International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Mixed Connective Tissue Disease - A Tertiary Centre Experience

Divya Y[1], Rajeswari S[2], Balaji C[3], Saranya C[4], Grishma D[5], Akanksha S[6], Vishwa Prakash T[7], Nidhi R P[8], Lakshmi Tejaswi K[9]

[1]Post Graduate, Department of Clinical Immunology and Rheumatology, Sri Rama Chandra Institute of Higher Education and Research (SRIHER), Chennai. (Corresponding author)

[2]Prof and HOD, Department of Clinical Immunology and Rheumatology, SRIHER, Chennai, India

[3]Associate Professor, Department of Clinical Immunology and Rheumatology, SRIHER, Chennai, India

[4]Associate Professor, Department of Clinical Immunology and Rheumatology, SRIHER, Chennai, India

[5, 6, 7, 8, 9]Post Graduate, Department of Clinical Immunology and Rheumatology, SRIHER, Chennai, India

Abstract: ***The diagnosis of MCTD is based on specific criteria. There are few Studies on MCTD available in Indian population. This study aims to describe the clinical profile, immunological profile and outcome in patients with MCTD. This is a retrospective observational study, data taken from hospital records over 4 years (2017-21) done at SRIHER. Patients were diagnosed as MCTD by Alarcon - Segovia criteria. The clinical data, immunological profile, treatment given and outcome on follow up were noted. On follow up, the disease predominant manifestations of MCTD were observed. Autoantibody profile using Line immune assay 15 was noted. CYC was given for 17 patients, MMF for 11 patients, RTX for 5 patients, MTX for 9 patients, AZA for 1. Patients were followed up for mean duration of 2.2 years. 2 patients died due to sepsis. Strong female preponderance was observed in our cohort. Musculoskeletal involvement was the most common manifestation. Systemic sclerosis predominant features were common.***

Keywords: Mixed connective tissue disease, Interstitial lung disease, Raynauds, Pulmonary artery hypertension, myositis.

1. Introduction

Mixed connective tissue disease (MCTD) is considered as a rare autoimmune disease as described in literature. It has overlapping features of systemic lupus erythematosis (SLE), systemic sclerosis (SSc) and inflammatory myositis[1]. It has clinical features with higher incidence of Raynaud's phenomenon and pulmonary artery hypertension[2]. It has variable presentations and is difficult to diagnose. Presence of specific antibody U1RNP (Uracil 1 Ribonucleoprotein) aids in the diagnosis[2]. Many criteria are used for the diagnosis of MCTD. Alarcon-Segovia criteria is the most commonly used criteria[3]. Alarcon-Segovia criteria consists of high titer U1RNP positivity (1: 1600) along with 3 out of 5 clinical features from the following manifestations. 1. Raynaud's phenomenon. 2. Puffy fingers. 3. Arthritis or synovitis. 4. Myositis. 5. Acrosclerosis. There is limited data on MCTD from India. The aim of our study is to describe the epidemiological and clinical profile in patients who were diagnosed with MCTD.

2. Methodology

This is a retrospective observational study done at the department of Clinical Immunology and Rheumatology at SRIHER, a tertiary care centre in South India. We included 60 patients who were diagnosed as MCTD as per Alarcon-Segovia criteria over a duration of 4 years [2018-2022]. We excluded patients who satisfied other classification or diagnostic criteria for other connective tissue diseases (CTD).

Data was obtained from electronic medical records. By using standard proforma, demographic details, clinical features and laboratory findings were collected. Rheumatoid factor (RF) test was done by nephelometry. Anti nuclear antibody (ANA) test was done by indirect immunoflouresence (IIF). ANA profile for autoantibodies detected by Line immunoassay (LIA-15/21) done at our centre. These patients were followed up for clinical manifestations and response to treatment during the disease course. Continuous and categorical variables were reported as mean with standard deviation and percentage or proportion respectively.

