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REVIEW

OVERLAP SYNDROMES IN AUTOIMMUNE CONNECTIVE TISSUE DISEASES

L. A. Dourmishev

Department of Dermatology and Venereology, Medical University – Sofia, Bulgaria

Abstract. *Autoimmune connective tissue diseases are a group of immune disorders, characterized by different clinical features, which affects not only the skin but also different organs and systems. Such diseases include: rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, systemic sclerosis, dermatomyositis and polymyositis. However, there are patients that fulfil the diagnostic criteria of more than one disorder, thus supporting the concept of the so called "overlap syndromes". The aim of this review is to present the history, clinical and immunologic hallmarks of these overlap syndromes. Such conditions are scleromyositis, lupus erythematosus/lichen planus overlap, Sharp's syndrome, Rhupus syndrome, Rowell's syndrome, Reynolds syndrome and Senear-Usher syndromes. Patients with these syndromes usually do not meet most of the diagnostic criteria of "classic" connective tissue diseases and this usually causes diagnostic difficulties. Overlap syndromes are commonly treated with corticosteroids, hydroxychloroquine and immunosuppressant drugs as a first-line treatment. The new therapeutic molecules that precisely interact with immune mechanisms will require accurate diagnosis and a better understanding of the pathogenesis of the overlap syndromes.*

Key words: *connective tissue diseases, overlap syndromes, Sharp's syndrome, Rhupus syndrome, Rowell's syndrome, scleromyositis, lupus erythematosus/lichen planus overlap syndrome, Reynolds syndrome, Senear–Usher syndrome*

Corresponding author: *Assoc. Prof. Lyubomir A. Dourmishev, MD, PhD, Department of Dermatology and Venereology, Medical University of Sofia, 1 "Sv. Georgi Sofiyski" Str, 1431 Sofia, Bulgaria, tel: +359 2 9230 438, e-mail: l_dourmishev@yahoo.com;*

ORCID ID: *0000-0001-8458-1241*

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INTRODUCTION

Autoimmune connective tissue diseases (ACTDs) are a group of disorders with autoimmune pathogenic mechanisms characterized by different clinical features, that affect not only the skin but also internal organs and systems. Such diseases are rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), systemic sclerosis (SSc), dermatomyositis (DM) and polymyositis (PM). All ACTDs are classified according to consensus criteria developed by various rheumatological and dermatological organisations such as the American College of Rheumatology (ACR) or the European League Against Rheumatism (EULAR), which consider specific or compatible clinical features, laboratory or immunological markers. However, in our practice we sometimes observe patients, who do not fit into the diagnostic criteria of only one disease, nevertheless, they definitely have ACTD. This sup-

ports the concept of existence of a so-called “overlap syndromes” with features of two or more autoimmune diseases [1, 2]. Schematic diagram showing the relationships among the general category of overlap syndromes is given below (Fig. 1). The aim of this review is to present the history, clinical and immunologic hallmarks of these OSs and to give clues and provide the current state of knowledge on the diagnostic workup and the therapeutic approaches in such patients.

SHARP’S SYNDROME

In 1972 Sharp et al. described 25 patients with overlapping features of SLE, RA, SSc, and PM, as well as circulating anti-extract nuclear antigens and speckled type immunofluorescence antinuclear antibodies (ANA) [3]. Later Rosenthal suggested the term “Sharp’s syndrome” (ShS) for this autoimmune disorder [4].

The originally described clinical features of ShS include arthralgia or arthritis; fingers and hands edema; Raynaud’s phenomenon; esophageal dysmotility; myalgias and muscle weakness; lymphadenopathy; fever; hepatomegaly or splenomegaly; serositis and thyroiditis. None of the patients from the original cohort had renal disease. However, most of these patients, when re-evaluated later, had developed SLE. The routine laboratory tests revealed anemia, leukopenia, thrombocytopenia and hypergammaglobulinemia, compatible with those observed in SLE [3]. The main immunological hallmark of the syndrome are antibodies against U-type small nuclear ribonucleoprotein particles (U1 RNP). The U1 RNP antigen is one of a series of uridine-rich RNA particles that are composed of eight polypeptides and are highly associated with the HLA-DR4 haplotype [5].

