

Discussion

Mixed connective tissue disease is an uncommon but distinct entity of connective tissue diseases that can make a straight forward diagnosis difficult. Patients often present with variable clinical and laboratory test features of Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), Scleroderma, Polymyositis, and Sjogren's syndrome.⁸ A very high titer of serum anti-U1 RNP antibody is the key laboratory criterion that distinguishes MCTD from the so called 'overlap syndrome'.^{9,10}

The case been reported here, a 52 year old lady without any known co-morbidity, was diagnosed

as a case of MCTD based on both Kasukawa and Alarcón-Segovia criteria. Though epidemiological studies on MCTD are scanty and the ones that exist, show a female preponderance with a mean age of affection around 40 years.^{5,15}

Our patient had joint pain and swelling with morning stiffness as found in RA, but showed negative serological reports (RA factor and anti CCP antibody). She had recurrent oral ulcer and strongly positive ANA suggestive of SLE, but specific test for this disease, the anti-ds DNA was negative. She gave history suggestive of Raynaud's phenomenon along with tight digits and dysphagia but both the anti-scl 70 and anti-centromere antibody tests were negative. However, skin histopathology and nailfold capillaroscopy strongly suggested scleroderma. Characteristic pattern in nailfold capillaroscopy is now a well-recognized diagnostic tool for systemic sclerosis and MCTD.¹⁶ Moreover, this non-invasive test has been positively correlated to myositis and pulmonary hypertension in MCTD patients in a number of studies.^{17,18}

About 50% of patients with MCTD have myositis but it is less common in SLE.¹⁹ Complaint of thigh pain, proximal muscle weakness, raised serum CPK and Aldolase all were in favor of presence of polymyositis though muscle histopathology and EMG features did not support this consideration and anti-Jo and anti-Smith antibody tests were also negative. MRI guided biopsy specimen collection and EMG could have revealed different results, as patchy involvement of muscles is common.²⁰ And immuno-histopathology of muscle would be better for demonstrating muscle specific VCAM-1 and ICAM-1 antibodies.²¹

Though the cases reported so far showed diverse clinical features, arthritis is found to be the commonest feature at presentation and presence of diffuse pulmonary lung disease and pulmonary

hypertension are found to be the most important contributors to mortality.¹²

Our case had exertional breathlessness and had been evaluated twice with high resolution CT chest only to find out chronic inflammatory shadows, but the typical ground glass opacities were missing and also there was no evidence of pulmonary hypertension in color Doppler echocardiogram. Studies have shown that the lung imaging might not conform to the clinical features and pneumonia like findings were frequently found among MCTD cases.²²

Prospective studies have demonstrated that the clinical picture of patients with MCTD may change with time and patients may also develop full blown pictures of one of the component CTDs after many years.^{18,23} The immunological and serological picture may remain elusive for unknown reasons.¹¹ As a result of an immunological phenomenon called 'epitope spreading' previously negative patients may become anti-Smith antibody positive, with less prevalent skin lesions and more prevalent interstitial lung disease during early years of diagnosis of MCTD.²⁴ For all these issues the development of a consensus diagnostic criteria has remained a challenge still now.

Conclusion

Mixed connective tissue disease is a rare entity of autoimmune connective tissue disease with a diverse clinical and obscure laboratory findings and it can place the physician in a state of difficulty. All such patients should undergo anti-U1 RNP antibody testing to distinguish this entity from overlap syndrome or undifferentiated connective tissue disease.

