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| RESEARCH ARTICLE

The Connective Tissue Diseases Overlap Syndromes: 5-Year Single-Center Experience at Ibn Rochd University Hospital in Casablanca

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| ABSTRACT

Overlap syndromes (OS) correspond to clinical entities characterized by the coexistence, in the same individual, of diagnostic criteria for at least two connective tissue diseases (CTDs). These manifestations can occur simultaneously or sequentially during the course of the disease. This was a retrospective descriptive observational study covering a period of five years, from January 2020 to December 2024. The research used existing medical data from the records of 15 patients treated for CTDs-OSs at the internal medicine department of Ibn Rochd University Hospital in Casablanca. Out of 1921 patients, 15 presented OSs (0.8%), with female predominance. The median age at diagnosis was 42 years, and the clinical symptomatology was dominated by Raynaud's phenomenon, polyarthritis, myositis, and skin eruptions. A complex combination of 40 CTDs was observed, including two cases of rhupus and three of sclerolupus. The prognosis was generally good after treatment. OS are complex entities requiring a multidisciplinary diagnostic approach integrating immunological markers and paraclinical complements to adapt therapeutic strategies.

| KEYWORDS

Connective tissue diseases, Ibn Rochd hospital, Overlap syndrome, Rhupus, Sclerolupus

| ARTICLE INFORMATION

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Introduction

CTDs are a heterogeneous group of autoimmune disorders characterized by multisystemic involvement and the production of specific autoantibodies. The coexistence or succession of two or more CTDs in the same patient is referred to as OS. This rare situation poses diagnostic and therapeutic challenge due to the overlap of clinical manifestations and diagnostic criteria of CTDs (1, 2).

Conducted within an academic context, this study reflects clinical practice by describing the clinical, immunological, therapeutic, and evolutionary characteristics of OS. This work provides insight into the diagnostic complexity and offers in-depth analysis of the peculiarities of OS within a real healthcare setting.

Patients and Methods

This study constitutes a retrospective observational descriptive study spanning a period of five years, from January 2020 to December 2024. The work was based on pre-existing medical data collected from the files of 15 patients followed for CTDs at the internal medicine department of Ibn Rochd University Hospital in Casablanca. Diagnoses were established using the 2019 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for systemic lupus (SL), 2013 ACR/EULAR criteria for scleroderma, Bohan and Peter criteria and for dermatomyositis (DM), 2011 ACR/EULAR criteria for rheumatoid arthritis (RA), 2016 ACR/EULAR criteria for Sjögren's disease (SD), 2023 ACR/EULAR criteria for antiphospholipid syndrome (APS), Solomon's criteria for antisynthetase syndrome (ASS) and CASPAR criteria for psoriatic arthritis (PsA).

Results

Among the 1921 patients followed for CTDs in internal medicine, a small group of 15 patients, representing 0.8%, presented with an OS (Fig.1), with a marked female predominance, as 87% of the cases were women (Fig.2). The median age at diagnosis was 42 years, with a median follow-up duration of 8 years. More than half of the patients (54%) came from urban areas, and the predominant symptoms were Raynaud's phenomenon, polyarthritis, myositis, and cutaneous eruptions.

