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Autoimmune disorders (SLE, MCTD & Overlap Syndrome): Vivid Presentation and Clinician Perspective

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Abstract:
Background: *This study aims to compare the clinical features and autoantibodies associated with mixed connective tissue disorder (MCTD) and overlap syndromes. MCTD and overlap syndromes present unique symptomatic and management challenges due to their varying clinical presentations and overlapping features with other autoimmune rheumatic diseases. Overlap syndromes encompass a range of conditions, including systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, polymyositis, and dermatomyositis.*
Materials and Methods*: In this case study, we present findings from 10 clinical cases focusing on the complexity and heterogeneity of mixed connective tissue disorder (MCTD) and overlap syndromes. Each case meets the criteria established by Alarcon-Segovia and Villareal for diagnosing MCTD or overlapping syndromes, demonstrating the diverse clinical presentations observed in these conditions. The study underscores the challenges inherent in diagnosing and managing MCTD and overlap disorders, emphasizing the importance of a comprehensive assessment, a multidisciplinary management approach, and regular clinical follow-up. By optimizing understanding and minimizing disease-related morbidity and mortality, this study aims to contribute to improved outcomes for patients with MCTD and overlap syndromes.*
Results*: The results of the study reveal several noteworthy findings regarding the clinical presentation, laboratory findings, and treatment approaches in patients diagnosed with Mixed Connective Tissue Disease (MCTD) who met the criteria defined by Alarcon Segovia and Villareal. Overall, the results of the study underscore the complexity and heterogeneity of MCTD, highlighting the importance of a comprehensive diagnostic approach and individualized treatment strategies in optimizing outcomes for patients with this challenging autoimmune disorder.*
Key Words*: Overlap syndrome, Autoantibodies, Alarcon Segovia criteria, Mixed connective tissue disease, multidisciplinary management, comprehensive assessment*

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I. INTRODUCTION

Mixed connective tissue disease (MCTD) is a multisystem disease with overlapping features of other autoimmune diseases, including systemic lupus erythematosus (SLE), polymyositis, and systemic sclerosis (SSc), along with the presence of anti-U1-ribonucleoprotein (RNP) antibodies [1]. A few studies recently suggested that mixed connective tissue disorders, during their long-standing course, begin to fulfil the criteria for other connective tissue diseases, and the diagnosis may potentially change [2, 3].

Overlap syndromes (OSs) satisfy the clinical and biochemical features of at least two connective tissue diseases (CTDs) sequentially or simultaneously [4]. The CTDs included systemic lupus erythematosus (SLE), systemic sclerosis, polymyositis, dermatomyositis, rheumatoid joint pain (RA), Sjogren's disorder, eosinophilic granulomatosis with polyangiitis (EGPA), immune system thyroiditis, and antiphospholipid counteracting agent disorder (APLA) [5].

Mixed connective tissue disorder (MCTD) and overlap syndromes represent complex entities within the spectrum of autoimmune rheumatic diseases and pose significant diagnostic and management challenges due to their heterogeneous presentations and overlapping manifestations.

The recognition of MCTD and overlap syndromes hinges on the identification of shared clinical, serologic, and histopathologic highlights, frequently requiring a comprehensive assessment by rheumatologists and other specialists. Whereas particular diagnostic criteria for MCTD have been proposed, the need for agreement and the evolving understanding of autoimmune illnesses contribute to the symptomatic complexity encompassing these conditions

Despite advances in serologic testing and imaging modalities, the optimal management of MCTD and overlap syndromes remains uncertain, with treatment regimens often guided by the severity of organ involvement and individual patient response. The diverse clinical phenotypes and variable disease courses underscore the need for a personalized approach to patient care, emphasizing the importance of multidisciplinary collaboration and long-term follow-up. Through the exploration of diverse clinical scenarios, we aim to enhance our understanding of these complex autoimmune disorders and provide insights into the challenges and opportunities in their diagnosis and management.