3. Results

60 patients were included in our study and were followed up for a mean duration of 2.2 years. The mean age at presentation was 41.6 +-11.2 years. Male to female ratio was 1: 30. 22.7% had vitamin D deficiency. Most common comorbidity in our cohort was hypothyroidism seen in 28.3%.

Table 1: Clinical profile:

Epidemiological data	N (No. of patients) (%)
Mean age	41.6+-11.2
Male: Female	1: 30
Clinical features	
Musculoskeletal	47 (78.9%)
Puffy fingers	21 (35%)
Synovitis	38 (63.3%)
Arthralgias	18 (30%)
Myositis	14 (23.3%)

Sclerodactyly	11 (18.3%)
Pulmonary artery hypertension (PAH)	**22 (36.7%)**
Raynauds	**34 (56.6%)**
Interstitial lung disease (ILD)	**30 (50%)**
Mucocutaneous	**14 (23.3%)**
Alopecia	5 (8.3%)
Oral ulcers	4 (6.6%)
Microstomia	3 (5%)
Skin tightening	12 (20%)
Salt and pepper pigmentation	4 (6.6%)
Haematological	**13 (21.6%)**
Anemia	8 (13.3%)
Thrombocytopenia	3 (5%)
Leukopenia	2 (3.3%)
Others	
Sicca	14 (23.3%)
Parotidomegaly	2 (3.3%)
Proteinuria	4 (6.6%)
Peripheral neuropathy	3 (5%)
Trigeminal neuropathy	2 (3.3%)
GERD	5 (8.3%)

Table 2: Immunological profile:

ANA (Anti nuclear antibody)	54 (90%)
RNP/Sm Ribonucleo protein/ Smith	60 (100%)
SS-A (Sjögren syndrome related Antigen A) (Ro-52)	15 (25%)
Ro-60	12 (20%)
SS-B (Sjögren syndrome related Antigen B)	3 (5%)
Sm (Smith)	3 (5%)
Pm-Scl (Polymyositis/scleroderma)	1 (1.7%)
RF (Rheumatoid factor)	12 (20%)
Anti CCP (Anti cyclic citrullination peptide)	1 (1.7%)

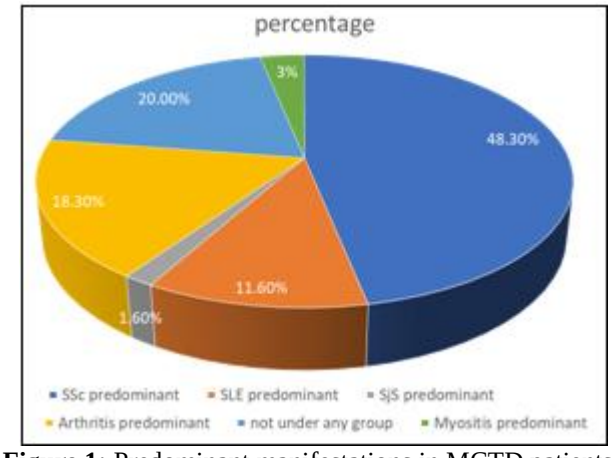

Figure 1: Predominant manifestations in MCTD patients:

Polyarthritis was the most common musculoskeletal manifestation observed in our cohort and the most common cutaneous manifestation was skin tightening. Pulmonary artery hypertension (PAH) was observed in 37% of patients and all of them had Raynaud's. Mild, moderate severe PAH were seen in 20%, 11.7% and5% of patients respectively. Raynaud's was observed in 57%, out of which 10% had ulcers and 1.6% had gangrene. Nonspecific interstitial pneumonitis (NSIP-ILD) was seen in 31.6% and 18.3% had Usual interstitial pneumonia (UIP-ILD).

Most common pattern of ANA was nucleus speckled pattern. Systemic sclerosis manifestations were the most predominant among the connective tissue diseases (CTD) [Figure 1].