References

1. Alves MR, Isenberg DA. Mixed connective tissue disease: a condition in search of an identity. *ClinExp Med*. 2020 May;20(2):159-166.
2. Pepmueller PH. Undifferentiated Connective Tissue Disease, Mixed Connective Tissue Disease, and Overlap Syndromes in Rheumatology. *Mo Med*. 2016 Mar-Apr;113(2):136-40
3. Martínez-Barrio J, Valor L, López-Longo FJ. Facts and controversies in mixed connective tissue disease. *Med Clin (Barc)*. 2018 Jan 12;150(1):26-32.
4. Gunnarsson R, Hetlevik SO, Lilleby V, Molberg Ø. Mixed connective tissue disease. *Best Pract Res ClinRheumatol*. 2016 Feb;30(1):95-111
5. Tarvin SE, O'Neil KM. Systemic Lupus Erythematosus, Sjögren Syndrome, and Mixed Connective Tissue Disease in Children and Adolescents. *PediatrClin North Am*. 2018 Aug;65(4):711-737.
6. Ortega-Hernandez OD, Shoenfeld Y. Mixed connective tissue disease: an overview of clinical manifestations, diagnosis and treatment. *Best Pract Res ClinRheumatol*. 2012 Feb;26(1):61-72.
7. Vegh J, Szodoray P, Kappelmayer J, Csipo I, Udvardy M, Lakos G, Aleksza M, Soltesz P et al. Clinical and immunoserological characteristics of mixed connective tissue disease associated with pulmonary arterial hypertension. *Scand J Immunol*. 2006 Jul;64(1):69-76.
8. John KJ, Sadiq M, George T, Gunasekaran K, Francis N, Rajadurai E, Sudarsanam TD. Clinical and Immunological Profile of Mixed Connective Tissue Disease and a Comparison of Four Diagnostic Criteria. *Int J Rheumatol*. 2020 Jan 29;2020:9692030.
9. 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 Jan;31(1):29-33
10. Dima A, Jurcut C, Baicus C. The impact of anti-U1-RNP positivity: systemic lupus erythematosus versus mixed connective tissue disease. *Rheumatol Int*. 2018 Jul;38(7):1169-1178.
 11. Nosáková L, Schnierer M, Bánovčin P, Stašková K, Uriček M, Hyrdel R. Gastrointestinal tract involvement in mixed connective tissue disease (Sharp syndrome). *VnitrLek*. 2020 Summer;66(6):53-57.
 12. Perelas A, Arrossi AV, Highland KB. Pulmonary Manifestations of Systemic Sclerosis and Mixed Connective Tissue Disease. *Clin Chest Med*. 2019 Sep;40(3):501-518.
 13. Narula N, Narula T, Mira-Avendano I, Wang B, Abril A. Interstitial lung disease in patients with mixed connective tissue disease: pilot study on predictors of lung involvement. *ClinExpRheumatol*. 2018 Jul-Aug;36(4):648-651
 14. 9. Kuzuya K, Tsuji S, Matsushita M, Ohshima S, Saeki Y. Systemic Sclerosis and Systemic Lupus Erythematosus Overlap Syndrome with Pulmonary Arterial Hypertension Successfully Treated with Immunosuppressive Therapy and Riociguat. *Cureus*. 2019 Mar 26;11(3):e4327.
 15. Ahsan T, Erum U, Dahani A, Khowaja D. Clinical and immunological profile in patients with mixed connective tissue disease. *J Pak Med Assoc*. 2018 Jun;68(6):959-962.
 16. van Roon AM, Huisman CC, van Roon AM, Zhang D, Stel AJ, Smit AJ et al. Abnormal Nailfold Capillaroscopy Is Common in Patients with Connective Tissue Disease and Associated with Abnormal Pulmonary Function Tests. *J Rheumatol*. 2019 Sep;46(9):1109-1116.
 17. Bernardino V, Rodrigues A, Lladó A, Panarra A. Nailfoldcapillaroscopy and autoimmune connective tissue diseases in patients from a Portuguese nailfoldcapillaroscopy clinic. *Rheumatol Int*. 2020 Feb;40(2):295-301.
 18. Ciang NC, Pereira N, Isenberg DA. Mixed connective tissue disease-enigma variations? *Rheumatology (Oxford)*. 2017 Mar 1;56(3):326-333.
 19. Maazoun F, Frikha F, Snoussi M, Kaddour N, Masmoudi H, Bahloul Z. Systemic lupus erythematosusmyositis overlap syndrome: report of 6 cases. *ClinPract*. 2011 Nov 2;1(4):e89.
 20. Endo Y, Miller TT. Myositis and Fasciitis: Role of Imaging. *SeminMusculoskeletRadiol*. 2018 Jul;22(3):286-298. doi: 10.1055/s-0038-1641572. Epub 2018 May 23. PMID: 29791957.
 21. Vianna MA, Borges CT, Borba EF, Caleiro MT, Bonfá E, Marie SK. Myositis in mixed connective tissue disease: a unique syndrome characterized by immunohistopathologic elements of both polymyositis and dermatomyositis. *Arq Neuropsiquiatr*. 2004 Dec;62(4):923-34.
 22. Yamanaka Y, Baba T, Hagiwara E, Yanagawa N, Takemura T, Nagaoka S et al. Radiological images of interstitial pneumonia in mixed connective tissue disease compared with scleroderma and polymyositis/dermatomyositis. *Eur J Radiol*. 2018 Oct;107:26-32.
 23. Cappelli S, BellandoRandone S, Martinović D, Tamas MM, Pasalić K, Allanore Y, Mosca M et al. "To be or not to be," ten years after: evidence for mixed connective tissue disease as a distinct entity. *Semin Arthritis Rheum*. 2012 Feb;41(4):589-98.
 24. Escolà-Vergé L, Pinal-Fernandez I, Fernandez-Codina A, Callejas-Moraga EL, Espinosa J, Marin A et al. Mixed Connective Tissue Disease and Epitope Spreading: An Historical Cohort Study. *J ClinRheumatol*. 2017 Apr;23(3):155-159.