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Case Report

Systemic Lupus Erythematosus in Men: Brief Description of Clinical and Laboratory Findings

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Abstract

Background: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by the presence of nuclear autoantibodies, which can cause autoimmune complex formation and inflammation of multiple organs. It is known to affect women more frequently than men and is typically diagnosed during reproductive age, where the female-male ratio has been reported as high as 12:1. The etiology of SLE is not fully understood, but both genetic predisposition and environmental triggers are believed to be involved. Because of the multitude of presentations, manifestations, and serological abnormalities in patients with SLE, diagnosis can be challenging. Chronic discoid lupus and photosensitivity have been found in men with SLE as far as skin findings are concerned, there is less joint involvement in these patients, however, severe systemic findings predominate, such as serositis, pleurisy, central nervous system involvement with the presence of seizures. , thrombotic events and lupus nephropathy of the acute proliferative glomeruonephritis variety, serologically there is no consensus yet, nor in the specific clinical characteristics but the presence of anti-dsDNA anti-Sm antibodies and anticardiolipin antibodies is also frequently found.

Therapeutic approaches predominantly involve immunomodulation and immunosuppression and are targeted to be the specific organ manifestation, with the aim of achieving low disease activity.

Conclusion: We considered that although male patients with lupus are not commonly seen, the manifestations are life threatening, and timely diagnosis and treatment of the disease will lead to a better outcome for these patients.

Background

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by immune system dysfunction and presents with a wide range of clinical manifestations, including dermatological, renal, neuropsychiatric, and cardiovascular symptoms [1].

The word lupus (Latin term for "wolf") has been used interchangeably since the Middle ages for various types of diseases characterized by ulcerative lesions, mainly in the lower limbs. In the mid-18th century, the French dermatologist Cazenave first mentioned the term "lupus erythematosus," while Kaposi reported discoid lupus as a separate entity. The real turning point in the history of lupus occurred in the early 19th century, when the distinction between lupus vulgaris (cutaneous tuberculosis) and cutaneous lupus in its modern sense slowly emerged. The important late contributions of Kaposi, Sequiera-Balean, and Osler made it possible to recognize the systemic nature of the disease, its modern history being marked by the recognition of DNA as the main target of antinuclear antibodies and the central role of interferons [2].

Epidemiology

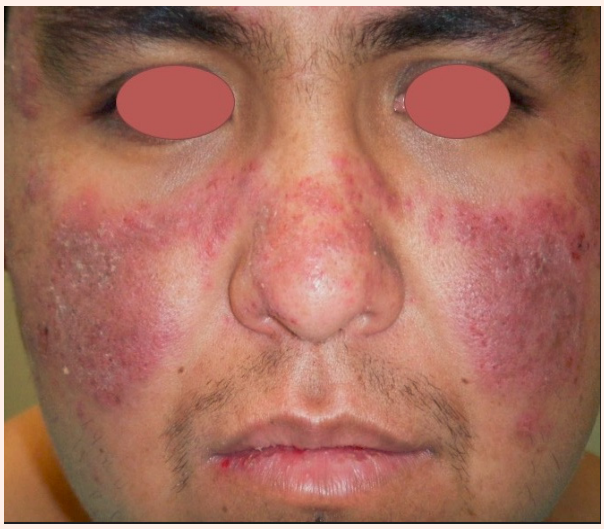

Figure 1: Rash malar 25-year-old man in a SLE with nefritis.

The incidence of SLE is 0.3 to 31.5 per 100,000 habitants per year, and the adjusted prevalence is close to, or even exceeds, 50 to 100 per 100,000 inhabitants [1]. SLE has a female predominance >90% in general [3] and even more so in the fertile years, where a female-male ratio of up to 12:1 has been reported [4].

