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A Case Report of Mixed Connective Tissue Disease Predominantly Manifesting as Systemic Sclerosis in a Middle-Aged Nepali Woman

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Abstract:-

➢ ***Introduction:***

Mixed connective tissue disease (MCTD) is a rare systemic autoimmune disorder, first described in 1972, that presents with overlapping features of systemic lupus erythematosus, systemic sclerosis, and polymyositis. The diagnosis of MCTD is complex and often delayed due to its varied clinical manifestations and the requirement of serological confirmation, particularly the presence of anti-U1 RNP antibodies. Despite its global prevalence, data on MCTD are limited, especially in the South Asian population.

➢ ***Case Report:***

We present the case of a 42-year-old Nepali woman with a decade-long history of myalgia, muscle weakness, and joint pain, initially misdiagnosed as rheumatoid arthritis. Over time, she developed Raynaud phenomenon, dysphagia, and progressive muscle weakness, which prompted further investigation. Serological testing revealed elevated levels of anti-U1 RNP antibodies and a positive antinuclear antibody (ANA) titer, confirming the diagnosis of MCTD according to the Alarcón-Segovia criteria. The patient was successfully managed with a regimen of corticosteroids, hydroxychloroquine, and nifedipine, resulting in significant symptomatic improvement.

➢ ***Discussion:***

This case underscores the diagnostic challenges associated with MCTD, a condition that may present with nonspecific symptoms and mimic other rheumatic diseases. The prolonged diagnostic journey of this patient highlights the need for heightened clinical suspicion and comprehensive serological testing in patients with overlapping connective tissue disease features. Furthermore, the case contributes to the limited body of literature on MCTD in the South Asian population, emphasizing the importance of early recognition and tailored management strategies to improve patient outcomes.

➢ ***Conclusion:***

MCTD is a complex and under-recognized autoimmune disorder, particularly in the South Asian context. This case report highlights the importance of considering MCTD in the differential diagnosis of patients with multi-systemic involvement and underscores the role of serological testing in confirming the diagnosis. Early diagnosis and appropriate management are crucial in mitigating disease progression and improving the quality of life for patients with MCTD.

I. INTRODUCTION

In 1972, Mixed connective tissue disease(MCTD) was initially described as a syndrome characterized by a combination of features from systemic lupus erythematosus, scleroderma, and polymyositis[1]. A prominent feature of systemic autoimmune diseases, such as MCTD, is the presence of high titers of serum antibodies targeting diverse nuclear autoantigens, including components of the U1 small nuclear ribonucleoprotein particle (snRNP) [2]. Diagnosing mixed connective tissue disease (MCTD) often requires several years, as overlapping features gradually emerge to confirm the diagnosis. Consequently, in its early stages, MCTD may present with symptoms indicative of undifferentiated connective tissue disease (UCTD)[3].

Data on the prevalence and incidence of mixed connective tissue disease (MCTD) are sparse [4-6]. MCTD affects people of all races globally, with peak incidence occurring during adolescence and in individuals in their twenties [7,8]. Annual incidence estimates for mixed connective tissue disease (MCTD) range between 0.2 and 1.9 cases per 100,000 adults [5,6]. MCTD is significantly more prevalent in females compared to males, with reported female-to-male ratios varying from 3:1 to 16:1 [5,9,10].

Since its identification in 1972, there has been debate among experts about whether mixed connective tissue disease (MCTD) should be classified as a distinct clinical condition or viewed as an early manifestation of a more established systemic rheumatic disease, such as systemic lupus erythematosus (SLE) or systemic sclerosis (SSc)

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[1,11]. Diagnosis of mixed connective tissue disease (MCTD) is based on the presence of anti-U1 RNP antibodies and at least three of the following clinical manifestations:

- Digital swelling
- Raynaud phenomenon
- Synovitis
- Myositis
- Acrosclerosis

This method is consistent with established diagnostic guidelines[12,13]. Here we present a case of 42 year female with features suggestive of mixed connective tissue disease.

