

## Overlap Syndrome among Patients with Connective Tissue Disease

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### Abstract

**Background:** Many patients diagnosed with autoimmune connective tissue disease cannot be categorised easily into one of the established clinical entities such as systemic lupus erythematosus, dermatomyositis, or systemic sclerosis. The term overlap syndrome is used to identify such patient and is useful in terms of clarifying prognosis and facilitating disease management. **Methods:** This was a retrospective study of the patients diagnosed with connective tissue diseases. The study was done among patients attending the outpatient clinic of a teaching hospital in the South Western Nigeria. The study spanned from July 2013 to June 2016. Data on clinical characteristics, diagnosis, age at onset of disease, and gender were extracted from their files. **Results:** Five hundred and two patients attended the rheumatology outpatient clinic over the study period. There were 41(8.2%) cases of connective tissue disease. Systemic lupus erythematosus constituted 29.3%, undifferentiated connective tissue disease 19.5%, and scleroderma 14.6%. Others were secondary Sjogren's syndrome 14.6% and overlap syndrome 7.3%. There were 3 overlap syndromes and all were females. A case of rheumatoid arthritis/systemic lupus erythematosus (RA/SLE), SLE/polymyositis, and Scleroderma/Polymyositis. Patients were aged 18 to 64 years, and the mean age was 42±5 years. Female constituted 85.4% of the total population with a female to male ratio of 5.8:1. **Conclusion:** There is the need to detect an overlap syndrome early. An early classification will guide the management plan of such patients. The traditional high dose steroid for the treatment of SLE and inflammatory muscle disease may be hazardous in overlap syndromes.

**Keywords:** Overlap syndrome, Connective tissue disease, Rheumatology.

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## INTRODUCTION

The formation of autoantibodies is a normal physiological process. However, excessive production of such antibodies can be harmful, resulting in disease or injury [1]. Autoimmune rheumatic disorders are characterised by autoantibodies to non-organ specific antigens [1].

Overlap syndrome is used where a patients cannot be assigned to a single disease category. Up to 25% of patients with early stage or mild variant disease fall into this category [2].

The connective tissue diseases (CTD) overlap syndromes are distinguished by the concomitant occurrence of clinical and serological features of the component diseases [3]. Any CTD can be a partner in an overlap disorder [4].

Mixed connective tissue disease (MCTD) is the prototypical overlap disease with features of lupus, rheumatoid arthritis, scleroderma, and inflammatory myositis [5].

Clinically, it is useful to define overlap syndromes to clarify prognosis and facilitate disease management [6]. Overall, the picture of overlap syndromes with respect to CTD is complex and heterogeneous [6]. The management of overlap syndromes is based on the usual treatment of the constituent features of its clinical components [7].

This research work studied the clinical and the immunological characteristics of overlap syndrome in autoimmune rheumatic diseases among our patients.

## MATERIAL AND METHODS

This was a retrospective study of the patients diagnosed with connective tissue diseases from July

2013 to June 2016 in a rheumatology outpatient practice of a teaching hospital in the South Western Nigeria. The medical records of the patients were retrieved from the medical record department of the hospital. Data regarding each patient's diagnosis, age at onset of disease, and gender were extracted from their files. Clinical presentations and available laboratory results were documented. Ethical clearance was obtained from the ethical committee of the institution. People with serological abnormalities only or with non-autoimmune rheumatic illness were excluded from this study.

### Case Definition [8-12]

The presence of autoimmune connective tissue disease was considered if a subject, after the history and clinical examination fulfilled the validated classification criteria to establish a diagnosis of SLE, scleroderma, inflammatory muscle disease, Sjogren's syndrome, anti-phospholipid syndrome and overlap connective tissue disease. We used the American College of Rheumatology (ACR) classification for SLE<sup>[8]</sup> and Scleroderma,<sup>[9]</sup> Bohan and Peter criteria for inflammatory muscle diseases [10], revised international classification criteria for Sjogren's syndrome [11] and revised Sapporo classification criteria for anti-phospholipid syndrome [12].