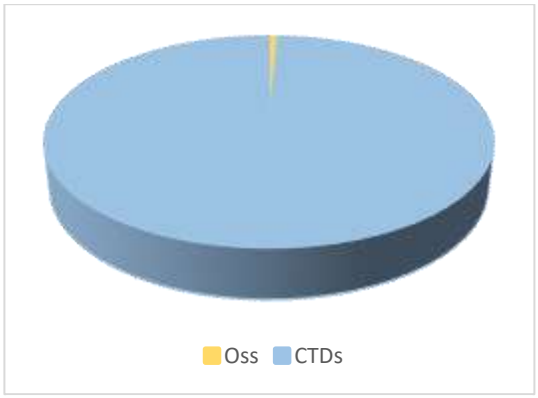

Fig.1 : The distribution of OSs among CTDs

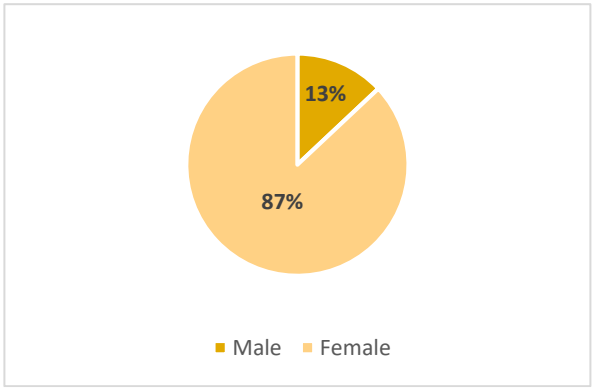

Fig.2 : The distribution of OSs by gender

Distribution and features of CTDs

A complex combination of 40 CTDs was observed (Table1), including two cases of rhupus and three cases of sclerolupus. Scleroderma was the most frequent CTD, accounting for quarter of the cases, followed by SL at 20%. RA represented 17,5% of the CTDs which 71,5% (5 cases) had already progressed to advanced bilateral carpal involvement. The rate of SD was 15%. Additionally, DM and APS were present at equal rates of 7,5%. Whereas ASS was detected in 5% of cases and PsA in 2,5% (Table 2). All patients with SSc and DM had Raynaud's phenomenon. However, in SSc, it was severe complicated by pulp ulcers. In DM, capillaroscopy had objectified irregular dilated capillaries and a reduction in capillary density. On the other hand, in the SSc, the appearance of the megacapillaries was tortuous, some of which were branched into fern leaves. At least microhemorrhage was noted in all patients and 50% had areas of capillary desert. No scleroderma renal crisis was reported in SSc. In LS, 62.5% or 5 patients had no renal involvement and 37.5% or 3 patients including one man had class V lupus nephritis. Muscle biopsy performed in patients having OS with DM revealed a perivascular lymphocytic infiltrate in 2 women and perivascular atrophy in one male patient. Notably, no neoplasia was associated with SSc or DM in our series. Organ-specific AIDs were detected in 4 patients. Patient 1 was found to have immune thrombocytopenia. Patients 3 and 4 were diagnosed with Hashimoto's autoimmune thyroiditis. In parallel, Patient 7 manifested autoimmune hepatitis of type 3. It is worth noting that, in addition to OS, a non-Langerhans cell histiocytosis was identified in Patient 1.

CTD	Female (n ;%)	Male (n ;%)
SSc	10 ; 25%	0 ; 0%
SL	7 ; 17,5%	1 ; 2,5%
RA	7 ; 17,5%	0 ; 0%
SD	5 ; 12,5%	1 ; 2,5%
DM	2 ; 5%	1 ; 2,5%
APS	2 ; 5%	1 ; 2,5%
ASS	1 ; 2,5%	1 ; 2,5%
Psoriatic arthritis	1 ; 2,5%	0 ; 0%
Total	35 ; 87,5%	5 ; 12,5%

Table 1 : The distribution of the 40 AIDs in OSs according to the gender

Patient 1 (F)	Rhupus
Patient 2 (F)	Rhupus+APS+SL
Patient 3 (F)	Sclerolupus
Patient 4 (F)	Sclerolupus
Patient 5 (F)	Sclerolupus+SD
Patient 6 (F)	SSc+DM
Patient 7 (F)	SSc+DM
Patient 8 (F)	SSc+RA
Patient 9 (F)	SSc+RA
Patient 10 (F)	SSc+RA+ SD
Patient 11 (F)	SSc+RA+ SD
Patient 12 (M)	ASS+APS+SD

Patient 13 (F)	ASS+APS+SL+SD
Patient 14 (F)	SSc+PsA+SL+SD
Patient 15 (M)	SL+DM

Table 2 : The various association of systemic AIDs in OSs. (F) : Female ; (M) : Male

Immunological markers

A notable proportion of patients demonstrated positive antinuclear antibodies (ANA), with a third showing a titer of 1/640 when tested by indirect immunofluorescence on HEp2 cells. This group consisted of five individuals, three of whom exhibited a homogeneous staining pattern, while two displayed a speckled pattern. Another third of the cohort had a significantly higher titer of 1/1280, with two cases presenting a homogeneous pattern, two showing cytoplasmic staining, and one displaying a speckled pattern. In contrast, the remaining patients tested negative for ANA on two consecutive occasions.

Scleroderma panel was negative for five cases. Two patients presented with anti-SCL 70 antibodies, one had anti-Ku antibodies, another had anti-PM/Scl antibodies, and one had anti-RNA polymerase III antibodies. For SL, 62,5% (5 patients) had positive native anti-DNA antibodies, while 25% had positive anti-Sm antibodies, and the remainder, 12.5% were seronegative for both antibodies. In RA, six patients had strongly positive anti-CCP and rheumatoid factor (RF), whereas only one case was seronegative. For DM, one patient had anti-TIF1γ, an other one had positive anti-Mi2, whereas one patient had a negative myositis panel. In both patients having ASS, anti-JO 1 were strongly positive with the presence of anti-SSA Ro 52. Additionally, triple positivity was noted in the APS profile for one patient.

