

Clinical and immunological profile in patients with mixed connective tissue disease

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Abstract

Mixed connective tissue disease (MCTD) is a rare disease and presents with varied overlapping symptoms of different connective tissue disorders. Many patients evolve into other connective tissue disorders with the passage of time.

The case series included 20 patients with the diagnosis of MCTD, registered at the Rheumatology Clinic of Jinnah Postgraduate Medical Centre (JPMC), Karachi, from June 2010 to May 2015. Of these, 16 (80.0%) were female and 4 (20.0%) patients were male. The mean age was 30.5 ± 8.9 years and the mean duration of illness was 4.5 ± 2 years. Commonest presenting symptom was arthralgia in 17 (85%) patients. All the patients had positive ANA and anti-RNP antibodies. Over the disease course of 6 years, 2 (10%) patients evolved into Systemic lupus erythematosus (SLE); One each (5%) into Sjogren's syndrome, Scleroderma and Rheumatoid arthritis.

Keywords: Mixed connective tissue disease (MCTD), Undifferentiated connective tissue disease (UDCT), anti-ribonucleoprotein antibody (RNP).

Introduction

Mixed connective tissue disease (MCTD), is characterized by the presence of overlapping features of two or more systemic connective tissue disorders, and associated with the presence of antibody against uridine-rich ribonucleoprotein (U1-RNP). The exact pathogenesis is not known, a complex interaction between the innate and adaptive immune response is thought to be responsible in the evolution of this autoimmune disorder.¹ The disease is rare, few population based surveys reporting 3.8 to 6.4 cases per 100000 population.^{2,3}

There is paucity of data to reflect the prevalence of rheumatological diseases from Pakistan. No studies have been reported from Pakistan with regard to the incidence and clinical aspects of MCTD so far.

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Case Series

This case series included patients registered at the Rheumatology Clinic of Jinnah Postgraduate Medical Centre, Karachi, from June 2010 to May 2015, with the diagnosis of MCTD. Patients with definitive diagnosis of MCTD, according to validated diagnostic criteria,^{4,5} were included in the study. Detailed history, examination and laboratory work-up was done for all patients. Data was recorded in pre-designed structured proforma. The frequency, clinical and immunological characteristics, demographic features and disease outcome were studied. Patients were regularly followed at 3 monthly intervals.

A total of 20 patients were diagnosed with MCTD. Of these, 16 (80.0%) were female and 4 (20.0%) were male. The mean age was 30.5 ± 8.9 years and the mean duration of symptoms was 4.5 ± 2 years. Most patients were in third decade of life. (Table-1) Majority patients had more than two or three presenting clinical signs and symptoms, commonest being arthralgia with clinically evident synovitis in 17 (85%) patients. Other features included oral ulcers in 12 (60%) patients; facial erythema in 9 (45%); photosensitivity in 9 (45%) and Raynaud's phenomenon in 5 (25%) patients. While alopecia, dry mouth and dry eyes, malar rash, reduced mouth opening, sclerodactyle, dysphagia and dyspnoea were reported in 1-4 patients, individually (Figure-1). All patients had positive anti-RNP in titre of >1.0 U. ANA (Anti-neutrophil antibody) was also positive in 17 (85%) patients. A low titre RF (Rheumatoid factor) was also positive in 11 (55%) patients. Other positive anti-bodies included Anti-Ro, Anti La in 4 (20%) patients, Anti-Scl-70 in 2 (10%) and Anti-DsDNA in 4 (20%) patients, while Anti-smith, Anti-centromere remained negative in all (Figure-2).

Over the disease course of 6 years, 2 (10%) patients

Table-1: Age group of patients with MCTD.

Age Group (Years)	No. of patients	Percentage %
< 20	2	10%
21-30	12	60%
31-40	3	15%
41-60	3	15%