DIAGNOSTIC CRITERIA:

For clinicians, diagnosing Mixed Connective Tissue Disease (MCTD) presents a significant challenge due to its overlapping features with other rheumatological conditions. While there are six diagnostic criteria available, the Alarcon-Segovia criteria are widely accepted, boasting a sensitivity of 62.5% and a specificity of 86.2%. In this case study, we have utilized these criteria for diagnosis.

However, several authors argue against considering MCTD as a distinct clinical entity. Reichlin et al. (6), LeRoy et al. (7), and Nimelstein et al. (8) do not regard MCTD as a separate diagnosis. They argue that many of the clinical features of MCTD resemble those of Systemic Lupus Erythematosus (SLE), and a majority of MCTD patients have positive anti-sn-RNP antibodies and may progress to SLE or Systemic Sclerosis (SSc) during the course of their illness (9, 10, 11).

Contrary to this viewpoint, a study by Susana Capelli et al. evaluated 161 patients with MCTD retrospectively and followed their diagnosis and evolution for over 7.9 years (12). The study found that more than half of the patients remained diagnosed with MCTD throughout the follow-up period, suggesting that MCTD may indeed represent a distinct clinical entity for some patients.

OBJECTIVE :

In this study, we have looked at the clinical presentation and serological autoantibodies of patients with MCTD that met the criteria of Alarcon-Segovia and Villareal (13).

II. METHODOLOGY:

case-based study of 10 patients with SLE, RA Or MCTD who fulfil the required criteria

Serological criteria	Serological criteria	Clinical criteria	Diagnosis
	Anti-RNP Antibody titer:^{3}1:1000	(1) Edema in hands (2) Synovitis (3) Myositis (4) Raynaud's phenomenon (5) Acrosclerosis	Serological criteria plus at least 3 clinical criteria, including either synovitis or myositis

Serological criteria and ≥ 3 of the clinical criteria (Raynaud's phenomenon, sclerodactyly, and oedema of the hands) require additional compliance with criteria 2 or 3 [13].

Exclusion criteria:

Patients are not fulfilling the clinical criteria for MCTD.
There were no confirmatory serological tests.

Methodology :

Clinical Case-based series of 10 patients fulfilling criteria for MCTD at a tertiary care centre at Indian Institute Of Medical Science and Research, Department of General Medicine at Warudi, Jalna
As per the criteria of Alarcon Segovia and Villareal, MCTD includes synovitis, joint swelling and The following features :
Raynaud's phenomenon seen in 7 patients
sclerodactyly presented in 6 patients
Anti-RNP was positive in 8 patients

CASE	1	2	3	4	5	6	7	8	9	10
Puffy hands	+	+	+	+		+	+	+	+	+
Synovitis	+	+	+	+	+	+	+		+	
Myositis	+	+			+	+		+		+
Raynaud's		+	+	+	+		+		+	+
Sclerodactyly			+		+	+	+		+	+
Anti-RNP ≥1:1600	+	+	+	+	+	+		+	+	

COMMON SYMPTOMS:

Figure 1: Patient with photosensitivity and Rash

Figure 2: Joint involvement

All patients exhibit fever, Arthralgia and asthenia (weakness fatigue). Most cases involve additional symptoms such as alopecia (hair loss), xerophthalmia (dry eyes), weight loss, skin rash, and anasarca (generalized swelling).

Some patients also experience anorexia, xerostomia (dry mouth), headache, dyspnea (shortness of breath), and photosensitivity.

LABORATORY FINDINGS

ANA (Antinuclear antibody) tests are positive in all cases, typically at a titer of 1:80 with a speckled pattern, suggesting autoimmune activity.

- Anti-DNA antibodies are found in three patients, indicating possible lupus involvement.
- Rheumatoid Factor (RF) is positive in 1 patient, 1 shows positivity for Anti-cyclic citrullinated peptide Antibody (ACPA), suggesting rheumatoid arthritis (RHUPUS)
- Acute-phase reactants are elevated in 6 patients, indicating inflammation.
- No patients exhibit hypocomplementemia, common in certain autoimmune diseases like lupus.
- Tests for anti-Scl70 or anti-Jo antibodies yield negative results.
- Elevated total creatine kinase in one case suggests muscle involvement, possibly myositis, although aldolase and LDH levels are normal.

