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CONNECTIVE TISSUE OVERLAP SYNDROMES: A CLINICAL STUDY

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ABSTRACT **BACKGROUND:** Connective tissue diseases are not often present in isolation. The distinction between classic autoimmune connective tissue disease and an Overlap syndrome was reported to be of prognostic and therapeutic significance. We performed this study to identify Overlap syndromes in autoimmune connective tissue disease patients and understand their clinical presentation. **MATERIALS AND METHODS:** This hospital based observational study was carried out in Assam Medical College and Hospital, Dibrugarh from 1st July 2018 to 30th June 2019. All patients with history and clinical examination findings suggestive of connective tissue diseases attending Rheumatology OPD or other outpatient department or in various wards of department of Medicine were screened for Overlap syndromes. After considering inclusion and exclusion criteria, a total of 642 clinically suspected connective tissue disease patients were included in the study. Overlap syndrome was diagnosed on the basis of patient fulfilling the classification criteria of two or more connective tissue disease at the same time and for specific Overlap MCTD, patient fulfilling the Alarcon segovia criteria. **RESULTS:** After screening of 642 clinically suspected connective tissue disease patients, we identified 54 patients of Overlap syndrome after detailed history, clinical examination and investigations. Among 54 Overlap syndrome patients, we found 25 patients with MCTD, 11 patients with SSc/RA overlap, 7 patients with SSc/SLE overlap, 2 patients with SSc/myositis overlap, 6 patients with SLE/RA overlap and 3 patients with SLE/myositis overlap syndrome. Most common manifestation in overlap syndrome was Mucocutaneous (100%) and musculoskeletal (90.7%) followed by constitutional symptoms (74.07%). **CONCLUSION:** Overlap syndromes are not uncommon. The diagnostic approach and prognosis of various overlap syndromes are different and it is very difficult to draw a distinct line in between the various AICTDs manifestations in overlap syndrome.

KEYWORDS : Overlap syndrome, MCTD, Connective tissue disease

INTRODUCTION:

Autoimmune Connective tissue diseases (AICTD) consist of a spectrum of multisystem autoimmune disorders characterized by immune dysregulation and immune mediated organ dysfunction. The classification of autoimmune connective tissue disease depends upon identifying clusters of clinical features and laboratory findings. According to current nosology, there are six classic autoimmune connective tissue diseases (AICTD).[1] 1Systemic lupus erythematosus (SLE) 2. Scleroderma (Scl) or Systemic Sclerosis (Ssc) 3.Polymyositis (PM) 4. Dermatomyositis (DM) 5. Rheumatoid arthritis (RA) 6. Sjögren's syndrome. All six autoimmune connective tissue diseases (AICTD) are descriptive syndromes without a "gold standard" for diagnosis. All Autoimmune connective tissue diseases are classified using widely accepted criteria considering peculiar clinical features and when available with specific serological markers.

Overlap syndrome is a condition where patient fulfills the classification criteria for more than one recognized autoimmune connective tissue disease at the same time with the exception of MCTD which is a special form of overlap associated with a specific antibody.[2] For example: Systemic lupus erythematosus, Rheumatoid arthritis, Scleroderma, Dermatomyositis, Polymyositis, Sjogrens syndrome in various combinations. And latter example of an Overlap syndrome is mixed connective tissue disease (MCTD), a specific overlapping condition characterized by the presence of anti-small nuclear ribonucleoprotein (snRNP) autoantibodies in association with overlapping clinical manifestations of SLE, Myositis, Rheumatoid arthritis, and Scleroderma.[3]

Connective tissue diseases are not often present in isolation. The distinction between classic autoimmune connective tissue disease and an Overlap syndrome was reported to be of prognostic and therapeutic significance. Studies on different Overlap syndromes has been reported from different parts of world. But very few studies are available from India. Thus their exists a gap in our understanding regarding Overlap syndrome and their clinical course. We performed this study to identify Overlap syndromes in autoimmune connective tissue disease patients and understand their clinical presentation presenting to tertiary care centre in North East India.

MATERIALS AND METHODS:

After obtaining an institutional Ethical committee clearance, this hospital based observational study was carried out in Assam Medical College and Hospital, Dibrugarh from 1st July 2018 to 30th June 2019.

Inclusion criteria: 1.All patients with history and clinical examination findings suggestive of connective tissue disease attending Rheumatology OPD or other outpatient department or in various wards of department of Medicine at Assam Medical College and Hospital.
2. Age more than 12 years.

Exclusion criteria: 1.Age less than or equal to 12 years.
2.Patient who do not give consent.