Cardio-Respiratory Evaluation

In respiratory evaluation, 25% of patients presented with non-fibrosing interstitial lung disease (ILD) with restrictive impairment, while another quarter had pulmonary fibrosis with restrictive impairment. However, 10% of ILDs were fibrosing without respiratory impairment, and for 15%, it was non-fibrosing ILD without respiratory impairment. The remaining 25% did not have ILD (Fig.3).

In OSs containing SSc, 8 patients (80%) had lung involvement. On the other hand, in OSs with associated SD, a restrictive ventilatory disorder was noted in all cases. In OSs containing ASS, ILD was present in both patients. However, in DM, Patient 6 had non-fibrotic ILD, Patient 7 had pulmonary fibrosis, and Patient 15 had no lung involvement (Fig.4)

No cases of pulmonary arterial hypertension (PAH) were reported in our series.

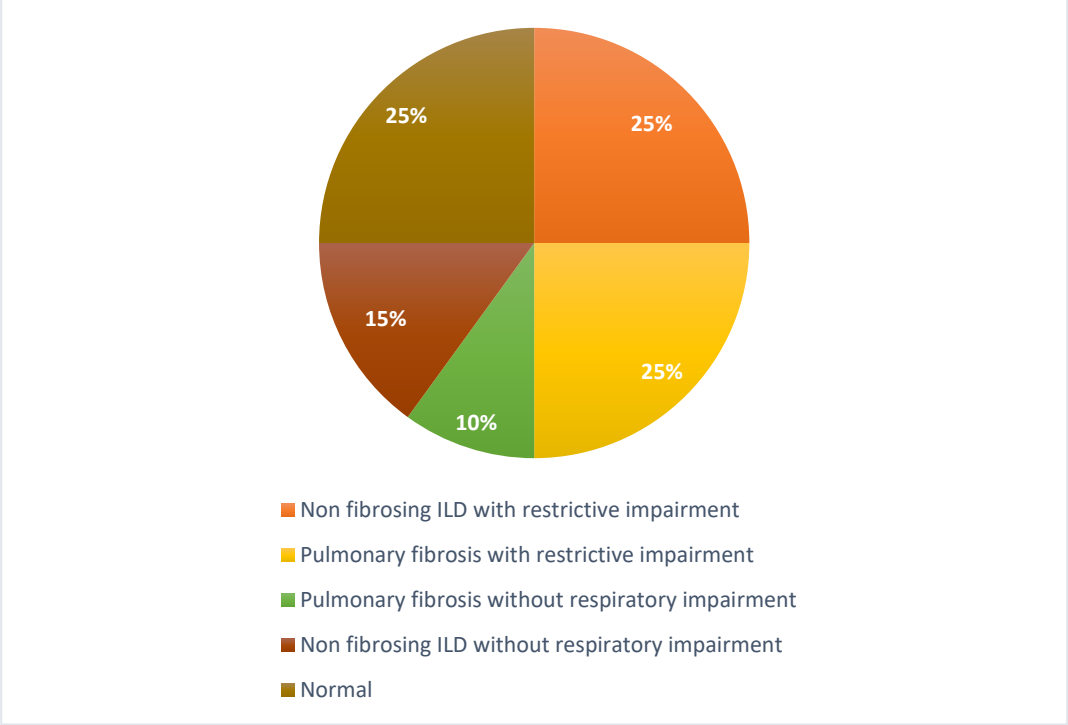

Fig.3 : The distribution of pulmonary involvement during OSs

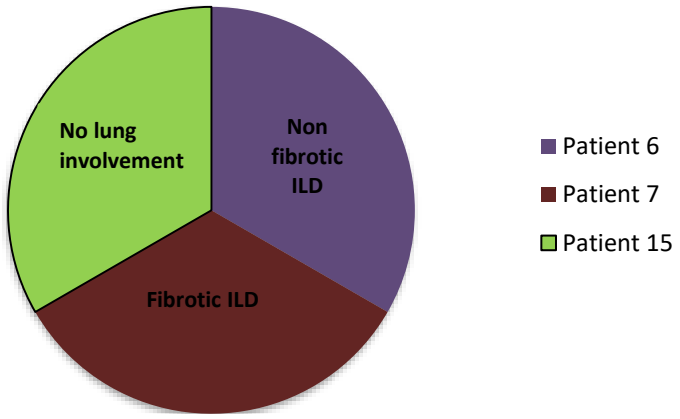

Fig.4 : Pulmonary involvement in patients having OSs with DM

Treatment and Prognosis

In terms of treatment, 75% of patients received calcium channel blockers, corticosteroids (CS) and mycophenolate mofetil (MMF). The combination of CS/MMF was mainly used for the renal and pulmonary involvement of SL and SSc. Sixty percent of patients were on hydroxychloroquine, 35% on methotrexate, and 15% on azathioprine.

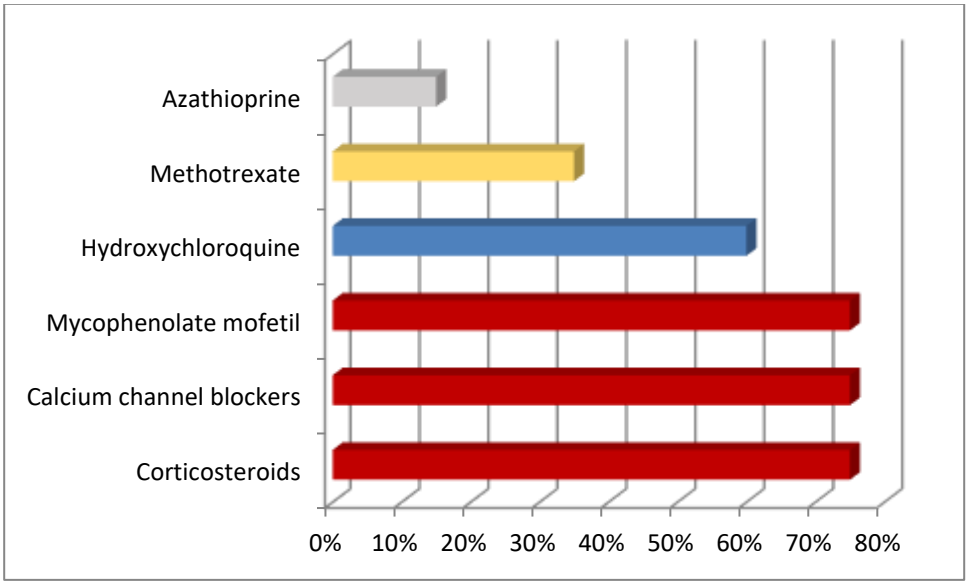

Fig. 4 :Distribution of the various drugs used in the OSs