II. CASE REPORT

A 42-year-old woman (BMI-20.83 kg/m2) presented to outpatient department(OPD) with complaints of myalgia and muscle weakness, particularly in the pectoral girdle, shoulder girdle and lumbosacral muscles. These symptoms have been progressively worsening over the past 10 years. Additionally, she experienced multiple joint pain and occasional low grade fever. Despite visiting several hospitals and being managed for suspected rheumatoid arthritis with methotrexate and NSAIDs, her symptoms continued to progress. Over time, she also noticed that her fingers would turn white or blue when exposed to cold and then turn red upon warming up, indicative of Raynaud phenomenon. The patient also sought treatment at an Ayurvedic hospital where she was given ayurvedic medications for six months, but her symptoms did not improve. Recently she had experienced difficulty getting out of a chair and climbing stairs, carrying heavy objects. She also reported difficulty swallowing food, fatigue and weight loss. She also has a history of hypothyroidism for 1 year, for which she is taking Tab Thyroxine 37.5mcg once daily. There was no history of shortness of breath or chest pain. She had no known family history of autoimmune diseases.

Upon clinical examination, the patient appeared fatigued. She exhibited swelling and tenderness in the small joints of the hands (Figure 2), along with muscle weakness in the proximal muscles. Additionally, she had puffy and taut skin in her hands and face, without wrinkles and her lips appeared thinned out (Figure 1). Cardiovascular and respiratory assessment indicated normal findings. Neurologically, the patient exhibited no focal deficits.

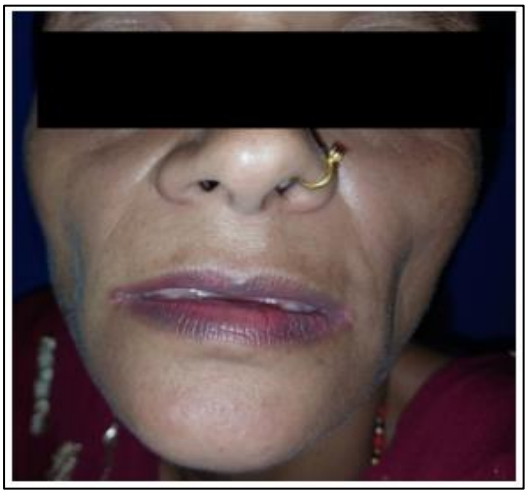

Fig 1 Showing Scleroderma Like Changes in the Face with Absence of Wrinkles and Thinned Out Lips

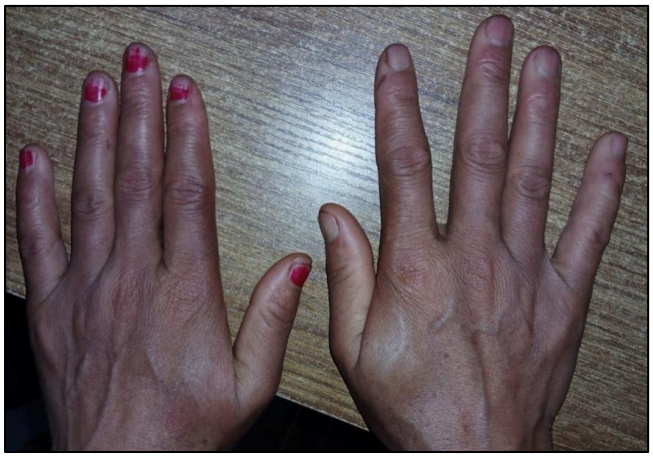

Fig 2 Showing Swollen Fingers of Hands with Taut Skin in Mixed Connective Tissue Disease

We performed laboratory investigations which revealed a strong positive result for Anti-RNP/Sm, Anti-RNP 70, Anti-RNP A, and Anti-Ro-52 recombinant antibodies on the Extractable Nuclear Antigen (ENA) profile test (Table 1). The patient's Antinuclear Antibody (ANA) level was 400 AU/ml. Additionally, C-Reactive Protein (CRP) level and ESR level was elevated (Table 2). Rheumatoid factor (RA) and Antistreptolysin O (ASO) were negative (Table 2). Uric acid level, Creatine phosphokinase and serum albumin were within normal ranges (Table 2). A chest X-ray was performed and returned unremarkable findings. Normal values were also found for complete blood count (CBC), random blood sugar (RBS), renal function tests (RFT), liver function tests (LFT), thyroid function tests (TFT), Vitamin B-12, Vitamin D, and lipid profile (Table 3). Urinalysis and electrolyte values were normal. Her values for thyroid-stimulating hormone (TSH) and Anti-thyroid peroxidase (Anti-TPO) antibody were within normal ranges (Table 3).