All patients with history and clinical examination findings suggestive of connective tissue diseases attending Rheumatology OPD or other outpatient department or in various wards of department of Medicine at Assam Medical College and Hospital were screened for Overlap syndromes. After considering inclusion and exclusion criteria, a total of 642 clinically suspected connective tissue disease patients were included in the study. Overlap syndrome was diagnosed on the basis of patient fulfilling the classification criteria of two or more connective tissue disease at the same time. And for specific Overlap MCTD, patient fulfilling the Alarcon segovia criteria. All patients were subjected to detailed history taking and thourough clinical examinations to look for clinical overlap features of two or more autoimmune connective tissue diseases which includes SLE, SSc, RA, DM, PM and Sjogrens syndrome as per their classification criteria. After detailed history and clinical examinations we identified patients with clinical overlap. In all patients with clinical overlap features, Routine investigations like Complete blood count, Renal function tests, Routine urine examinations, ESR, CRP and ANA, ANA blot, Nailfold capillaroscopy were done. In patients with clinically overlap features we screened for elevated muscle enzymes like CPK,AST, ALT

and RA factor, Anti-CCP,24 hour urinary proteins, ECG, ECHO, Chest x-ray, X-ray of joints, X-ray Barium swallow, USG Abdomen, HRCT Thorax, Muscle and skin biopsy as per requirement. Disease activity for SLE and RA were assessed in SLE and RA overlap patients with other connective tissue disease by SLEDAI score for SLE and DAS28 score for RA. After detailed history, clinical examinations and investigations, we categorised the patients as:

1. Mixed Connective Tissue Disease (MCTD)
2. Scleroderma overlaps
3. Any other overlaps

STATISTICALANALYSIS:

The data collected was tabulated in Microsoft Excel Worksheet and computer based analysis was performed using the SPSS 20.0 software and Microsoft excel 2010. Results were shown in terms of Percentage and Mean ± S.D.

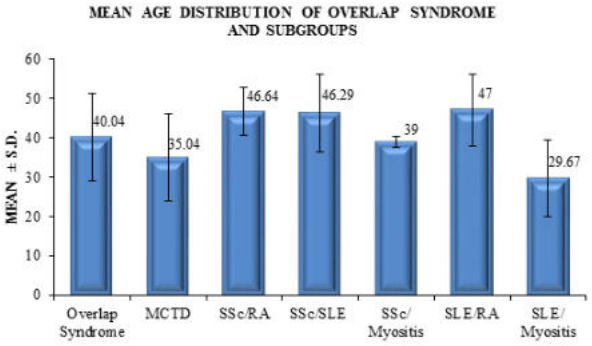
RESULTS:

After screening of 642 clinically suspected connective tissue disease patients, we identified 54 patients of overlap syndrome after detailed history, clinical examination and investigations. The distribution of overlap syndrome is shown in table-1. Mean age distribution of overlap syndrome and subgroup is shown in fig-2 and sex distribution in fig-3. Fatigue was the commonest manifestations in overlap and subgroup. Mucocutaneous manifestations were seen in 100% patients of Overlap syndrome and most common manifestation was Raynaud's phenomenon (81.48%) followed by skin tightening (53.70%). Raynaud's phenomenon being most common presentations in MCTD, SSc/RA, SSc/myositis, and SSc/SLE overlap (100%). Musculoskeletal manifestations were seen in 49 patients (90.7%) of overlap syndrome group and arthritis was most common manifestations (83.33%) followed by synovitis (50%). Most common manifestation in MCTD was arthritis (100%) followed by synovitis (84%).Cardiovascular manifestations were present in 21 patients (38.9%) in Overlap group and dyspnea on exertion was the commonest manifestation in 16 patients (29.63%).Pericardial effusion was present in 6 patients (11.11%) of Overlap syndrome group and 2 patients(8%) of MCTD. Anemia was most commonest hematological manifestation (42.59%). In subgroup in MCTD, SSc/RA, SSc/SLE and SLE/RA anemia was present 40%, 36.36%, 42.86% and 50% patients respectively. Renal manifestations were seen in 25.93% patients in overlap syndrome group and 13 patients (24.07%) had proteinuria>0.5 g per 24 hours and raised creatinine in 5 patients (9.25%). In subgroup in MCTD, renal involvements were seen in 28% patients. Gastrointestinal manifestations were present in 37 patients (68.51%) in overlap group and dysphagia, esophageal dysmotility were present in 37.04% patients. Among subgroup, MCTD and SSc/RA overlap esophageal dysmotility was seen in 52% and 36.36% respectively. Pulmonary manifestations were seen in 28 patients (51.85%) in Overlap syndrome and most common manifestations were cough, pleuritic chest pain, ILD, PAH in 26 (48.15%),15 (27.78%),15 (27.78%),7 (12.96%) patients respectively. In the subgroup, in MCTD, ILD and PAH were seen in 28% and 16% patients respectively. In SSc/RA overlap pulmonary fibrosis, ILD and PAH were present in 45.45%, 18.18% and 9.09% patients respectively. In Overlap syndrome group ANA was positive in 52 patients (96.3%). Among subgroup, in MCTD, ANA was positive in 100% patients, in SSc/RA overlap 81.82% patients. In SSc/SLE, SLE/RA, SSc/myositis and SLE/myositis overlap, all patients were ANA positive (100%). In Overlap syndrome group U1SnRNP was the commonest antibody in 27 patients (50%). Among subgroup, in MCTD, U1SnRNP was present in 100% patients. In SSc/RA overlap group commonest antibody was CENP-B (45.45%) followed by Scl70 (36.36%) Mean SLEDAI score in SSc/SLE overlap was 9.43±2.70 and in SLE/RA overlap was 9.67±2.88.Mean mDAS28 score in SSc/RA overlap was 5.33±0.59 and in SLE/RA overlap was 5.85±0.27. Most common Nail fold Capillaroscopic findings in Overlap syndrome was early scleroderma pattern in 21 (38.9%). In subgroup, MCTD most common finding was early scleroderma pattern in 14 patients (56%).