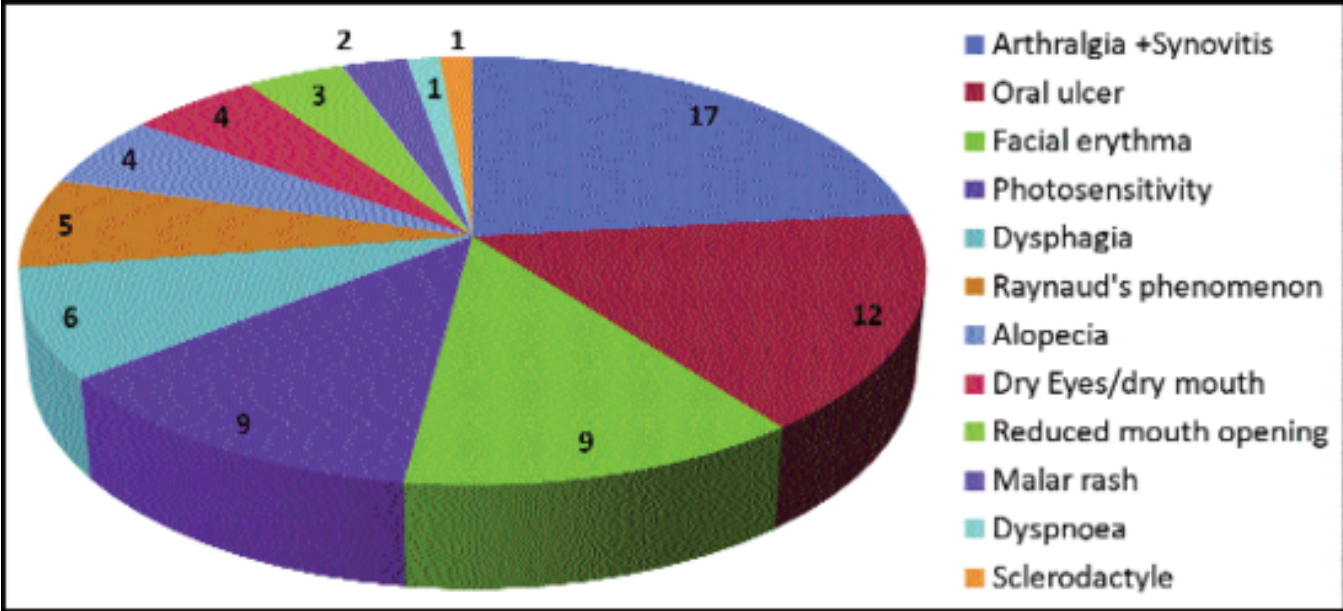


Figure-1: Clinical sign and symptoms in patients with MCTD.

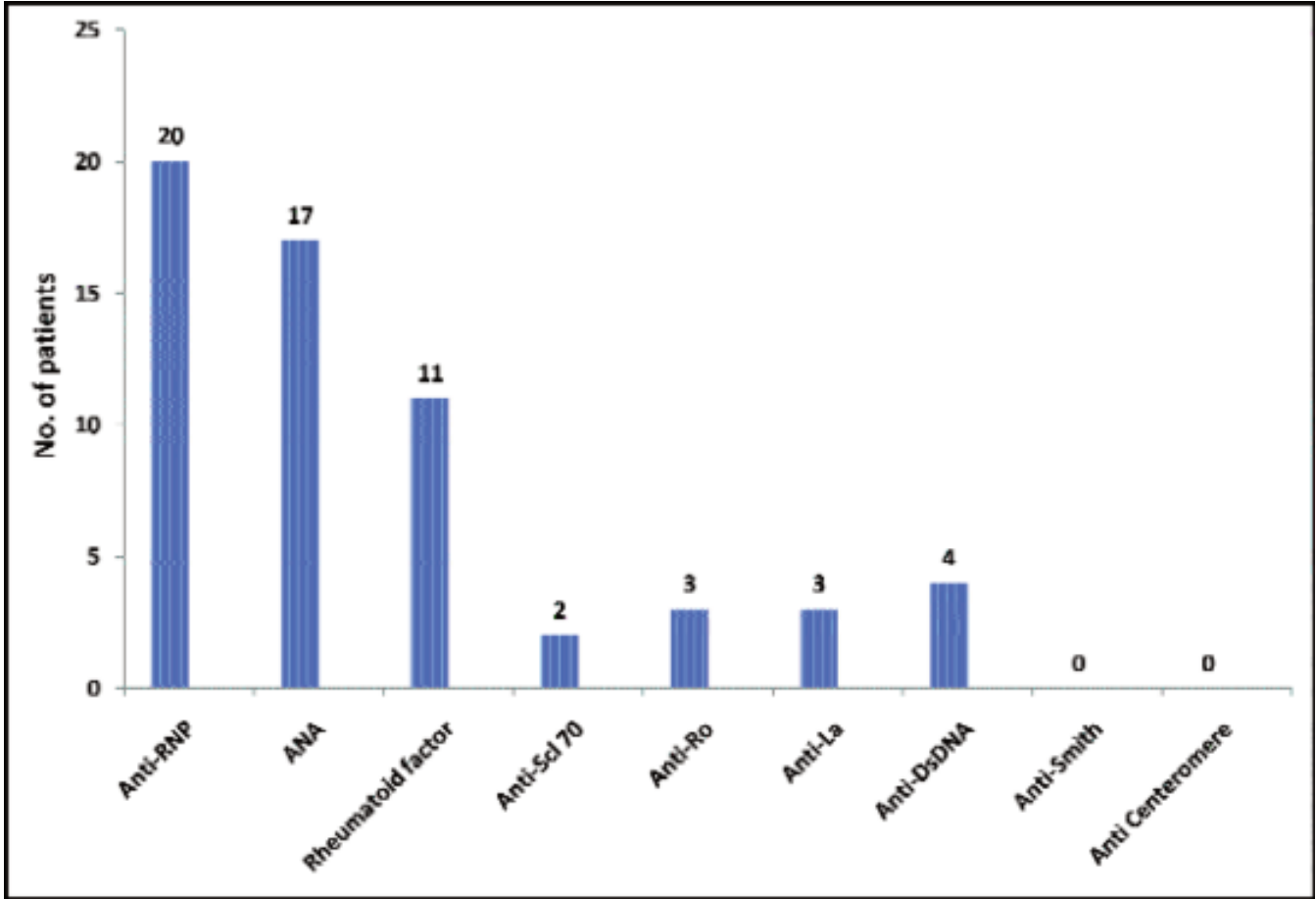


Figure-2: Immunological profile in patients with MCTD.

evolved into SLE; one each (5%) into Sjogren's syndrome, Scleroderma and Rheumatoid arthritis. While 1 (5%) was re-classified as un-differentiated connective tissue disease. One patient reported with dyspnoea developed severe pulmonary hypertension.

