OVERLAP IN CONNECTIVE TISSUE DISEASES EVALUATION OF 119 CASES

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Abstract – *The overlap syndrome is a vague entity in the group of connective tissue diseases. It is unclear whether it is fortuitous association of two or more connective tissue diseases (CTD), or a distinct disease. The early description of this syndrome was "a collection symptoms of CTD and the existence of anti - nRNP antibody". Many studies however, show that the anti - nRNP antibody is not specific for diagnosis. The aim of this study was to demonstrate the clinical and laboratory features of the overlap syndrome in 70 patients with SLE and 49 patients with PM/DM. The main features were then compared with those of the non overlapped disease (SLE or PM/DM) to search for any differences. Sharp, who first described this syndrome believed that the disease was a benign one. We compared the type of the treatment and the mortality rate. Our results seem to show that the overlap syndrome is not a fortuitous association of two or more diseases. There are differences separating an overlap syndrome from any of the original CTD. In contrast to the original belief of Sharp, the overlap syndrome is not a benign entity.*

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INTRODUCTION

It is not clear whether the overlap syndrome is a fortuitous association of 2 or more definite diseases, or it is a ditsinct clinical entity (1). As the etiology of most of the connective tissue diseases (CTD) remains unknown, classification criteria based on clinical and serologic manifestations may be of help as an aid to the diagnosis and the comparison of patients.

In the early 1970, Sharp and his colleagues attempted to add a further disease entity to the family of the autoimmune/ rheumatic diseases (2). They named it mixed connective tissue disease (MCTD).

In the original description, MCTD had four major characteristics (3):

1. The syndrome was clinically identifiable by a particular group of features. Clinical manifestations in these patients included a combination of features of systemic lupus erythematosus (SLE), progressive systemic sclerosis (PSS), rheumatoid arthritis (RA), and polmyositis / dermatomyositis (PM/DM) (4).
2. The presence of high titers of antibodies to RNP was a unique (and hence diagnostic) serological feature.
3. Cerebral involvment, pulmonary involvement, renal involvement, and vasculitis did not occur.
4. The condition had a benign prognosis and responded to small doses of corticosteriods.

Lazaro demonstrated that the presence of high titers of antibodies against the nuclear ribonucleoprotein fraction of the extractable nuclear antigen (nRNP) did not allow the identification of a particular subgroup (1). The definition of MCTD was therefore changed as bellow (5):

1. Certain internal organs were at risk for serious complications, e.g. lung, kidney and heart.
2. Patients were not always responsive to steroids.
3. The prognosis was not always good.

To overcome the created confusion by the above changes, 3 new sets of classification criteria were proposed by Sharp and coworkers, Alarcon-segovia and Villarreal, and the Japanese MCTD Research Committee (6).

However, there are still controversies on the existence of MCTD. Some authors believe that MCTD is a transient phase of a known connective tissue disease which has not yet expressed its real picture (7).

The measurement of antibodies against nRNP as a routine test is not yet possible in Iran. In our study, therefore, we evaluated the frequency of clinical and laboratory features of the overlap

syndrome and compared them with other reports.

MATERIAL AND METHODS

Patients

Our study is a retrospective one based on the data of 1180 SLE patients and 124 PM/DM patients retrieved from the electronic database of the Rheumatology Research Center.

Patients who had the clinical manifestations of SLE or PM/DM and another connective tissue disease were selected for the study. There were 3 subgrups in the SLE group: overlap with RA, overlap with PSS, and overlap with PM DM. The same division was made for PM/DM: Overlap with RA, or SS, or SLE. Overlap of SLE with PM/DM and overlap of PM/DM with SLE formed two different subgroups according to the main features of symptoms being in favor of SLE or PM/DM. Patients were classified according to the following classification criteria. SLE by the 1982 ARA revised criteria for SLE. Scleroderma by the ACR criteria for PSS. RA by the ARA criteria for RA, and PM/DM by the Bohan Peter's criteria.

Statistical Analysis

The electronic record of each lupus patient contained 266 topics and for PM/DM patient 266 topics. The topics included sex, presenting signs and symptoms, clinical manifestations, laboratory and immunologic findings, the treatment, modalities, and the cause of death.