Table/Fig-1:Distribution of overlap syndromes

CLINICAL DIAGNOSIS	NUMBER OF CASES (n = 54)	PERCENTAGE (%)
1. MCTD	25	46.30
2. Systemic Sclerosis Overlap:	20	37.04
• Systemic Sclerosis + Rheumatoid Arthritis	11	20.37
• Systemic Sclerosis + SLE	7	12.96
• Systemic Sclerosis + Myositis	2	3.70
3. Others:	9	16.67
• SLE + Rheumatoid Arthritis	6	11.11
• SLE + Myositis	3	5.56

Table/Fig-2: Mean age distribution of overlap syndrome and subgroup



Table/Fig-3: Sex distribution of overlap syndrome and subgroup

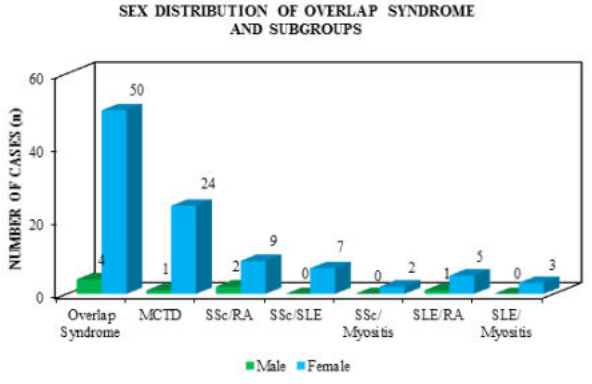


Table-4: Disease manifestations of overlap syndrome and subgroup

MANIFESTATIONS					Ssc OVERLAP						OTHERS			
	Overlap syndrome (n=54)		MCTD (n=25)		SSc/RA (n=11)		SSc/SLE (n=7)		SSc/Myositis (n=2)		SLE/RA (n=6)		SLE/Myositis (n=3)	
	n	%	N	%	n	%	n	%	n	%	n	%	n	%
Constitutional	40	74.07	19	76.00	8	72.72	5	71.42	2	100.00	4	66.66	2	66.66
Mucocutaenous	54	100.00	25	100.00	11	100.00	7	100.00	2	100.00	6	100.00	3	100.00
Musculoskeletal	49	90.7	25	100.00	11	100.00	2	28.57	2	100.00	6	100.00	3	100.00
Cardiovascular	21	38.88	11	44.00	4	36.36	3	42.85	0	00.00	1	16.66	2	66.66
Respiratory	28	51.85	11	44.00	7	63.63	5	71.42	1	50.00	3	50.00	1	33.33
Nervous system	16	29.62	8	32.00	2	18.18	2	28.57	1	50.00	2	33.33	1	33.33
Gastrointestinal	37	68.51	21	84.00	8	72.72	4	57.14	2	100.00	1	16.66	1	33.33
Hematological	26	48.14	10	40.00	4	36.36	4	57.14	1	50.00	5	83.33	2	66.66
Sicca symptoms	17	31.48	10	40.00	5	45.45	1	14.28	1	50.00	0	0.00	0	0.00
Renal	14	25.93	7	28.00	1	9.09	2	28.57	1	50.00	2	33.33	1	33.33