Men and women with SLE present different clinical and serological profiles, and it is a fact men presenting a more severe disease [5]. The influence of hormones and chronobiology have been explored, but the non-hormonal influences of menstrual cycles and other unrecognized variables are only just being determined [6]. Recent data suggest that the number of X chromosomes instead of sex may be of critical importance for the sexual predilection of SLE [7,8]. Therefore, gender, race, and age at diagnosis have a considerable impact on the clinical course and treatment of SLE.

Factors that explain the possible causes of the female predilection for SLE include the effects of estrogen and its hydroxylation, decreased androgen levels, hyperprolactinemia, and differences in gonadotropin-releasing hormone (GnRH) signaling [9]. Therefore, SLE seems to be one of the most differentiated diseases by sex [10].

Etiopathogenesis

It is etiopathogenesis is complex and not well known. In general terms, it is due to a primary alteration of the innate and adaptive immune response that leads to the appearance of autoreactive B and T lymphocytes and circulating autoantibodies, which implies the global loss of self-tolerance. This abnormal immune response is triggered in genetically predisposed individuals (more than 30 susceptibility genes have been implicated to date, such as STAT4, IRF5 and ITGAM) after exposure to certain environmental, hormonal and emotional factors [11]. There are also examples of mutations rare monogenic genes leading to SLE and SLE-like phenotypes, these include genes known to be involved in DNA damage repair (eg, TREX 1), nucleic acid sensing, and type 1 interferon overproduction (eg, STING and TREX 1), apoptosis, tolerance, and autoantigen clearance, in addition to early complement deficiencies.

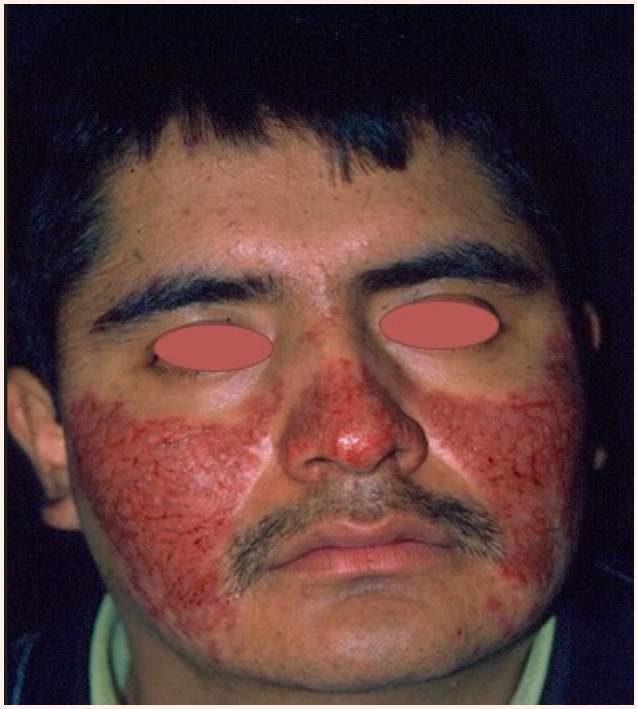

Figure 2: Rash malar 32-year-old man in a SLE *courtesy by Profr. Fermin Jurado.

Historically, studies with gonadectomy/hormone deprivation and hormone supplementation in male and female lupus prone mice have shown a clear association of sex hormones with lupus, where estrogen accelerates or worsens disease and estrogen removal ameliorates disease in females. Male gonad removal increases susceptibility to disease in male mice and androgen supplementation improves disease in female mice [12]. Environmental triggers (eg, exposure to ultraviolet radiation, smoking, medications, viruses such as Epstein-Barr virus, low levels of vitamin D, and environmental pollutants) and epigenetic modification play a role in the pathogenesis of SLE [13].