The data of each overlap group was compared with the data of patients in the corresponding group, but without overlap. For example the data of patients with SLE and PSS were compared with those having only SLE. A standard error of percentage (SE %) and its confidence interval (CI) at 95% was calculated for each item (topic) in each subgroup. Comparison between items was done by the Chi-square test. Yates adjustment was applied to the calculations, when necessary. P value was then calculated for each data.

RESULTS

There were 70 overlap syndromes among 1180 Lupus patients (6%, CI = 1.4) and 49 overlap among 124 PM/DM patients (40%, CI= 8.6). The detail is shown in figure 1 for SLE patients and figure 2 for PM/DM patients.(fig. 1, fig. 2)

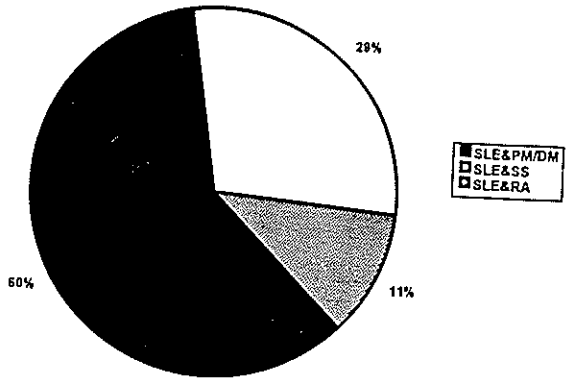

Fig. 1. Overlap in SLE

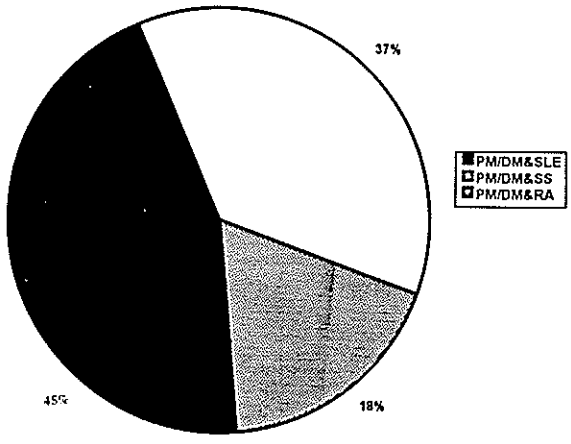

Fig. 2. Overlap in PM/DM

The Raynaud's phenomenon as the presenting symptom of overlap SLE and PM/DM was 11.9%,(CI = 9.8) in comparison to SLE alone which was 4% (CI = 1.1). The difference was statistically significant ($p<0.03$). The Raynaud's phenomenon as the presenting symptom of overlap of SLE and SS was 25%,(CI = 19).The difference when compared to SLE alone was statistically significant ($p<0.00005$). There was no reticuloendothelial system involvement as presenting sign of overlap SLE and RA in comparison to SLE alone(0.3%, CI= 0.3). The difference was statistically significant ($p<0.0002$).

Gastrointestinal lesions were not detected as the initial presenting symptom of the overlap of SLE and RA in comparison to SLE which was 0.8% (CI = 0.5) with $p < 0.02$. Pulmonary involvement was not detected as the initial presenting symptom of the overlap of SLE and RA in comparison to SLE, which was 0.4% (CI=0.4) ($p<0.003$). Cardiac manifestations were not detected as the initial presenting symptom of the overlap of SLE and RA in comparison to SLE, which was 0.2% (CI= 0.2) with $p<0.00001$.

Ophthalmologic presentations were not detected in the overlap of SLE and RA in comparison to SLE, which was 0.2% (CI= 0.2) with $p<0.00001$.

There was no hepatic lesion as the presenting sign of overlap SLE and RA in comparison to SLE alone (0.3%, CI = 0.3). The difference was statistically significant ($p<0.001$).

Patients with overlap SLE and SS had no constitutional symptom as the presenting symptom in contrast with SLE alone (19.3%, CI=2.3). The difference was statistically significant ($p<0.01$). The clinical manifestations of overlap in SLE in shown in (Table 1).

Mucocutaneous lesions were seen in 52.4% (CI= 15.1)of SLE and PM/DM patients and in 37.4% (CI=2.8) of SLE patients alone ($p<0.04$).