Regarding biologic therapy, only one patient (Patient 10) with a refractory OS « SSc/RA/ SD» benefited from tocilizumab, which was replaced by rituximab following the development of pulmonary tuberculosis. The prognosis was generally favorable for all patients, with no fatalities recorded in our series.

Discussion

It is crucial to recognize that CTDs may present diagnostic complexity through three entities termed undifferenciated connective tissue diseases (UCTD), mixed connective tissue diseases (MCTD) and OS (1). These conditions share common etiopathogenic links (immune dysregulation, genetic, and environmental factors) and often exhibit blurred clinical boundaries. UCTD represents an

incomplete clinical picture that does not yet meet criteria for a defined systemic disease (2). Conversely, MCTD is characterized by overlapping features of multiple CTDs, notably scleroderma, lupus, and dermatomyositis/polymyositis, frequently associated with high titers of anti-U1-ribonucleoprotein (anti-U1-RNP) antibodies, serving as a specific immunological marker (3). Clinical manifestations include Raynaud's syndrome, arthritis, myositis, and cutaneous signs like sclerodactyly. MCTD requires personalized diagnostic and therapeutic approaches due to its clinical variability and potential progression to other systemic CTDs (4). Researchers have proposed four diagnostic criteria variants (5,6 ,7,8,9).

OSs are rare and their prevalence is still unknown (10). They involve the coexistence of complete diagnostic criteria for ≥2 CTDs, forming distinct nosological entity where patients exhibit sufficient clinical manifestations. Disease evolution may stabilize or progress toward a specific CTD over time.