Various comorbidities associated with ShS are reported so far, including trigeminal and facial nerve paralysis [6]; pulmonary hypertension and lung fibrosis [7]; vagal neuropathy [8]; erythema nodosum [9]; bilateral pulmonary tuberculosis [10]; cervical schwannoma [11] and ileus with ascites [12].

There is no standard therapy for Sharp syndrome since the former claims of a relatively favorable prognosis and easy therapeutic response are true only for part of the patients. Contemporary treatment depends on the pattern of clinical involvement. A recent retrospective study showed that hydroxychloroquine, prednisone, methotrexate and rituximab are more

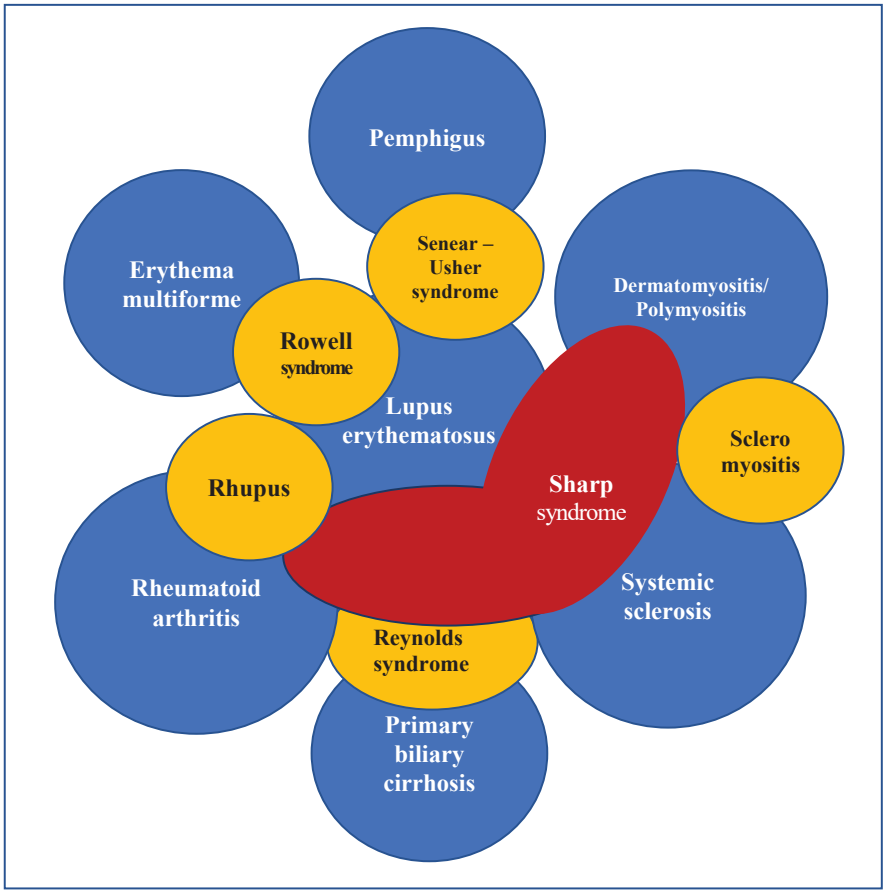

Fig. 1. Schematic presentation of overlap syndromes

often used for the treatment of such patients, than mycophenolate mofetil, azathioprine, cyclophosphamide and anti-TNF-α-antagonists [13].

RHUPUS SYNDROME

Rhupus syndrome (RhS) is a rare autoimmune entity, comprising 0.2% of all patients with ACTD [14]. Although incompletely described, the syndrome is present if a patient develops symptoms of both RA and SLE. RhS was first described by Peter Schur in 1971, nevertheless, some cases were observed earlier [15]. The syndrome affects mostly female patients, who develop RA at young age and SLE symptoms come later.