Muscle weakness was seen in 78.6% (CI = 12.4) of SLE and PM/DM patients and in 11.9% (CI = 1.9) of SLE patients alone ($p<0.00000$).

Table 1. Clinical manifestations of overlap of SLE in Comparison SLE

Symptom	SLE&PM	SLE&SS	SLE&RA	SLE
	%	%	%	%
Constitutional symptom	81	-	-	73.1
Fever	81*	-	38*	60.8
Chills	38*	-	-	24.5
Anorexia	57*	-	-	37.8
Weight loss	64*	-	-	40.8
Cutaneous symptom	91	60*	38*	83.9
Nonspecific erythema	50	-	-	30.7
Hypo/hyper-pigmentation*	-	50*	-	18.1
Mucosal lesion	52*	-	0*	37.4
Musculoskeletal symptom	100*	100	100	86.4
Transient arthritis*	-	25*	13*	44.1
Fixed arthritis	-	60*	100*	27.7
Articular deformity*	-	30*	75*	5.2
Articular erosion*		-	25*	1.6
Muscle weakness	79*	-	-	15.7
Myalgia	36*	-	-	11.9
Osteoporosis	10*	-	-	2.6
Vascular lesion	21	65*	-	2.7
Aterial thrombosis	0*	-	-	0.1
Visceral thrombosis	0*	-	-	0.2
Pulmonary manifestation	38	45	-	26.4
Intersititial fibrosis*	-	20*	-	0.8
Pulmonary hypertension*	-	0*	-	0.3
Pleuritis	21*	10*	-	20.8
Gastrointestinal symptom	41	40	-	31.4
Dysphagia	12*	35*	-	3.1
Pancreatities	0*	-	0*	0.1
Reticuloendothelial symptom	48*	-	-	29.1
Anterior uveitis	0*	-	-	0.2

*$p<0.05$

Myalgia was detected in 35.7% (CI = 14.5) of SLE and PM/DM patients and in 37.4% (CI = 2.8) of SLE patients alone ($p<0.0000$). Pleuritis was seen 21.4% (CI = 12.4) of SLE and PM/DM patients and in 20.8% (CI=2.3) of SLE patients alone ($p<0.01$).

Reticuloendothelial involvement was found in 47.6% (CI= 15.1) of SLE and PM/DM patients

and in 29.1% (CI= 2.6) of SLE patients alone (p<0.009). Dysphagia was seen in 11.9% (CI=9.8) of SLE and PM/DM patients and in 3.1% (CI=1) of SLE patients alone (p<0.02).

Diffuse renal involvement in SLE and PM/DM (4.8%, CI=6.4) was lower than in Lupus's patients alone (23.4%, CI=2.4) with (p<0.0001).Vascular lesion was seen in 65% (CI=20.9) of SLE and SS and in 2.7% (CI= 0.9) of SLE itself (p<0.00001).

Articular deformity was present in 30% (CI=20) of SLE and SS patients, while it was seen only in 5.2% (CI= 1.3) of SLE patients alone (p<0.0001). Malar rash was in 30% (CI=20) of SLE and SS and in 62.8% (CI= 2.8) of SLE alone (p<0.02). Pulmonary fibrosis was seen in 20% (CI= 17.5) of SLE and SS and in 0.8% (CI= 0.5) of SLE itself (p<0.004).

Dysphagia was present in 35% (CI= 20.9) of SLE and SS and in 3.1% (CI=1) of SLE alone (p<0.0000). Fixed arthritis was detected in 100% of overlap SLE and RA and in 27.7% (CI= 2.6) of SLE alone (p<0.001).

Transeint arthritis was seen in 12.5% (CI=22.9) of overlap SLE and RA and in 44.1% (CI=2.8) of SLE alone (p<0.01). Articular deformity was present in 75% (CI=30) of overlap of SLE and RA and in 5.2% (CI=1.3) of SLE alone (p<0.0000).

Articular erosions were detected in 25% (CI=30) of overlap of SLE and RA and in 1.6% (CI=0.7) of SLE alone (p<0.001). Table 2 demonstrates the treatment and frequency of death in overlap SLE.