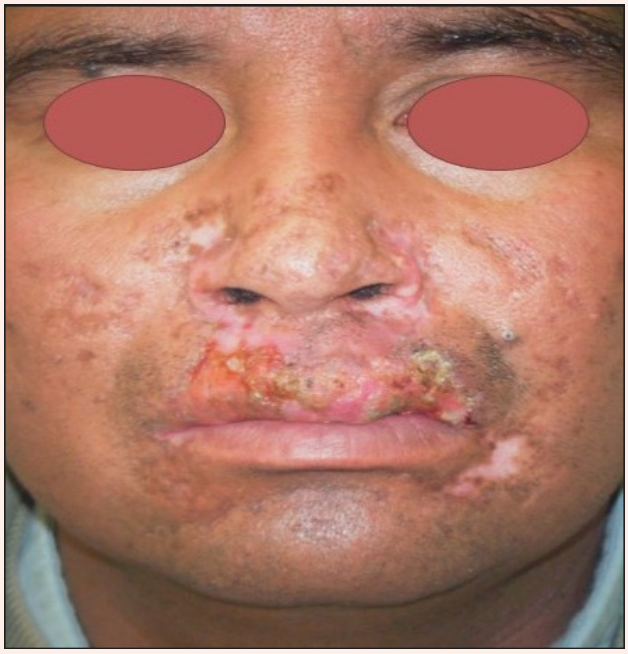

Figure 3: Chronic discoid eruption in a 38 years old man with progression to SLE.

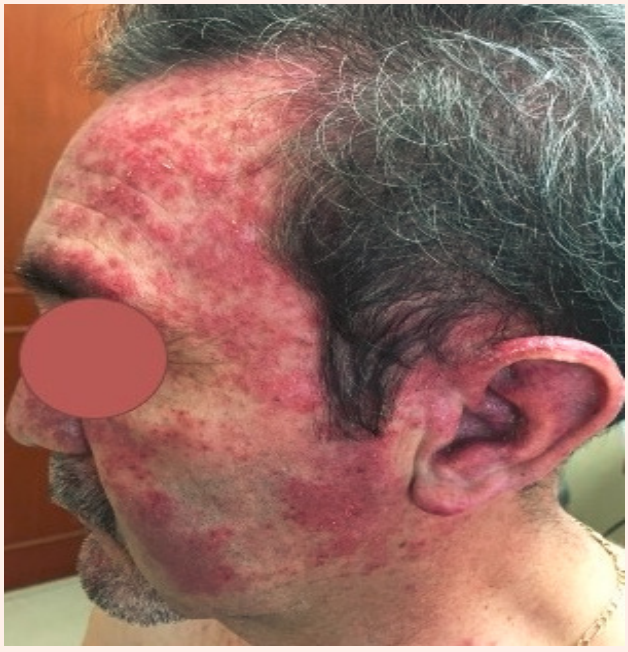

Figure 4: Photosensitivity in a 50-year-old man with SLE and kidney damage.

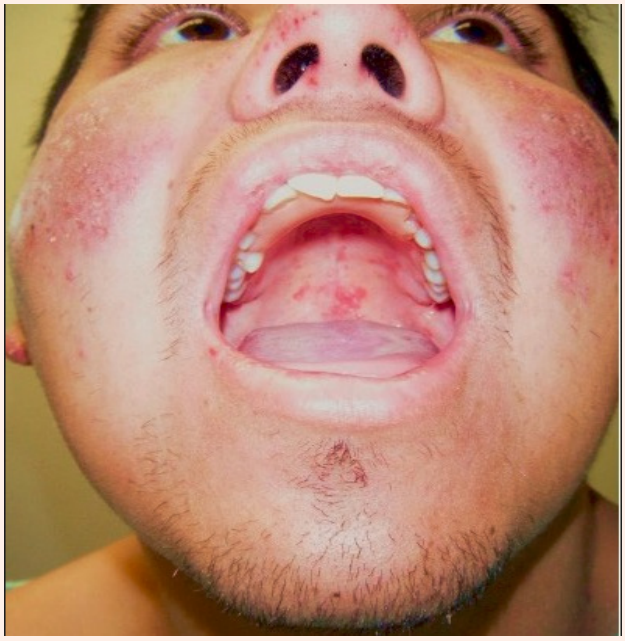

Figure 5: Oral and nasal ulcers in 25-year-old male with SLE.