A retrospective study of six RhS patients showed, that RA manifests with chronic symmetric arthritis, subcutaneous nodules, positive rheumatoid factor (RF) test and joint erosions, while SLE symptoms include malar rash, discoid skin lesions, lupus nephritis, photosensitivity, leuko- and thrombocytopenia, positive antinuclear antibodies, hypocomplementemia and histology findings compatible for lupus in skin biopsy [14]. A study of 40 RhS patients with two control cohorts with SLE and RA patients each demonstrated, that the main clinical affections include arthritis in 94% of cases, followed by cutaneous affection in 78% of patients and immunological changes, while renal and neurological involvement were rare compared to the SLE group [16]. RhS affects mainly hands, wrists and knees, and clinically presents as severe non-erosive polyarthritis, non-erosive deforming arthritis or arthritis with joint deformities and erosion. The erosive progression of arthritis can result in severe disability.

Laboratory investigations showed significantly more frequently observed abnormalities in RF, erythrocyte sedimentation rate, C-reactive protein and anti-cyclic citrullinated peptide (CCP) antibodies in patients with RhS compared to those with SLE, while the prevalence of ANA and other autoantibodies showed no difference [16].

The treatment and prognosis of RS syndrome are different from those in RA or SLE alone. Most of the patients are treated with classic disease-modifying antirheumatic drugs. Long-term open-label studies suggested, that rituximab [17] and anti-TNF-α-antagonists are effective and safe in patients with RS unresponsive to other treatment [18].

ROWELL'S SYNDROME

Rowell's syndrome (RwS) is an overlap of LE with erythema multiforme (EM)-like skin lesions, positive serum RF, a speckled pattern of ANA and a precipitating antibody to saline extract of human tissues, observed in four patients and published in 1963 [19]. Most of the RwS patients are middle-aged women. The etiology of the disease is unclear, however, drugs and infections are suspected as potential triggering factors in half of the patients [20, 21], while the other half of RwS cases are idiopathic. Cutaneous manifestations of LE are found in at least 30% of patients and resemble those in subacute cutaneous LE, and seldom chronic discoid LE, SLE or bullous LE [22]. EM lesions are symmetrically distributed on trunk or extremities and manifest as rounded or polycyclic lesions with central erythematous macules, papules or vesicles, surrounded with concentric erythematous borders with classic target-type pattern (Figure 2). In 2000 Zeitouni et al. proposed a classification with major and minor diagnostic criteria for the diagnosis of RS [23]. The major criteria include: LE-type lesions; EM-like lesions and elevated titers of speckled pattern ANA, while minor criteria are: chilblains; high titers of anti-Ro or anti-La antibodies in sera and elevated RF. Diagnosis is confirmed if all three major criteria and at least one of the minor criteria are fulfilled [23]. Torchia et al. have proposed an even more sophisticated classification, including negative direct immunofluorescence (DIF) on EM-like lesions in the major criteria group and the absence of infectious or pharmacologic triggers and atypical EM location among the minor criteria [24].

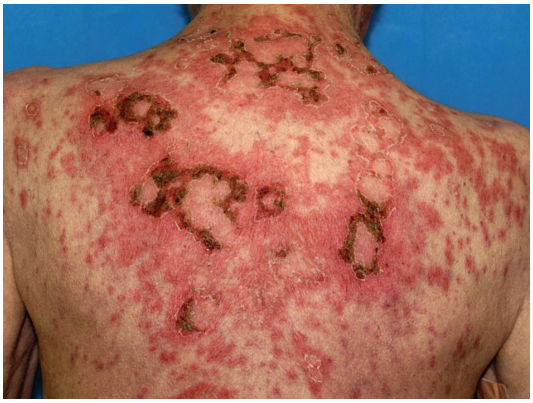

Fig. 2. Annular and target erythematous plaques with hemorrhagic crusts on the back of 67-year-old woman with Rowell's syndrome

Some authors argue, that RS is not a separate entity, but a subset of the subacute cutaneous LE with targetoid-type lesions, while the association of EM and LE, or lichen planus (LP) is considered a coincidence [25, 26]. Others, however, insist that the lesions in RwS are recurrent, in contrast with classical self-limited and drug-associated EM [27, 28].