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Table 1 Antibody Profile

ANTIGEN	QUANTITATIVE RESULT (RU/ml)	RATIO	QUALITATIVE RESULT (0,(+), +, ++, +++)
RNP/Sm	109	9.9	+++
RNP 70	87	7.9	+++
RNP A	135	12.3	+++
Ro-52 recombinant	72	6.6	+++
dsDNA	0	0	0
Jo-1	0	0	0
Scl-70	1	0.1	0
Centromere B	1	0	0
Sm	0	0	0
RNP C	4	0.3	0
SS-A	1	0	0
SS-B	0	0	0
Histones	0	0	0
Ribosomal Protein	1	0.1	0
INTERPRETATION:			
QUANTITATIVE RESULT(RU/ml)	Ratio	QUALITATIVE RESULT	EXPLANATION
0-5	0.00-0.45	0	NEGATIVE
6-10	0.46-0.91	(+)	BORDERLINE
11-25	0.92-2.27	+	POSITIVE
26-50	2.28-4.55	++	POSITIVE
51-256	4.56-23.27	+++	STRONG POSITIVE

Table 2 Lab Values

TEST	RESULTS	NORMAL VALUES
ANTI NUCLEAR ANTIBODY(ANA)	400AU/ml	<40
CRP	50.83mg/L	0-6.45
ESR	27	<15
RA FACTOR	NEGATIVE	NEGATIVE
ASO	NEGATIVE	NEGATIVE
URIC ACID	5.71mg/dl	3.6-7.7
SERUM ALBUMIN	4.25g/dl	3.8-5.1
CREATINE PHOSPHOKINASE	78.86U/L	34-145

Table 3 Showing CBC, RFT, LFT, TFT and Lipid Profile

TEST	RESULTS	NORMAL RANGE
Complete Blood Count:		
TLC	6800/cumm	4000-11000
DLC- NEUTROPHILS	77%	40-75
LYMPHOCYTES	21%	20-40
EOSINOPHILS	2%	1-6
HAEMOGLOBIN	14gm/dl	12-16
PLATELETS	175000mil/cumm	150000-450000
PCV	42.8%	33-55
RBC	4.54 mil/cumm	4.5-5.5
MCV	87.4fl	76-96
MCH	29.7pg	26-36
MCHC	34gm/dl	31-37
RBS	95mg/dl	70-140
RENAL FUNCTION TEST:		
SODIUM	138mmol/L	135-145
POTASSIUM	3.8mmol/L	3.5-5.5
UREA	23mg/dl	15-45
CREATININE	0.9mg/dl	0.4-1.4
CALCIUM	9.78mg/dl	8-10.2
LIVER FUNCTION TEST:		
TB	0.8mg/dl	0.6-1.3

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DB	0.2mg/dl	0-0.25
AST	39IU/L	5-35
ALT	19IU/L	5-40
ALP	132IU/L	42-306
THYROID FUNCTION TEST:		
FT3	3.72pg/ml	1.84-4.04
FT4	1.34ng/dl	0.94-1.64
TSH	2 µIU/ml	0.3-5.1
Anti TPO Antibody	<5 IU/ml	<35
VITAMIN B-12	590pg/ml	210-950
VITAMIN D	37.48ng/ml	30-100
LIPID PROFILE:		
CHOLESTEROL	145mg/dl	<200
TRIGLYCERIDE	96mg/dl	<150
HDL	42mg/dl	>40
LDL	83mg/dl	<100

With the clinical findings and laboratory reports as shown in Table 1, a diagnosis of Mixed Connective Tissue Disease (MCTD) was made following the Alarcón-Segovia criteria. The patient was started on a tapering dose of prednisolone, beginning at 20 mg for 10 days, then decreased to 10 mg for the next 10 days, and continued on 5 mg once daily. Additionally, she was prescribed oral hydroxychloroquine at a dose of 400 mg daily. To manage episodes of Raynaud phenomenon, she was given nifedipine 20 mg. Other supplements, including oral vitamin D, calcium, and zinc tablets, were also provided. Patient was advised to avoid cold exposure to mitigate Raynaud phenomenon. Her symptoms have significantly improved with these medications. She is currently stable and continues to have regular monthly follow-ups.