Table 2. Treatment and frequency of death in overlap of SLE

Treatment	SLE&PM/DM	SLE&SS	SLE&RA	SLE
	%	%	%	%
Low dose steroid	7*	20	25	21.8
Moderate dose steroid	12*	40	50	29.2
High dose steroid	79*	30	0*	33.6
Pulse steroid	17	10	0	12.6
Oral cytotoxic	12	20	0	17.6
Pulse cyclophosphamide	43	40	38	29.9
Death	17	25*	0*	7.7

*p<0.05

Steroid therapy specially in high dose had statistically signifcant value in overlap SLE and PM/DM 78.6% (CI=12.4) than in SLE alone 33.6% (CI=2.7) with p<0.0000. Mortality rate was significantly higher in SLE and SS 25% (CI=19)than in SLE alone 7.7% (CI=1.5) with p<0.01.

Laboratory data in overlap SLE is shown in (Table 3). Anemia was detected in 66.7% (CI=14.3) of SLE and PM/DM and in 47.7% (CI=2.8) of SLE alone (p<0.01). Leukopenia was seen in 45.2% (CI=15.1) of SLE and PM/DM and in 29.6% (CI=2.6) of SLE alone (p<0.02). FANA of diffuse pattern was seen in 31% (CI=14) of SLE and PM/DM and in 17.3% (CI=2.2) of SLE alone (p<0.04). FANA of speckled pattern was seen in 40% (CI=21.5) of SLE and SS and in 14.2% (CI=2) of SLE (p<0.01). High circulating immune complex was not detected in SLE and RA, it was detected in 0.2% (CI=0.2) of SLE (p<0.00001). Crygloulinemia was not found in SLE and RA, while in SLE it was 0.6% (CI=0.4) with p<0.01. LE cell was found in 12.5% (CI=22.9) of SLE and RA and in 55.4% of SLE patients alone (CI=2.8, p<0.006).

Table 3. Laboratory data in overlap SLE

	SLE&PM/DM	SLE&SS	SLE&RA	SLE
	%	%	%	%
Raised muscle enzymes	88*	-	-	7.2
Proteinuria>3gr	5*	-	-	17.5
Renal biopsy(grade 4 WHO)	5*	-	-	23.4
Hepatic enzyme raised	31*	-	0*	11.5
HBs Ag+		-	0*	0.6
Leucopenia	45*	-	-	29.6
Lymphopenia	67*	-	-	38.4
Anemia	67*	-	-	47.7
Cryoglobuline	-	-	0*	0.6
Raised IgM	-	0*	0*	0.8
FANA				
Diffuse	31*	-	-	17.3
Speckled	-	40*	-	14.2
Positive LE cell	-	-	13*	55.4
Circulating Immun Complex	0*	0*	0*	0.2
Raised anti SM	-	0*	0*	0.8
Low CH50	-	0*	-	13.7

*p<0.01

The Clinical features of overlap in PM/DM are shown in Table 4. Fever was detected PM/DM and SLE in 94.1% (CI=12.1) of cases and of in PM/DM in 52.4% (CI=8.9) with $p<0.002$. Skin rash over joints was seen in 11.8% (CI=16.6) of PM/DM and SLE patients and in 34.7% (CI=8.5) of PM/DM ($p<0.02$).

Malar rash was seen in 76.5% (CI=21.9) of PM/DM and SLE patients and in 25.8% (CI=7.7) of PM/DM ($p<0.0001$). Mucosal lesions were detected in 64.7% (CI=24.7) of PM/DM and SLE patients and in 16.1% (CI=6.5) of PM/DM ($p<0.00002$). Hair loss was seen in 64.7% (CI=24.7) of PM/DM and SLE patients and in 29.8% (CI=8.1) of PM/DM ($p<0.01$) photosensitivity was seen in 64.7% (CI=24.7) of PM/DM and SLE and in 21.8% (CI=7.3) of PM/DM ($p<0.0005$). Proximal muscle weakness of lower limb as 2/5 was not detected in PM/DM and SLE (CI=0) and of in PM/DM in 17.7% (CI=6.7) with ($p<0.02$). Pleuritis was found in 17.6% (CI=25.5) of PM/DM and SLE and in 2.4% (CI=5.6) of PM/DM ($p<0.02$). Renal involvement was detected in 58.8% (CI=25.1) of