Discussion

MCTD appears to be a rare disease in our patients, as very few of the patients fulfilled the criteria for diagnosis, despite overlapping features of ≥ 2 features of autoimmune connective tissue diseases. There are several, internationally recognized, classification criteria for MCTD used in clinical practice. The Alarcon-Segovia criterion^{4,6} was used in our clinic, because it is easy and can be quickly applied in a clinical setting. In addition, it has the highest sensitivity and specificity in identifying patients with MCTD.

The disease predominantly affected females, as reported in other studies also.⁷ Despite majority of our patients presenting more like SLE, in terms of clinical manifestations, immunological markers remained negative for that, providing additional support for the notion that MCTD exists as a separate disease entity of its own.⁸ Other studies have also reported varied clinical features in patients with MCTD, and overlapping features tend to occur sequentially during the disease course.^{9,10} Patients had varied manifestations, commonest being arthralgia as evident in this case series. It has been reported that during early disease course, patients with MCTD may have unexplained fatigue, poorly defined myalgias and Arthralgias.¹¹ Raynaud's phenomenon with trophic abnormalities in digits, is frequently seen in MCTD and represents the initial manifestation of the disease.¹² However, it was less evident in our patients. This could be attributed to geographical variations, as Raynaud's phenomenon is more prevalent in areas of high altitude with colder climate. The study participants belong to a temperate region, therefore vasospasm induced finger blanching was less evident in our patients. Many patients in the study group had other cutaneous manifestations like photosensitivity and facial erythema. Cutaneous features of our patients differed from those reported by Sen et al.¹³ One patient in our study reported with severe pulmonary hypertension. Pulmonary hypertension, secondary to the vasculopathy is the most important factor per se in prognostication.¹⁴ Another important factor predicting mortality is the appearance of lung fibrosis, which ultimately leads to pulmonary hypertension.

As autoimmunity is a complex process which involves both genetic and environmental factors, hence the

susceptibility to develop disease varies among individuals. There are possibly other, yet unknown factors which may co-exist for disease expression. The presence of anti-RNP antibody remains the sine qua non for the diagnosis of MCTD.¹⁵ Beyond elucidation of the underlying mechanism, the pathogenic role of auto-antibodies in the emergence of disease may have therapeutic implications as well. All the study participants had positive anti-RNP antibodies, though the titres were variable. A high titre of anti-RNP anti-bodies in any patient with features of UCTD is a powerful predictor of later evolution into MCTD.¹⁶ In the majority of patients, antibody profile remains constant throughout the disease course. However, the utility of antibody biomarker in disease classification appears to be elusive, as occasionally fluctuations may occur. Antibodies may sequentially disappear or new antibodies emerge with changes in the clinical spectrum of disease. These changes do not necessarily reflect the clinical disease activity. Nevertheless, it has been reported that patients with MCTD may evolve into other connective tissue disorders during the course of the disease. This phenomenon is reflected in this small cohort of patients as well. It has been reported that after 7-9 years of disease, 9.1%, 2.5% and 17.3% patients diagnosed as MCTD, developed SLE, RA and Scleroderma, respectively.¹⁷ It is very important to appropriately distinguish MCTD with 'Undifferentiated connective tissue (UDCT) disorders' where a clear rheumatological disorder may or may not emerge with time. The initial clinical features and immunological profile may predict the evolution of future phenotype in these patients.^{18,19} Though, a very small number of patients have been identified with MCTD over a long time span. The precise epidemiological data is not available to reflect the exact prevalence of this disease, hence it points towards the rarity of disease per se. A population based study reported that MCTD occurs in about 2 persons per 100,000 per year.⁷ So far no study has been reported from Pakistan to reflect the disease spectrum of MCTD, hence this study would be important in providing clues to the clinical presentation and prevalent immunological markers and disease progression, as seen in our patients. It also emphasizes the need to distinguish MCTD from UDCT disorders, as the latter may present with ambiguity of signs and symptoms and a subset of patients may slowly emerge into a clear connective tissue disease.

Conclusion

The study points towards the existence of MCTD in our population with varied manifestations, which somewhat differs from the west. It identifies groups of patients, in whom ongoing surveillance for evolving manifestations

of connective tissue diseases is mandatory, in order to improve the outcome and prognosis.

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