Diagnosis

The clinical and serological heterogeneity in SLE represents a challenge. There are multiple classification criteria for SLE, however, the revised criteria of the American College of Rheumatology (ACR) [12] are the most widely used criteria. The diagnosis of SLE is made if four or more of the manifestations are present. These criteria have a sensitivity of about 96% [14].

American College of Rheumatology (ACR) criteria for the diagnosis of Systemic Lupus Erythematosus.

Criterion Definition

a) **Malar rash**: Erythema and slight infiltration over the malar eminences, with a tendency to spare the nasolabial folds. (Figures 1 & 2).

b) **Discoid eruption**: Raised erythematous patches with adherent scale and follicular plugging; atrophic scarring can occur in older lesions. (Figure 3).

c) **Photosensitivity**: Skin rash as a result of an unusual reaction to sunlight. (Figure 4).

d) **Oral ulcers**: Oral or nasopharyngeal ulceration, usually painless, observed by a physician. (Figure 5).

e) **Non-serosive arthritis**: Affects two or more peripheral joints and is characterized by tenderness, swelling, or effusion.

f) **Pleurisy or pericarditis**

i. Pleurisy -- Convincing history of pleuritic pain or rub hear by a physician or evidence of pleural effusion

ii. Pericarditis -- Documented by electrocardiogram or rubbing or by evidence of pericardial effusion.

g) **Renal disorder**

i. Persistent proteinuria > 0.5 g/day or > 3g if quantification is not performed.

ii. Cellular cylinders that can be red blood cells, hemoglobin, granular, tubular or mixed.

h) **Neurological disorder**

i. Seizures: in the absence of drugs that cause them or metabolic disorders (eg, uremia, ketoacidosis, or electrolyte imbalance)

ii. Psychosis in the absence of offending drugs or known metabolic disorders (eg, uremia, ketoacidosis, or electrolyte imbalance).

i) **Haematological disorder**

i. Haemolytic anemia with reticulocytosis or,

ii. Leukopenia <4,000/mm3 on two or more occasions,

iii. Lymphopenia <1,500/mm3 in the absence of drugs that produce it

iv. Thrombocytopenia <100,000/mm2 in the absence of causative drugs

j) **Immunological disorder**

i. Anti-DNA: antibody against native DNA in normal titer.

ii. Anti-Sm: presence of antibody against the nuclear antigen (Smith)

iii. Positive findings for antiphospholipid antibodies based on (1) an abnormal serum level of IgG or IgM anticardiolipin antibodies (2) a positive test result for lupus anticoagulant using a standard method or (3) a false positive serologic test result for syphilis (VDRL) known to be positive for at least six months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test.

k) **Antinuclear antibody**

An abnormal antinuclear antibody titer by immunofluorescence or equivalent assay at any time and in the absence of drugs known to be associated with "drug-induced lupus syndrome".

Lupus Erythematosus in Men

SLE is a chronic, sometimes life-threatening, multisystem disorder. Patients suffer a wide range of symptoms and have a variable prognosis depending on the severity and the type of organ(s) involved. It has long been recognized that SLE has a hereditary component [15,16]. Familial clustering of SLE has been demonstrated in the general population, with 7-12% of SLE patients having a first-degree relative with this disease, compared to a mean prevalence of 1 lupus patient per 2000 population in Europe [16]. A high concordance rate of up to 20% between monozygotic twins also suggests a strong genetic component in the development of SLE [17,18].

Although SLE predominantly affects women of childbearing age, it can also occur in men and at any age. According to data accumulated in the medical literature, approximately 4 to 22% of patients with SLE in reported lupus series or populations are men, even reaching 30% in studies that consider familial aggregations.