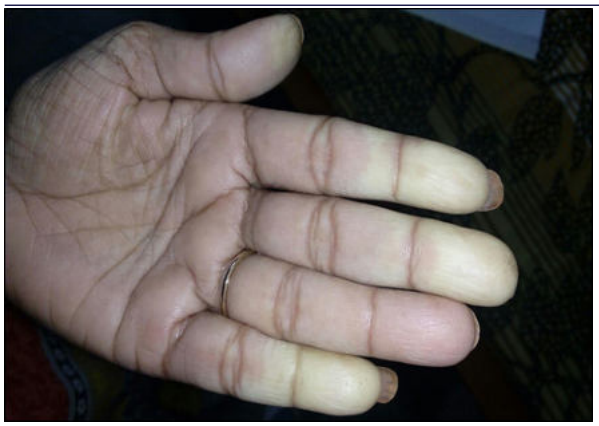


Fig-5:Raynaud's phenomenon in a patient with MCTD

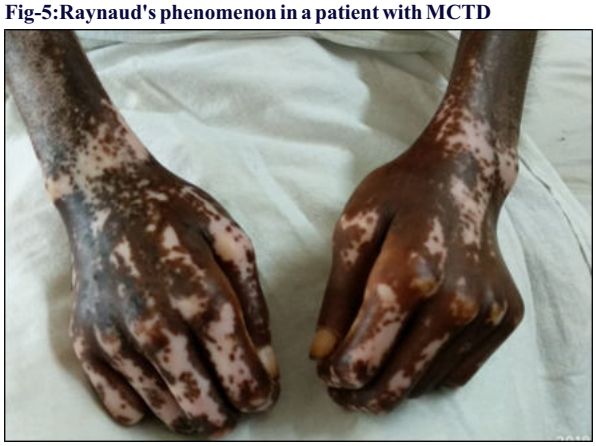


Fig-6: Skin Sclerosis and marked contracture of phalanges in a patient with SSc/RA Overlap

DISCUSSION :