Overlap Syndromes was defined as entities satisfying classification criteria of at least two connective tissue diseases (CTDs) occurring at the same or at different times in the same patient [13].

Undifferentiated connective tissue disease was diagnosed [14] when

- Signs and symptoms suggestive of a CTD are present, but not fulfilling the criteria for any of the defined CTDs.
- The presence of antinuclear antibodies (ANAs) identified on two different occasions.

### Statistical Analysis

SPSS software (Statistical Package for the Social Sciences) 20 was used for data entry and analysis. Continuous data was shown as mean and standard deviation (mean±SD), and categorical variables were shown as percentages.

## RESULTS

Five hundred and two rheumatology cases were seen over a three year period (July 2013- June 2016). There were 41(8.2%) cases of connective tissue

disease. Systemic lupus erythematosus constituted 29.3%, undifferentiated connective tissue disease 19.5%, and scleroderma 14.6%. Other were secondary Sjogren's syndrome 14.6% and overlap syndrome 7.3%.

Patients were aged 18 to 64 years, and the mean age was 42±5 years. Female constituted 85.4% of the total population with an overall female to male ratio of 5.8:1. Table-1 shows the distribution of the patients.

There were 3 overlap syndromes and all were females. A case of RA/SLE, SLE/polymyositis, and Scleroderma/Polymyositis. The patient with RA/SLE presented with polyarticular peripheral symmetrical synovitis, significant early morning joint stiffness and sub-cutaneous nodules. Other presentations were malar rash, photosensitivity rash, non-scarring alopecia and recurrent oro-pharyngeal ulcers. Haematological presentation was that of pan-cytopenia. Erythrocyte sedimentation was above 100mm/hr, speckle pattern of anti-nuclear antibody (ANA) was 1/320 and antibodies to double stranded DNA was positive. Anti-citrullinated peptide was positive but rheumatoid factor and anti U1 ribonuclear protein (RNA) were negative. Radiology showed peri-articular osteopenia but no erosion.

The patient with SLE/polymyositis also presented with malar rash, photosensitivity rash, and recurrent oro-pharyngeal ulcers. Other clinical presentations in the patient were proximal weakness of both the shoulder girdle muscles and the pelvic muscles. Patient was unable to dress herself and unable to get out of seat unaided. There was Coomb's positive anaemia with thrombocytopenia. Erythrocyte sedimentation rate was 85mm/hr, rheumatoid factor was 1/80, lactate dehydrogenase and creatine kinase were markedly elevated. Anti U1RNA was however negative.

The patient with scleroderma/polymyositis presented with proximal and distal skin thickness, hypo and hyper-pigmented (salt and pepper) skin changes, finger pulp ulcers and restricted mouth opening. Other feature was proximal muscle weakness affecting the pelvic girdle more than the shoulder girdle with inability to climb stairs. ESR was 80mm/hr, ANA was 1/640. Creatine kinase was elevated but anti U1 RNA was negative.

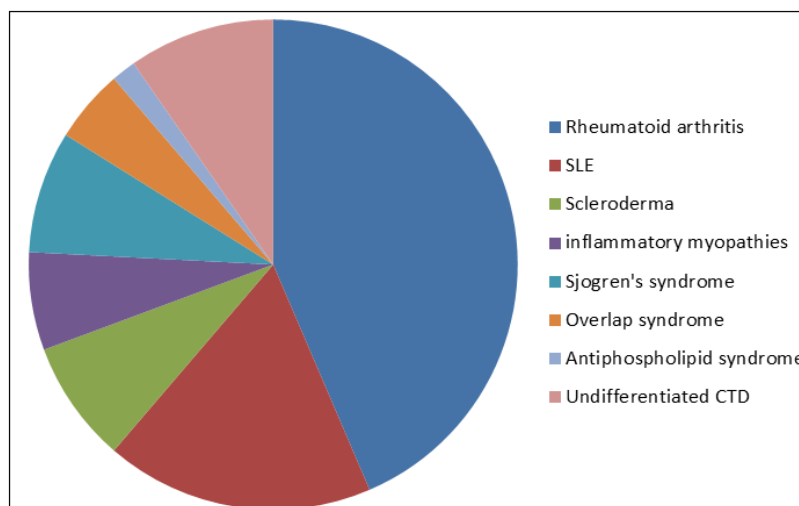
Electromyography, muscle biopsy and other serological tests specific for overlap syndrome were however not carried out.