Mean duration for the improvement of dyspnea by 1 scale as per MMRC was less with rituximab (RTX) [3.5 months] compared tocyclophosphamide (CYC) [4.2 months] in patients with UIP pattern of ILD, whereas in patients with NSIP pattern of ILD, we observed that mycophenolatemofetil (MMF) and CYC had similar out comes. Progression of ILD was less with CYC and RTX. Mean FVC decline with CYC was3.2%/year and RTX was 3%/ year, whereas with MMF it was 5.2%/year. CYC showed better response to Raynaud's with complications and pulmonary artery hypertension. The mean improvement in mPAP (mean pulmonary artery pressure) was 16 mm of Hg with CYC compared to 9mm of Hg with MMF and 14 mm of Hg with RTX. [Figure 2]. The mean duration of follow up was 2.2 years and most of the patients remained as MCTD [Figure 3].

There are no proper guidelines or Randomised controlled trials (RCTS) for management of MCTD14. Although the state of art on Clinical practice guidelines in MCTD was collected from various resources, but it had not mentioned any specific guidelines.14The treatment given in our cohort is based on major manifestation. In patients with UIP pattern of ILD, RTX showed better outcome as in Rheumatoid arthritis. In NSIP ILD both MMF and CYC had similar outcomes as in other CTD associated ILDs. We also observed that CYC showed good response to PAH compared to RTX and MMF when given along with vasodilators as per ESC/ERS guidelines on treatment of PAH15. As mentioned by several case series 16, 17, PAH can have vasculitis component along with vasculopathy, these manifestations showed response to immunosuppressants along with vasoldilators. Raynaud's without complications, responded well to vasodilators whereas, Raynaud's with digital ulcer or gangrene responded well to CYC. As Raynaud's was considered as common manifestation of MCTD, systemic sclerosis phenotype was most commonly seen in our population.