Histologic and immunofluorescence findings of RS are controversial since the presence of necrotic kera-

tinocytes may also be found in subacute cutaneous LE lesions and negative DIF cannot exclude lupus [24]. Other diseases associated with RwS are histiocytic necrotizing lymphadenitis [29], antiphospholipid syndrome [30], lupus nephritis, lobar pneumonia [31], macrophage activation syndrome [32], Rufus syndrome [33] and lupus hepatitis [34].

Therapeutic options for RwS are systemic steroids and immunomodulators like azathioprine, hydroxychloroquine, methotrexate or ciclosporin [35]. Anifrolumab, a monoclonal antibody that binds to the type I interferon-α (IFN-α) receptor (IFNAR1) subunit 1 showed an excellent improvement in a female patient with RwS [36].

SCLEROMYOSITIS

In 1987 Mimori described 27 patients with criteria for both SSc and DM/PM [37]. The condition was termed scleromyositis (SM) and all these patients had muscle weakness with elevation of muscle enzymes, scleroderma-like skin lesions and Raynaud's phenomenon, while pulmonary fibrosis, esophageal disfunction and arthritis were rarely observed. Compared to the DM/PM cohort, the SM group showed no significant differences in creatine phosphokinase (CPK) levels, electromyography or muscle biopsy findings, however, a heliotrope rash and Gottron's sign were not frequent [37]. Blaszczyk et al. reported 14 patients with childhood SM, distinguished from SSc because of the lack of indurations of the hands, digital pitting, fingers contractures, thinning of the lips and pronounced radial furrowing around the mouth [38]. CPK and other muscle enzymes in these patients were normal or slightly elevated, even in pronounced myalgia, in contrast to "classic" DM. Moreover, pathognomonic cutaneous lesions such as Gottron sign and periorbital erythema were present only temporary [38].

The main immunological marker of SM is the PM-Scl antibody, showing a homogeneous nucleolar fluorescence pattern on HEp-2. PM/Scl autoantibodies are directed against two molecules of 100 kDa and 75 kDa, respectively and are found in about 30% of SM patients [38]. Their strong association with the HLA DR3 genotype suggests the relevance of a genetic background [39]. Other SM associated autoantibodies are anti-Ku, anti-U1RNP and anti-U3RNP antibodies [40].

The disease course of SM is chronic and relatively benign, hence the therapy with corticosteroids could control the disease resulting in a long-lasting remission. However, some authors report an increased mortality rate due to cardiopulmonary death in SM patients, compared to those with SSc without myositis [41].

The cases resistant to corticosteroids require a combination with immunosuppressive agents such as azathioprine, methotrexate, mycophenolate or second-line therapeutic modalities, such as intravenous immunoglobulins, rituximab or tofacitinib [42].

LUPUS ERYTHEMATOSUS/LICHEN PLANUS OVERLAP SYNDROME

Lupus erythematosus/lichen planus overlap syndrome (LE/LP-OS) is an entity that combines the clinical and immuno-histological features of both LE and lichen planus. It was described as "a mixed LP-LE disease" by Piamphongsant et al. in 1978 [43]. More than 50 cases of LE/LP OS have been reported in the literature, however, some authors suggest that the disease is underreported [44]. LE/LP-OS patients have chronic, lupus-like lesions on the head, the face and the upper trunk, while reticular, whitish plaques are often found in the oral mucosa, associated with lichenoid papules, papulo-nodular, and verrucous LP lesions [43]. Demirci et al. [44] reported a patient with a malar rash, erythema of the back and classic LP lesions on the extremities, while Nagao and Chen [45] argued that the genuine overlap has to be within a single skin lesion. Histopathological findings show pathological features consistent with either LP or LE or both, while DIF is essential, finding predominantly IgM cytoid bodies, complement and granular fibrin depositions along the dermal-epidermal junction [46].

Treatment of LE/LP-OS requires systemic corticosteroids and topical calcineurin inhibitors; however remarkable clinical results have been obtained with acitretin and cyclosporine [44].