Rhupus syndrome is a rare overlap of RA and SL, characterized by symmetric erosive polyarthritis alongside SL features like malar rash or serositis. Rhupus syndrome typically involves a staggered diagnosis timeline, with 83% of cases showing RA preceding SL by a median of 7.8 years, while the remaining cases involve either SL preceding RA by 6.5 years or both conditions manifesting simultaneously. The median diagnostic delay between RA and SLE varies significantly depending on which condition appears first (11). Key diagnostic markers include anti-dsDNA/anti-Smith for SL and rheumatoid factor/anti-CCP for RA (12,13). Unlike isolated SL, rhupus patients often exhibit less severe renal involvement and lower disease activity scores (14,15). Those clinical, immunological and prognostic features of rhupus already described in litterature are consistent with the results of our observational study.

In parallel, sclerolupus is also a rare OS combining SL and SSc .Its prevalence varies significantly across studies, with the largest cohort (1252 SSc patients in Toronto) reporting 6.8% prevalence (86 cases)(16), while smaller studies like a French cohort of 534 SSc patients found only 0.7% prevalence (4 cases)(17). Raynaud's phenomenon is frequently observed in sclerolupus, occurring in up to 63.2% of cases as an initial manifestation. In contrast, calcinosis cutis, telangiectasias, and diffuse skin involvement are less commonly noted (18). In our series, our 3 patients with sclerolupus had severe Raynaud's phenomenon in the clinic (presence of pulp ulcers) and on capillaroscopy objectifying several areas of microhemorrhages and capillary desert. However, skin involvement was limited and there was no calcinosis or telangiestasias.

Clinically, sclerolupus exhibit higher rates of pulmonary arterial hypertension (PAH) that seem to be associated more frequently with limited and distal cutaneous manifestations (19).In addition to the inherent risk of PAH, renal dysfunction lies in distinguishing between lupus nephritis and scleroderma renal crisis. The treatment approaches for these conditions are different since lupus nephritis often requires high-dose steroids, whereas this attitude can worsen outcomes of SSc (20). in our study, sclerolupus was not associated with high mortality and no case of scleroderma renal crisis was detected in our series despite the occasional increase in the dosage of CS≥ 15mg/d.

In OS combining SL and myositis, patients are more prone to presenting with alopecia, oral ulcers, erosive joint disease, and pulmonary manifestations, while renal involvement appears to be less common compared to other manifestations (21). A modified Bohan and Peter classification was introduced to refine the original framework for idiopathic inflammatory myopathies (IIM). This purely clinical approach centered on assigning diagnostic significance to the presence of CTDs overlap features. Within this classification, DM rash associated with myositis, in the absence of overlap features, leads to a diagnosis of pure DM (22).

Overlap myositis (OM) is characterized as patients meeting the diagnostic criteria for IIM in conjunction with criteria for another CTD, such as SSc, SL, SD or RA. Overlap autoantibodies (anti-Jo-1, anti-PL-7, anti-PM-Scl, anti-U1RNP, anti-U5-RNP) are widely encountered (22,23).

In patients with OM, the initial manifestations often includ proximal muscle weakness or other musculoskeletal symptoms. The skin rash associated with DM may appear at diagnosis or during follow-up, characterized by limited extent and a transient nature. The presence of dermatopathic DM is highly predictive indicator of OM-DM (PPV 100%). Although OM-DM is not linked to cancer, 15-year survival may significantly decrease (24). This clinical description was exactly the same for our patients with OM. In addition to the muscle deficit they had, all of them had the association of heliotrop rash, Gottron's papules and shawl sign. Despite the positivity of neoplasia-causing antibodies (anti-TIF1 γ and anti-Mi2), no tumor pathology was detected at diagnosis. However, the limitation of our study is the fact that it is retrospective and the need for regular follow-up remains indisputable.

ASS is an autoimmune disorder marked by antibodies targeting aminoacyl transfer RNA synthetase commonly identified with anti-Jo1. In our retrospective study, both patients with ASS had strongly positive anti-JO 1. The co-presence of anti-SSA Ro 52 was noted.

In ASS, key clinical features include ILD, myositis, Raynaud's phenomenon, and arthritis. ILD is more prevalent and severe in ASS compared to DM, IIM it often overlaps with phenotypically (25). In our series, ILD was present in our two patients but without objective impact on the respiratory function at diagnosis.

On the other hand, APS is an acquired thrombophilia, characterized by the occurrence of venous and arterial events. It is marked by antiphospholipid antibodies, the most thrombogenic of which is the circulating lupus anticoagulant (26).

The overlap between ASS and APS is exceptionally rare. In addition to an interesting case of ASS with anti-EJ-1 antibodies and APS (27), only a few documented cases in the literature were described (28,29,30).