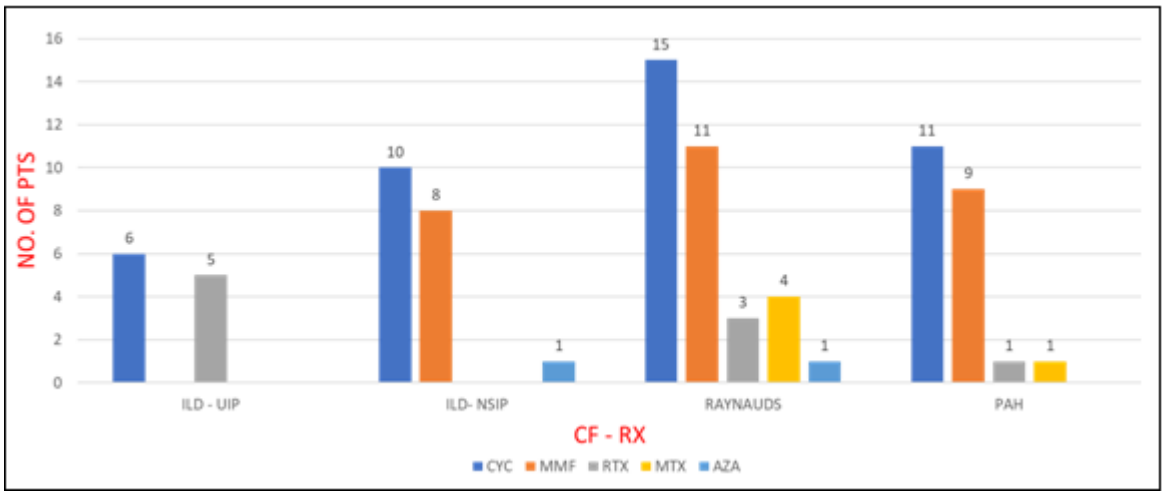

Figure 2: Treatment given for various clinical manifestations in MCTD patients

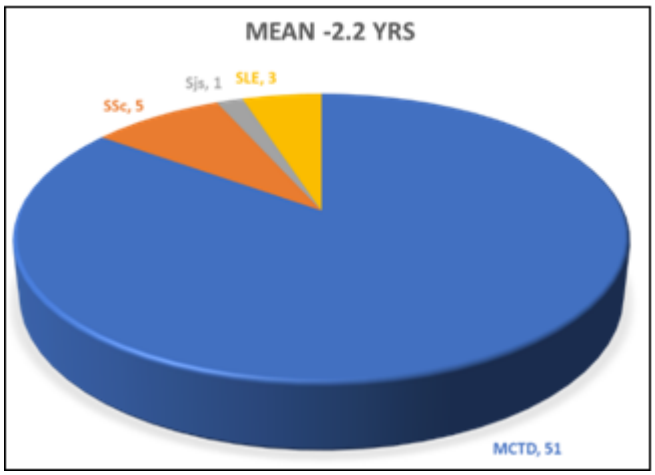

Figure 3: Follow up of MCTD patients.

4. Discussion

There are only few studies on MCTD from India. This is a retrospective study from a South Indian tertiary care centre. We compared our data with other studies from different parts of the country. The mean age of our population was higher compared to other Indian studies and as described by Gunnarson etal[5]. There was significant female preponderance with female to male ratio of 30. Indian studies from different region also had similar ratio whereas, Gunnarson etal[5]study found much lower ratio of 3.3.

Musculoskeletal involvement was the most common manifestation in our study whereas Raynaud's was the most common feature in North Indian studies. This difference in Raynaud's may be attributed to climatic conditions, as Southern India is warmer compared to northern side. Digital gangrene was less common in our cohort. Arthritis and myositis were less common in our population, similar to another South Indian study when compared to data from other regions. PAH, ILD and puffy fingers were similar compared to other studies. GERD was less common whereas, neuropathy and nephropathy were seen in variable proportions in all the studies [Table 3]. In our study, Systemic sclerosis phenotype was more common which was similar to other studies.

ANA positivity was seen in 90% of patients similar to other studies. 20% and 1.7% patients in our cohort had positive Rheumatoid factor and anti-CCP respectively. A meta-analysis done by Garcia etal[4] and Takasakietal[5] revealed a much higher RF and anti-CCP positivity (65% and 50% respectively). Other autoantibodies seen in our cohort included SS-A seen in 35%, SS-B and Sm are seen in 5% of patients. Pm-Scl positivity was seen in 1.7% of patients. On follow up 3% had anti dsDNA positivity and all of them had nephropathy. Chaigneetal[12]., Tanietal[13]., also described these autoantibodies being positive in their study groups.

Table 3: Comparison of clinical profile with other studies

Study Data	Our Study	CMC KevinJohn etal	PGI V Dhir etal	KALINGA Debashis etal	SGPGI Lawrence et al	IPGMER Sumitsen etal
N	60	111	41	30	16	23
DURATION (YR)	4	10	20	2	1	3
MEAN AGE	41.6 ± 11.2	39.3	33.8 ± 10.7	41.3 + 13	36	31.22 ± 7.4
M: F	1: 30	1: 13	1: 40	1: 9	1: 15	1: 7
ARTHRITIS	63.3 %	69.4 %	81 %	77 %	81 %	87 %
MYOSITIS	23.3 %	20 %	49 %	63 %	31 %	52 %
PUFFY FINGERS	35 %	36.9 %	46 %	36.6 %	81 %	39 %
RAYNAUDS	56.6 %	66.7 %	75 %	100 %	93 %	78 %
PAH	36 %	8.1 %	44 %	40 %	12 %	40 %
ILD	50 %	38.7 %	57 %	60 %	56 %	21 %
GERD	8.3 %	56 %	-	93 %	50 %	-
NEUROPATHY	5 %	9 %	-	75 %	-	-
NEPHROPATHY	6.6 %	17 %	-	7 %	-	-
ANA +	90 %	89.2 %	82 %	88 %	-	87 %

5. Conclusion

Higher mean age and strong female predominance was observed in our South Indian population. Musculoskeletal manifestations were more common and Raynauds was less common. Patients having nephropathy with massive proteinuria and higher anti dsDNA levels on follow up had higher chances for progression to SLE. UIP-ILD responded well to Rituximab. Raynauds and pulmonary artery hypertension showed a good response to cyclophosphamide.

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