**Table-1: Socio-demographic characteristics of the patients with connective tissue disease**

Parameter	Result
Females	62 (78.5%)
Male	17 (21.5%)
Age range	18-64
Mean age	42±5
Duration of disease	1.6 -8 years
Mean duration of disease	3.8± 2 years
Education level	
No formal education	36 (45.6%)
Primary school	24 (30.4%)
Secondary school	12 (15.2%)
Post secondary	07 (8.7%)

**Table-2: Connective tissue diseases spectrum seen during the study**

Disease	Female (n,%)	Male (n,%)	Total (n,%)
Rheumatoid arthritis	27 (71.1)	11 (28.9)	38 (48.1)
SLE	11 (91.7)	1 (8.3)	12 (15.2)
Scleroderma	5 (83.3)	1 (16.7)	06 (7.6)
Dermatomyositis	2 (100)	0 (0)	02 (2.5)
Polymyositis	2 (66.7)	1 (33.3)	03 (3.8)
Sjogren's syndrome	5 (83.3)	1 (16.7)	06 (7.6)
Overlap * RA/Dermatomyositis * RA/SLE * Scleroderma/Dermatomyositis	3 (100)	0 (0)	03 (3.8)
Antiphospholipid syndrome	1 (100)	0 (0)	01 (1.3)
Undifferentiated	6 (75)	2 (25)	08 (10.1)
Total	62	17	79

**Fig-1: Pie chart representative of the connective tissue diseases seen**

## DISCUSSION

Six major diffuse connective tissue diseases (DCTD) exist according to current classification schema: systemic lupus erythematosus (SLE), scleroderma (Scl), polymyositis (PM), dermatomyositis (DM), rheumatoid arthritis (RA) and Sjögren's syndrome (SS) [15]. Sjögren's syndrome is commonly associated with each of these diseases, but when it occurs alone it is called primary Sjögren's syndrome. The classical clinical descriptions of these disorders are

well known and most patients with well-differentiated disease are easily recognized. It was however noted that two or more of the connective tissue diseases may co-exist and this occurs in about 25 percent of patients, who are then said to have an overlap syndrome [4].

The diagnosis of Rhupus was made in our patient based on the following criteria Inflammatory symmetrical polyarthritis, clinical features suggestive of SLE and positive dsDNA antibody. Recognition of

these patients is important, since their therapy and outcome differ from those having RA or SLE alone.

Schur *et al.*, [16] in 1974 first described overlap of RA and SLE and named it Rhupus. The first clinical observations that helped to identify this entity was made by Toone [17] in 1960. In his original paper, he described the presence of LE cell phenomenon in patients with RA, which was till then considered an exclusive feature seen in SLE patients.

RHUPUS patients present with features of RA but later on develop features of SLE. Few of them present simultaneously with features of RA and SLE, but SLE as the initial presenting manifestation is not common [18], when this occurs, it is seen more frequently as patients become menopausal, when long standing SLE evolves into a more rheumatoid picture, with erosive joint disease [18]. In the majority, features of RA dominate: symmetrical erosive polyarthritis is most common and rheumatoid nodules are seen in around 40% of these patients [18]. Most common features of SLE in Rhupus are: cutaneous (butterfly skin rash, photosensitivity and alopecia), hematological (leukopenia and thrombocytopenia), serositis (pleural and pericardial effusion) and mucosal involvement. Major organ involvement such as central nervous system and renal is rare [18]. These patients have increased frequency of ACLA positivity in high titers, although symptomatic thrombosis is rare [18]. The precise clinical behavior of individual diseases when they coexist in Rhupus is not known [19].

This overlap must be distinguished from nonerosive Jaccoud's arthropathy seen in SLE, which is characterized by mild joint pain without synovitis, radiographs that show prominent ulnar deviation, swan neck deformities, and Z deformity of the thumb [20].