The OS SSc/RA is rare representing 6,6% in Brazilian study, while the frequency of clinical arthritis observed in patients with SSc was 32.8% (31). The particularity of SSc in this OS is that it may combine manifestations of CREST syndrome including calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias. The coexistence of autoantibodies characteristic of both CTDs is helpful (32). These literature data are consistent with the results of our analytical work.

SD is a chronic autoimmune exocrinopathy primarily characterized by xerophthalmia and xerostomia (33). As with most CTDs, SD has a strong female predominance (34). Although it can manifest at any age, the condition typically emerges between the 4th and 5th decades of life (35). SD can present as either primary occurring independently or associated with other CTDs such as RA, SL, or SSc (36).

The diverse clinical and immunological manifestations of primary SD often overlap with other CTDs, complicating the distinction between primary SD, SD associated, and SD-like presentations of other CTDs, highlighting limitations in current classification criteria for clear differentiation (37).

Patients with both SL and SD exhibit a unique clinical and laboratory profile, characterized by older white women with prevalent features such as photosensitivity, oral ulcers and Raynaud's phenomenon. Conversely, they show a lower incidence of major internal organ involvement such as renal disease, and a more specific autoantibody profile (anti-dsDNA, and anti-RNP). Clinical prognosis is generally favorable (37,38). In our patients, the combination of SD in the OSs did not aggravate the prognosis. However, the impact on respiratory function was notable compared to OSs without SD.

The OS between PsA and SL is rare but documented in the literature, primarily through case reports. A Malagasy study describes a 48-year-old woman with pre-existing psoriasis and PsA later diagnosed with SL (39), while three French cases highlight the simultaneous presence of cutaneous psoriasis, PsA, and SL, emphasizing diagnostic and therapeutic complexities (40). Treatment challenges include hydroxychloroquine potentially worsening psoriasis, systemic corticosteroids risking psoriatic flares during withdrawal, and methotrexate often preferred for its efficacy in both conditions.

PsA can overlap with SSc in rare cases. This particular OS has been documented in several studies and case reports. A 2018 study found that psoriasis was significantly associated with SSc, with a 2-fold higher frequency (3%) compared to the general population. Among 180 SSc patients, 6.1% had a dermatologist-confirmed diagnosis of psoriasis, and 27.2% of these patients also had PsA. Interestingly, these patients often had a low modified Rodnan Skin Score (mRSS) and a high prevalence of anticentromere antibodies (41). Another study highlighted that SSc is independently associated with psoriasis, and patients with both conditions were almost exclusively ANA-negative, showing better survival rates compared to those with SSc alone (42). Additionally, a case report described a patient with both SSc and PsA, emphasizing the need for individualized treatment approaches due to the complex interplay between these conditions (43). In our series, our patient had the particularity of simultaneously combining the manifestations of PsA with SL and SSc, making this OS newly described in our retrospective study.

OSs in CTDs encompass conditions that exhibit clinical features of multiple well-defined rheumatic disorders. Early diagnosis and aggressive treatment are crucial to prevent severe organ damage and improve outcomes of this complex entity. Treatment is tailored to the predominant clinical manifestations and typically involves CS and immunosuppressants like azathioprine, cyclophosphamide, and MMF (44). In our study the combination of CS and MMF for renal and pulmonary involvement has shown encouraging results. Biologic therapies, including anti-tumor necrosis factor α (anti-TNFα), anti-IL6 and anti-CD20 monoclonal antibodies such as rituximab, are increasingly used in refractory cases, though caution is advised with anti-TNF agents due to the risk of exacerbating systemic autoimmune diseases (45). Among all patients of our series, only one (Patient 10) with a treatment-resistant overlap syndrome (SSc/RA/SD) experienced improvement with tocilizumab, which was later substituted with rituximab due to the onset of pulmonary tuberculosis. Hydroxychloroquine is often employed for its immunomodulatory effects especially in OSs with SL (46). Vasodilators and prostacyclin analogues, such as iloprost, are beneficial for managing vascular complications like Raynaud's phenomenon and PAH (47). In our series, we have succeeded in treating Raynaud's phenomenon with hygienic measures and calcium channel blockers, even in severe cases. No cases of PAH have been reported in our patients.

Conclusion

OSs represent a real complexity of CTDs requiring a genuine diagnostic and therapeutic management. In-depth knowledge of the condition is essential for early detection and appropriate treatment. OSs impose heightened clinical vigilance in the face of evolving symptoms, multidisciplinary collaboration, and the integration of innovative biomarkers.

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