III. DISCUSSION

Mixed Connective Tissue Disease (MCTD) is a rare and complex autoimmune disorder characterized by overlapping features of systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and polymyositis (PM)[1]. This case illustrates the significant diagnostic challenges associated with MCTD, as evidenced by a decade-long delay in diagnosis.

- *Diagnostic Challenges:*

Early in the disease course, MCTD often presents with nonspecific symptoms such as puffy fingers, fatigue, arthralgias, myalgias, low-grade fever, and Raynaud phenomenon[14]. These initial symptoms can be easily mistaken for other rheumatic conditions, complicating the diagnostic process. In this case, the patient experienced a decade-long journey before a definitive diagnosis of MCTD was established. Initially presenting with myalgia, muscle weakness, and joint pain, she was managed for rheumatoid arthritis without significant improvement. It was only after the progression of additional symptoms, including Raynaud phenomenon, difficulty swallowing, and fatigue, coupled with a detailed serological workup, that the diagnosis of MCTD became apparent.

A comprehensive serological evaluation played a crucial role in reaching a diagnosis. The presence of anti-U1 RNP antibodies and elevated ANA levels were pivotal findings. However, the heterogeneity in disease presentations and potential for evolution into other systemic rheumatic diseases further complicates the diagnosis. Studies have shown that a significant proportion of patients initially diagnosed with MCTD may evolve into another rheumatic disease over time[6,11,15].In one study that tracked the clinical progression of 118 patients initially diagnosed with MCTD, 12% of them went on to develop a different, well-defined rheumatic disease over a period of 17 years [16]. Therefore, the presence of anti-U1 RNP antibodies, along with clinical manifestations such as Raynaud phenomenon, synovitis, and myositis, should prompt consideration of MCTD, especially in patients with a constellation of symptoms that do not fit neatly into the diagnostic criteria for other rheumatic diseases.

- *Etiology and Pathogenesis:*

The etiology of MCTD remains poorly understood, with limited evidence suggesting potential environmental and genetic factors. Drug-induced MCTD is rare but has been associated with anti-tumor necrosis factor (TNF) therapy[17]. Environmental agents such as vinyl chloride and silica have also been linked to MCTD[18,19]. Additionally, COVID-19 infections have been reported to trigger disease flares in MCTD patients[20].

Genetic factors, including the association with HLA-DRB1*04:01 and variations in DNA methylation of genes in the type I interferon pathway, have been identified[21,22]. Despite these associations, the precise mechanisms underlying the development of MCTD remain elusive.

- *Clinical Features:*

Several clinical observations support MCTD as a distinct entity. Raynaud phenomenon is an early and nearly ubiquitous feature in MCTD patients, presenting similarly to SSc but differing from classical SLE[23]. Pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD) are more common in MCTD compared to SLE or SSc, contributing to significant morbidity[9]. Patients with MCTD are also more likely to test positive for rheumatoid

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factor (RF) or anti-citrullinated peptide antibodies (ACPA), with a higher likelihood of developing erosive arthritis[24,25].

- *Management and Outcomes:*

The management of MCTD requires a multidisciplinary approach tailored to the specific manifestations of the disease. The treatment of MCTD is largely extrapolated from treating similar symptoms in other rheumatic diseases [26]. This patient responded well to a regimen including corticosteroids, hydroxychloroquine, and nifedipine, along with supportive therapies such as vitamin D, calcium, and zinc supplements. Regular follow-ups and continual reassessment are essential to monitor for new or evolving disease manifestations.

The prognosis of MCTD varies, with studies reporting mortality rates ranging from 16 to 28 percent at 10 to 12 years post-diagnosis[27-29]. However, some reports indicate higher survival rates, emphasizing the importance of early recognition and appropriate management.

IV. CONCLUSION

This case highlights the diagnostic complexity and prolonged disease course often associated with MCTD. Increased awareness and understanding of MCTD among clinicians are crucial for timely diagnosis and effective management. Comprehensive serological testing and a high index of suspicion are essential in diagnosing MCTD, particularly in patients with undifferentiated connective tissue disease symptoms. Enhanced recognition and targeted treatment strategies can significantly improve outcomes for patients with this challenging condition.

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