Overlap syndrome is rare in India. But recent studies show it's not as rare as described earlier. Mixed connective tissue disease (MCTD), a special form of Overlap syndrome has been subject of debate till today. Many authors do not regard MCTD as a distinctive disease entity. In our study we included MCTD in Overlap syndrome group. No similar studies were found in Overlap syndrome which includes MCTD, when we searched the literature. However the subgroups of Overlap syndromes are discussed with related studies published in the literature. After screening of 642 clinically suspected connective tissue disease patients, we identified 54 patients of Overlap syndrome. Among 54 Overlap syndrome patients, we found 25 patients with MCTD,11 patients with SSc/RA Overlap,7 patients with SSc/SLE Overlap,2 patients with SSc/myositis Overlap,6 patients with SLE/RA Overlap and 3 patients with SLE/myositis Overlap. A recent study done by Jacinth Angel *et al*.(2018)[4] in India, after screening of 442 patients with clinically suspected Connective tissue disease found 34 patients with MCTD. Sumit *et al.*(2014)5 from Eastern India described 23 patients of MCTD and 22 patients of other Overlap syndrome. Another study done by Pradhan *et al*.(2014)[6] in Western India described 8 patients of SSc/RA Overlap,5 patients of MCTD,4 patients of SSc/SLE Overlap and 5 patients of SSc/myositis overlap. In the subgroup, in MCTD, most common age group was found to be 30-39 years and mean age was 35.04 ± 11.10 years which is similar to study done by Sharp *et al.* (1972)[7], where the mean age was 36 years. In the subgroup, in MCTD out of 25 patients 1 was male (4%) and 24 were female (96%). A study done by Sumit *et al.*(2014)5,out of 23 MCTD patients, found 20 females and 3 male. Among 11 patients with SSc/RA overlap, 2 were male (18.18%) and 9 were female (81.81%) where a study done by G. Szu¨cs *et al*.(2007)[8] found 16 female and 6 male among 22 SSc/RA overlap patients. Among 7 patients with SSc/SLE overlap all were female (100%) where Alharbi *et al*. (2018)[9] described 92% female in his study. In MCTD, most common manifestation was Mucocutaneous (100%) and musculoskeletal (100%) which is similar to a study done by Sharp *et al*. (1972)[7] who found musculoskeletal manifestations in 96% patients. In MCTD Fever was present in 11 patients (44%) where in a study by Sharp *et al*.(1972)[7]found 32% patient having fever. In MCTD Raynaud's phenomenon being most common presentation and was present in all 25 patients (100%) and swollen hand, acrosclerosis, mucosal ulcer and talengactasia were present in 21 (84%),16 (64%), 11 (44%) and 6 patients (24%) patients respectively which is similar to an Indian study by Sumit *et al*.(2014)5 who found Raynaud's phenomenon in 78.3% and acrosclerosis in 73.9% patients. In SSc/RA overlap Raynaud's phenomenon and skin tightening were present in all 11 patients (100%) which is similar to a study done by G. Szu¨cs *et al*.(2007)[8] who found Raynaud's phenomenon in 100% patients. In SLE/RA overlap, mucosal ulcer, alopecia, malar rash and Ryanauds phenomenon were present in 4 (66.67%), 2 (33.33%), 1 (16.67%) and 1 (16.67%) patient respectively where Li *et al*.(2014)[9] described mucosal ulcer, alopecia, malar rash and Raynaud's phenomenon in 25%,33.9%,10.7% and 17.9% patients respectively. Most common musculoskeletal manifestation in MCTD was arthritis in 25 patients (100%) followed by synovitis in 21 (84%) and myositis in 13 (52%) patients which is comparable with the study done by Lawrence *et al*.(2007)[10] in India who found arthritis in 90% patients, myositis in 45.5% patients. In MCTD, Cardiovascular manifestations were seen in 11 patients (44%) and dyspnea on exertion was commonest manifestations in 10 (40%) patients followed by palpitations in 5 (20%) followed by pericarditis in 3 (12%) patients and pericardial effusion in 2 (8%) patients. A study by Bennett *et al*. (1980)[11] with 20 patients with MCTD found pericarditis in 4 (20%)patients, pericardial effusion in 1 (5%) patient. Most common hematological manifestations in MCTD was anemia in 10 patients (40%) and thrombocytopenia in 2 patients (8%) which is similar to a study done by Bennett *et al.*(1980)[11] found anemia in 15 patients among 20 MCTD patients. In subgroup in MCTD, renal involvements were seen in 7 patients (28%) and 5 patients (20%) had proteinuria more than 0.5g per 24 hour and raised creatinine in 2 patients (8%) which is similar to the study done by Kitridou *et al*. (1986)[12],where they found renal involvement in 40% patients and proteinuria more than 0.5 g in 36.67% patients. In SSc/RA overlap group dysphagia and esophageal dysmotily were present in 4 patients each (36.36%) which is similar to a study done by G. Szu¨cs *et al*.(2007)[8] who found esophageal dysmotility in 54.5% patients. In MCTD Cough, pleuritic chest pain, ILD and PAH were seen in 11 (44%), 9 (36%),7 (28%),4 (16%) patients respectively. An Indian study done by Lawrence *et al.*(2001)[10] with 20 patients with MCTD found ILD in 7 (35%) patients and PAH in 2 (18.2%) patients. In MCTD, ANA was positive in all 25 patients (100%). A study done by Nedumaran *et al*.(2001)——13 found ANA positive in 100% patients with MCTD. ANA was positive in 9 patients of SSc/RA overlap (81.82%) which is similar to a study done by Szu¨cs *et al*.(2007)[8] who found ANA positive in 100% patients. Among subgroup, in MCTD, U1SnRNP was the commonest antibody and was present in all 25 patients (100%) which is similar to the study done by Nedumaran *et al*.(2011)[13] and Sharp *et al*.(1972)[7] where U1SnRNP was positive in 100% patients. Mean SLEDAI score in SSc/SLE overlap was 9.43±2.70 and in SLE/RA overlap was 9.67±2.88.A study done by Li *et al*.(2014)[9] showed lower disease activity of SLE in SLE/RA overlap (mean SLEDAI score was 8.43±5.37). In MCTD most common Nail fold capillaroscopy finding was early scleroderma pattern in 14 patients (56%),non-specific morphological changes in 9 patients (36%) and active scleroderma pattern in 1 patient (4%) which is similar to the study done by A de Holanda Mafaldo Diógenes *et al*. (2007)[14] who found scleroderma pattern in 65% patients.

Limitations of the study:

In our study, U1Sn RNP antibody was not detected by hemagglutination methods, we detected it by ANA blot by Line Immune Assay. EMG facility was not available at our institution. We didn't do lip biopsy which is useful in diagnosis of Sjogrens syndrome.

CONCLUSION:

Autoimmune connective tissue diseases are not often present in isolation. The diagnostic approach and prognosis of various overlap syndromes are different and it is very difficult to draw a distinct line in between the various AICTDs manifestations in overlap syndrome. However a large cohort including patients of all age group and following them for a long duration will give us a better datas related to clinical course, long term prognosis and response to therapy of overlap syndrome in this part of country.

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