REYNOLDS SYNDROME

Opposite to the well-known Raynaud's syndrome, Reynolds syndrome (RS) is a rarely described condition, characterized by the association of SSc and especially its CREST variant, with primary biliary cholangitis (PBC) [47]. PBC is a chronic autoimmune cholestatic disease leading to the destruction of intrahepatic bile ducts and resulting in liver cirrhosis.

RS usually presents with pronounced pruritus, jaundice, hepato-, or splenomegaly, Raynaud's phenomenon, calcinosis cutis and telangiectasias on palms and mucosa, resembling Rendu-Osler-Weber syndrome. Laboratory investigations show a marked elevation of serum alkaline phosphatase and are positive for anti-mitochondrial antibodies (AMA) in sera [47]. In a recent study of 24 RS cases, most of the patients had limited cutaneous SSc, half of them - digital necrosis and almost all - anti-centromere and

AMA in sera [48]. However, RS patients have an increased risk to develop pulmonary hypertension and this complication should not be overlooked [48].

Since the initially described patients by Reynolds, few case reports have been published in PubMed, showing association with SS [49, 50], pseudoainhum [51], Hashimoto's thyroiditis [52], malignant thymoma [53], and chondrodermatitis nodularis helicis [54].

Patients with RS and pronounced pruritus were treated with ursodeoxycholic acid, obeticholic acid, or antihistamines. Disease-modulating drugs such as corticosteroids, immunosuppressants (methotrexate and azathioprine) are found useful in most of these patients [55].

SENEAR – USHER SYNDROME

Senear-Usher syndrome (S-US) also known as pemphigus erythematosus was first described in 1926 in eleven patients [56]. This rare autoimmune skin disease represents approximately 8% of all pemphigus cases and shows a clinical overlap of LE and pemphigus foliaceus (PF) [57]. S-US is considered as a localized variant of PF, but also may evolve into a generalized form, and according to some authors it can even progress to pemphigus vulgaris [58]. Skin lesions are typically distributed on the face or trunk, presenting with erythematous plaques, erosions and rarely loose bullae, with scales and crusts, and resemble those of LE or seborrheic dermatitis [59]. They have a tendency to exacerbate and spread after sunlight exposure. Mucous membranes are rarely involved [60]. Systemic involvement, if present, resembles SLE with nephritis, pleuritis, pericarditis, Raynaud's phenomenon, arthralgias, leukopenia and anemia [61].

Cutaneous histopathology of S-US includes superficial epidermal acantholysis, subcorneal blistering, dermal edema and perivascular infiltrate, while in long-lasting lesions epidermal hyperplasia with parakeratosis is evident [58]. In contrast to PF, S-US has a positive DIF along the dermal-epidermal junction in about 80% of cases and elevated ANA in more than 30% of patients [61].

Similar to other autoimmune disorders, S-US was found to be associated frequently with thymoma and myasthenia gravis [61]. Various medication such as d-penicillamine [62], propranolol, captopril [63], cefuroxime [64] and atorvastatin [65] are also presumed to be a disease trigger.

Treatment of S-US includes corticosteroids and rarely immunosuppressive agents, since most of the cases are controllable with low doses of prednisolone [66]. Alternate treatments in steroid-resistant cases include dapsone or rituximab [59].

CONCLUSION

It is well known that autoimmune diseases tend to associate with each other and the clinical picture in a single patient may vary due to the influence of genetic background and the modulating effect of environmental factors. Therefore, in some cases, these associations may define a specific clinical entity, and if a diagnostic marker exists, a particular syndrome emerges. This is the case with scleromyositis, LE/LP overlap, Sharp's syndrome, Rhupus syndrome, Rowell's syndrome, Reynolds and Senear-Usher syndromes.

Patients affected by these OSs do not meet all diagnostic criteria of "classic" ACTDs and this causes diagnostic difficulties, but their clinical manifestations are usually milder and the prognosis is generally better.

Currently, we still rely on well-known corticosteroids, hydroxychloroquine and immunosuppressant drugs as a first-line treatment in patients with OS. However, future treatment with new molecules that precisely interact with immune mechanisms will require accurate diagnosis and a better understanding of the pathogenesis of the OSs.

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