There were two patients with scleroderma overlap syndrome in the study. Scleroderma overlap syndrome seems to be a distinct subset of scleroderma, different from limited cutaneous and diffuse cutaneous scleroderma. It has a different autoantibody pattern, organ involvement, progression of disease, and possibly holds a middle position between limited cutaneous and diffuse cutaneous scleroderma [21]. However, presence of anticentromere antibodies in SLE patients does not necessarily indicate scleroderma [21].

Scleroderma- SLE Overlap combination can have a fatal outcome if not efficiently treated. Polyserositis, pancreatitis, avascular bone necrosis and leukoencephalopathy have been reported in scleroderma- SLE overlap [21]. Scleroderma- SLE overlap patients often develop pulmonary arterial hypertension and when it is ascribed to SLE, requires prompt immunosuppression with corticosteroids and cytotoxic drugs along with vasodilators [21]. In scleroderma- SLE overlap patients who develop renal

dysfunction and hypertension, efforts should be made to distinguish between lupus nephritis and scleroderma renal crisis, because treatment is completely different [21].

In the article by Foocharoen *et al.*, [22] on scleroderma overlap syndrome, analyzed data from a historical cohort of 403 Thai scleroderma patients were obtained. The frequency of occurrence of scleroderma overlap syndrome in their study was 16.9% (68/403), of which scleroderma polymyositis overlap remains the commonest (70.6%) followed by scleroderma- SLE overlap and scleroderma- RA overlap.

The term "sclerodermatomyositis" was used originally to define a group of patients with features of both scleroderma and dermatomyositis [23]. The aetiology and pathogenic mechanisms of PM-Scl overlap remain unknown. The main features of this syndrome are myalgia or myositis, arthralgia, sclerodermalike cutaneous changes, Raynaud's phenomenon, and an association with specific autoantibodies: anti-PM-Scl, anti-Jo-1, anti-Ku, and anti-U2 RNP [24]. The detection of specific autoantibodies or autoantibody profiles assists accurate diagnosis, allowing provision of optimal treatment. Overlap syndrome of inflammatory myopathy with Scl, has been reported as more common than the classic description of PM [24].

A 2006 clinical and longitudinal study of 100 consecutive French-Canadian patients with idiopathic inflammatory myopathies concluded that the original Bohan and Peter classification of inflammatory myopathies should be abandoned, because 60% of patients with inflammatory myopathies were found to have overlap syndrome [25].

In the cohort of patients analysed by Foocharoen *et al.*, [22] scleroderma- PM overlap syndrome patients had younger age at onset, less frequent anti-topoisomerase positivity, and needed moderate to high-dose steroids at onset. Also, the scleroderma overlap subset had more digital ulcers, interstitial lung disease (ILD), pulmonary hypertension and renal involvement, in comparison with pure scleroderma.

In line with the French-Canadian study finding on treatment, Our patient with scleroderma-SLE responded well to a high dose steroid. The study reported that the distinction between classic PM/DM and an overlap syndrome was of prognostic and therapeutic significance, because classic PM nearly always manifested a chronic course, with 50% of patients initially unresponsive to corticosteroid therapy. Pure DM was almost always chronic, but most patients had an initial response to corticosteroids. On the other hand, patients with myositis overlap syndroms were

almost always responsive to corticosteroids [25]. (about 90% response rate).

An European review of 114 Scl overlap patients reported a 95% PM-Scl [26]. Muscle biopsies in PM/Scl overlap patients are distinguished by a high frequency of necrotic muscle fibers. Another report reported that patients with Scl overlap syndrome were predominantly female and developed musculoskeletal involvement more frequently than patients with limited Scl or diffuse Scl [27].

The major limitation of our study is small number of patients. Also, detailed autoantibody work-up was not done, which would have significantly contributed to better characterization of overlap syndrome subsets.

The identification of overlapping clinical features in a given patient are important because treatment might need to be directed specifically at some of these features. Further prospective studies are however required to understand various epidemiological, clinical and immunological characteristics of different overlap syndromes.

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