OVERALL IMPRESSION

- The clinical presentation and laboratory findings suggest a systemic autoimmune disorder, likely lupus due to the presence of FANA and anti-DNA antibodies. However, the absence of hypocomplementemia and Anti-Sm antibodies may indicate a variant of lupus or another connective tissue disorder.
- Other potential diagnoses based on symptoms and findings include mixed connective tissue disease (MCTD) or Sjogren's syndrome, considering dry eyes and mouth.
- Further evaluation, including additional antibody testing and possibly biopsy, may be necessary for confirmation and treatment guidance.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
ANA	+	+	+	+	+	+	+	+	+	+
Anti-DNA								++	+++	
Anti-Sm		++		++	+	++	+	++	++	
RA	+									
CRP		+		+	++	+		++		+

ESR										
Nucleosomes										+
ACPA										
Anti Scl 70			++	+++						
Anti -JO										
Anti RNP	++	+++	++	+++		++	+++	++	++	++
Anti SSA/Ro	+++				+	+++			+++	
Anti-SSB/La	++									
Proteinuria ≥ 500 mg/24 hrs.										
Ribosomal-p					+++					++
Histones							++	++	++	

Anti-RNP was positive in 9 cases with titles greater than 1:1600.
Four patients with positivity for Anti-SSA/Ro were found; however, there was 1 positive for Anti-SSB/La
Common laboratory alterations found were haematology and urinalysis in 4 patients; 2 had normal routine clinical laboratory studies.

Treatment consisted of a combination of DMARDS, NSAIDs, and steroids in some cases: Calcium antagonists, ARA II, ACEI, phosphodiesterase 5 inhibitors, and prokinetic and proton pump inhibitors.
DMARDS were used for arthritis control when there were predominant clinical SLE-like features. Mycophenolate mofetil was used in case 2 because it was the most complicated case due to cardiopulmonary involvement and the need to use an additional phosphodiesterase 5 inhibitor.
Drugs were used for specific clinical situations, such as Raynaud's phenomenon, with the use of calcium antagonists. In addition, proton pump inhibitors for control of gastroesophageal reflux

III. DISCUSSION:

MCTD is characterized as a rare disorder, with an estimated prevalence of 6.4 per 1,000 people in the USA [6]. There have been many criteria proposed for the diagnosis of MCTD, including The Alarcon-Segovia diagnostic criteria, the Japan research committee criteria, the Kasukawa diagnostic criteria, Sharp's criteria and Khan's criteria. The Alarcon-Segovia diagnostic criteria for MCTD consist of a high titer of positive anti-U1-RNP (over 1 per 1600) and three or more manifestations among Raynaud phenomenon: hand oedema, synovitis, histologically proven myositis, and acrosclerosis.[7] The Japan Research Committee of the Ministry of Health, Labour, and Welfare for Systemic Autoimmune Diseases divided the features of MCTD into four categories. [8] These include:

1. Common manifestations: Raynaud's phenomenon, Puffy fingers, and/or swollen hands
2. Immunological manifestation: Positivity for anti-U1 ribonucleoprotein antibody
3. Characteristic organ involvement: Pulmonary arterial hypertension, Aseptic meningitis, Trigeminal neuropathy
4. Overlapping manifestations:

a. Systemic lupus erythematosus-like manifestations: Polyarthritis, Lymphadenopathy, Malar rash, Pericarditis or pleuritis, Leukopenia (4,000/μL or less) or thrombocytopenia (100,000/μL or less)
b. Systemic sclerosis-like manifestations: Sclerodactyly, Interstitial lung disease, Esophageal dysmotility or dilatation
c. Polymyositis/Dermatomyositis-like manifestations: Muscle weakness, Elevated levels of myogenic enzymes, Myogenic abnormalities on electromyogram

The Kasukawa diagnostic criteria [9] are based on common symptoms and mixed symptoms, while Sharp's criteria consist of 5 major and 11 minor criteria. Khan's criteria on the other hand; is based on serologic and clinical criteria. These criteria though distinct, have many overlapping features; but
Alarcón-Segovia and Khan's criteria have been proven to be the most efficient in the diagnosis of MCTD. [10]