Table 4. Clinical features of overlap of PM/DM in Comparison Total

Symptom	PM/DM&SLE %	PM/DM&SS %	PM/DM&RA %	PM/DM %
Constitutional symptom	94	71	80	77.4
Fever	94*	30*	60	52.4
Cutaneous sympton	88	47*	80	81.5
Subcutaneous nodule	0	0	0*	32.3
Urticaria	6	0*	0*	0.8
Articlar rash	12*	-	20	34.7
Facial rash	18	6*	40	35.5
Malar rash	77*	-	0	25.8
Mucosal lesion	65*	-	20	16.1
Hair loss	65*	12	20	29.8
Photosensitivity	65*	12	20	21.8
Osteoarticular symptom	100	94	100	83.9
Arthralgia	53	47	60	55.6
Arthritis	71	64	100	56.5
Periarthritis	0	0	0	12.1
Joint deformity	0	24	20	9.7
Articlar erosion	-	6	40*	2.4
Contracture	-	71*	20	12.9
Proximal muscle weakness upper limb		100	100	97.6
-2/5	0*	18	0	17.7
-3/5	24	18*	20	35.5
Vascular lesion	18	71*	60	18.5
Raynaud's phenomenon	18	77*	60*	20.2
Renal manifestation	59*	6	0	12.1
Pulmonary manifestation	24	59*	40	24.2
Pleuritis	18*	0	0	2.4
Gastrointestinal symptom	6*	71	40	47.6
Reticuloendothelial symptom	47*	18	20	21
Neuropsychiatric	-	6	20	4

*$p<0.01$

PM/DM and SLE in 12.1% (CI=5.7) of PM/DM ($p<0.0000$). Proteinuria above 500 mg/day was found in 35.3% (CI=25.8) of PM/DM and SLE and in 7.3% (CI=4.9) of PM/DM ($p<0.0001$).

Gastrointestinal manifersta tions were seen in 5.9% (CI=12.1) of PM/DM and PM/DM and SLE and in 47.6% (CI=8.9) of PM/DM ($p<0.002$).

Reticuloendothelial involvement was seen in 47.1% (CI=25.5) of PM/DM and SS and in 21% (CI=7.3)of PM/DM ($p<0.02$).

Fever was seen in 29.4% (CI=24.1) of PM/DM and SS and in 52.4% (CI=8.9) of PM/DM ($p<0.03$). Cutaneous symptoms were found in 47.1% (CI=25.5) of PM/DM and in 81.5% (CI=6.9) of PM/DM ($p<0.004$).

Facial rash was seen in 5.9% (CI=13.1) of PM/DM and SS and in 35.5% (CI=7.5) PM/DM ($p<0.03$).

Urticaria was not seen in PM/DM and SS and in 0.8% (CI=1.5) of PM/DM ($p<0.01$).

Contracture deformity of joints was seen in 70.6% (CI=23.5) in PM/DM and SS and in 12.9% (CI=5.9) of PM/DM ($p<0.0000$). Proximal muscle weakness in upper limb as 3/5 was seen in 17.6% (CI=19.4) of PM/DM and SS and in 39.5% (CI=8.7) of PM/DM ($p<0.03$). Vascular lesions were found in 70.6% (CI=23.4) of PM/DM and SS and in 18.5% (CI=6.9) of PM/DM ($p<0.00001$).

Raynaud's phenomenon was seen in 76.5% (CI=22.2) of PM/DM and SS and in 20.2% (CI=7.4) of PM/DM ($p<0.00004$).

Pulmonary invlovement was seen in 58.8% (CI=25.1) of PM/DM and SS and in 24.2% (CI=7.5)of PM/DM ($p<0.01$).

Subcutaneous nodule was not seen in PM/DM and RA in contrast with 2.4% (CI=3.8) of PM/DM ($p<0.0004$). Morning stiffness was seen in 80% (CI=46) in PM/DM and RA and in 23.4% (CI=7.5) of PM/DM ($p<0.04$).

Articular erosions were detected in 40% (CI=56.3) of PM/DM and RA and in 2.4% (CI=2.7) of PM/DM ($p<0.0000$). Raynaud Phenomena was seen in 60% (CI=69.9) of PM/DM and RA and in 20.2% (CI=7.4) of PM/DM ($p<0.01$).

Laboratory findings in overlap are shown in (Table 5), ESR lower than 50/lh was seen in 5.9% (CI=12) of PM/DM and SLE and in 34.7% (CI=8.5) PM/DM ($p<0.03$). Anemia as hemoglobin less than 10 mg/dl was seen in 52.9% (CI=27.3) of PM/DM and SLE and in 19.4% (CI=7.2) of PM/DM ($p<0.001$). LE cell was seen in 64.7% (CI=24.5) of PM/DM and SLE and in 12.9% (CI=5.9) of PM/DM ($p<0.0001$). Low C4 was found in 52.9% (CI=25.6) of PM/DM and SLE and in 12.9% (CI=5.9) of PM/DM ($p<0.003$).

Table 5. Laboratory data in overlap of PM/DM in Comparison total PM/DM

	PM/DM&SLE	PM/DM&SS	PM/DM&RA	PM/DM
	%	%	%	%
Proteiuria > 500mg	-	0*	0	7.3
ESR				
Normal	18	24	0	23.4
20-50	6*	53	20	34.7
Hemoglobin < 10	53*	6	0	19.4
Antiphospholipid antibody	88	-	-	42.7
FANA + perinuclear	6	0	0*	2
Positive LE cell	65*	0*	20	12.9
Low C4	53*	6	20	12.9

*$p<0.01$

FANA of type perinulear was not seen in PM/DM and RA in contrast with 1.6% (CI=2.1) of PM/DM ($p<0.01$).

The treatment and the mortality rate in overlap of PM/DM is shown in Table 6. Mortality rate was significantly lower in overlap of PM/DM than in PM/DM alone (Table 6).

Table 6. Treatment and mortality rate in overlap of PM/DM in comparison total

	PM/DM&SLE	PM/DM&SS	PM/DM&RA	PM/DM
	%	%	%	%
Treatment				
Oral steroid	100	100	80*	99.2
Pulse steroid	18	0	0	6.5
Cytotoxic oral	35	53*	40	36.3
Pulse cyclophosphamide	59*	18	0	16.9
Death	0*	0*	0*	6.5

*$p<0.05$

DISCUSSION

While the etiology of the overlap syndrome remains unknown, the classification of individual cases will continue to depend on the identification of certain patterns of clinical and labratory features (8). Few reports have been undertaken to examine, as we have done here, the clinical and the laboratory data, the treatment modalities and the death of patients with overlap syndrome, and their comparison with those without any overlap.

In this study the rate of the overlap syndrome was higher than other reports such as that of Maddison who reported 25% (8). In India, the overlap syndrome was reported rarely. The screening of 1000 consecutive patients with systemic connective tissue diseases showed only 3 cases of overlap syndrome (9). In our study, the overlap syndrome was more common in PM/DM in contrast to Lazaro who believed it was more common in RA (1).

Our findings do not concord with the original description of MCTD as "a mild disorder without major organ involvement". In our study, the prognosis of SLE and SS was poor in contrast to Sharp's belief of a benign entity (5).

Our study demonstrates that the overlap syndrome is not a simple combination of two or more diseases as thought by Kallenberg (10), because there are many differences in the manifestations of an overlap in comparison to the orignal disease.

We had not signifcant hypergammaglobulinemia in our overlap cases in comparison to SLE alone, in contrast with Hameenkorpi's study (11). However and similar to Hameenkorpi's study, major organ involvement specially renal involvement, was seen less in overlap cases with SLE than in SLE alone. We found that the clinical expression of overlap syndrome differs according to different combinations. Kasukawa (12), belives that the difference is related to the existence of anti-Sm or anti-uLRNP antibody.

In conclusion, the patients with SLE and PM/DM had more diffuse FANA and lower major organ involvement. Patients with SLE and SS had more Raynaud's phenomenon and speckled FANA.

Patients with PM/DM and SLE had high ESR, accompanied with major organ involvement.

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