Overlap syndromes meet the criteria for more than one autoimmune connective tissue disease. Over time, it has been noticed that these present with similar groups of overlapping clinical features and have been persistently linked with antibody associations. These include Anti U1-snRNP Ab (MCTD) associated with SLE+ myositis+ scleroderma+ RA; Anti PM-Scl Ab associated with myositis + Raynaud's; Anti synthetase Ab (Jo-1, etc.) associated with myositis + arthritis + interstitial lung disease; Anti SSA/B + RF+ anti-CCP Ab associated with RA + Sjogren's. [11] A mixed connective tissue disease whose existence has been a topic of much debate over the past years has now been considered to be a type of overlap syndrome.

‘’Rhupus’’ is a term used for the overlap between SLE and RA features [11]. Schur used the term "Rhupus syndrome" to describe patients with a mixture of signs and symptoms of systemic lupus erythematosus and related diseases such as rheumatoid arthritis.[12] M G Cohen and J Webb reported 11 cases of concurrent rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Their association with well-described serological overlap led to the contention that these two diseases coexist more than by chance alone. [13] a similar case was recently reported by Lam et al. of a patient with a long-standing history of rheumatoid arthritis and mixed connective tissue disease, which later progressed to lupus nephritis. [14] Another uncommon association of ANCA–associated vasculitis with Rhupus has been reported recently by Emma Resoor et all. [15]

The cases presented in this series illustrate the heterogeneous nature of MCTD and overlap syndromes, reflecting the diverse spectrum of autoimmune manifestations observed in affected individuals. Despite sharing common autoimmune pathways, each patient exhibited a unique combination of clinical symptoms and laboratory findings, underscoring the complexity of these rheumatologic disorders.

Lab studies in MCTD usually demonstrate anaemia, leukopenia, hypergammaglobulinemia, and elevated ESR. Immunological markers include high-titer speckled pattern anti-nuclear antibody, high-titer anti-U1-RNP antibody, and anti-U1 70kd antibody. Urinalysis will show proteinuria. 65% of the patients show positive RF, while 50 % show positive anti-CCP. [16, 17] Patients may show falsely positive VDRL and reduced levels of complement. APLA is associated with pulmonary hypertension, as seen in our patient. [18] Imaging studies required for MCTD and overlap syndrome include CXR, X-ray joints, ECG, EKG, PFTs, CT, angiograms, and right heart catheterization.
Management includes treatment of Raynauds phenomenon, arthritis, arthralgia, and associated joint problems, pleuritis, pericarditis, myositis, myocarditis, and aseptic meningitis. AIHA, thrombocytopenia, pulmonary hypertension, and oesophagal disorders must be managed as indicated.

IV. CONCLUSION

In conclusion, the diagnosis and management of overlap syndromes represent a complex and challenging aspect of autoimmune rheumatic diseases. Through comprehensive clinical evaluation, serologic testing, and imaging studies, healthcare providers can identify patients presenting with overlapping features of multiple autoimmune disorders.

The multidisciplinary management of overlap syndromes involves collaboration among rheumatologists and various specialists to address the diverse clinical manifestations and potential complications associated with these conditions. Pharmacotherapy, including immunosuppressive agents, disease-modifying drugs, and biological therapies, aims to suppress autoimmune activity, alleviate symptoms, and improve overall patient outcomes.

Regular monitoring of disease activity, treatment response, and potential adverse effects is paramount in ensuring optimal patient care and preventing disease progression. Patient education and support play a crucial role in empowering individuals to actively participate in their treatment plans and adhere to prescribed therapies.

Despite the challenges posed by overlap syndromes, ongoing research and clinical trials offer hope for improved understanding, diagnostic accuracy, and treatment strategies in the management of these complex autoimmune disorders.

In conclusion, by embracing a comprehensive and collaborative approach to diagnosis and management, healthcare providers can effectively address the needs of patients with overlap syndromes, optimize treatment outcomes, and enhance the quality of life for individuals living with these challenging conditions.

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