Since 1975, 26 articles addressing male SLE have been published in an attempt to identify the distinctive clinical features of these lupus patients. Men with SLE are reported to have serositis, cardiovascular disease, cytopenias, hemolytic anemia, nephritis, positive antiphospholipid antibodies, thrombotic events, and seizures. The most frequent characteristics associated with SLE in men include smoking, alcohol consumption, the presence of lupus anticoagulant, and renal involvement. Although men with SLE experience nephritis at a higher rate than women, progression to end-stage renal disease does not differ by sex. In some studies, diffuse proliferative glomerulonephritis was observed as the dominant histologic finding on renal biopsy in men. Regarding skin involvement, most of the results showed a significantly higher prevalence in men than in women. Several authors stated that discoid lesions and/or subacute lesions were more common in male SLE patients, but malar rash was much less common. With regard to arthritis, a significant controversy remains. Meanwhile, Raynaud's phenomenon, photosensitivity, mucosal ulcers, and lymphadenopathy were found less frequently in male SLE [19]. Regarding serological findings, a decrease in the prevalence of anti-Ro and anti-LA antibodies has been reported in some studies. As characteristics of SLE, anti-dsDNA and anti-Sm antibodies proved to be more frequent among men. Men had anticardiolipin antibodies more frequently, and lupus anticoagulant was found to occur more frequently in some studies. Anti-U1RNP, low C3, and low CH50 antibodies were also observed to be more frequent in men with SLE in several studies [19].

Tze Chi Tan et.al. [20] made comparisons between male and female patients with SLE in the Hopkins Lupus cohort, which included a total of 1979 patients. The cohort consisted of 157 men (66.2% White, 33.8% African American) and 1822 women (59.8% White, 40.2% African American). The follow-up was 6.02 years. Ninety-five percent of the patients met the revised criteria of the American College of Rheumatology (ACR) for SLE. Male and female SLE patients were compared with respect to demographic characteristics, clinical manifestations, serologic results, and therapy. Accordingly,

men were more likely than women to have disability, lymphopenia, thrombocytopenia, positive anti-Sm, direct Coombs test, LAC, low C3, and anti-dsDNA. Men were also more likely to have had renal involvement, thrombotic events, and hypertension, compared with women. Also, men had less likely than women to have had a malar rash, photosensitivity, oral ulcer, alopecia, and arthralgia. In general, the differences between men and women were more numerous and striking in white race, especially with regard to lupus nephritis, abnormal serologies, and thrombosis. Therefore, their study suggests that there are important clinical differences between male and female patients with SLE (Table 1).

Table 1: Comparison of clinical features between male and female in 1979 SLE patients from the "multiethnic population" cohort.

Clinical features	Male, n = 157 n (%)	Female, n = 1822 n (%)
Malar rash	62 (39.7)	953 (52.4)
Discoid rash	38 (24.7)	360 (19.8)
Photosensitivity	63 (40.4)	1007 (55.5)
Oral ulcer	53 (34.0)	961 (52.9)
Alopecia	44 (28.2)	1023 (56.4)
RP	56 (35.7)	987 (54.4)
Subacute cutaneous lupus	11 (7.1)	93 (5.1)
Bullous lupus	2 (1.3)	13 (0.7)
Vasculitis (cutaneous)	19 (12.3)	270 (14.9)
Arthralgias	137 (87.3)	1688 (92.7)
Arthritis	109 (70.3)	1347 (74.4)
Pleuritis	65 (41.7)	810 (44.7)
Pericarditis	39 (25.0)	403 (22.3)
Proteinuria	78 (50.0)	732 (40.4)
Nephrotic syndrome	36 (23.8)	299 (16.6)
Hematuria	54 (34.8)	492 (27.2)
Renal insufficiency	49 (34.1)	343 (18.9)
Renal failure	24 (15.3)	138 (7.6)
Renal biopsy	56 (35.7)	470 (25.8)
Hemolytic anemia	19 (12.8)	178 (10.1)
Leukopenia	74 (47.4)	785 (43.3)
Lymphopenia	77 (49.4)	698 (38.8)
Thrombocytopenia	45 (28.8)	353 (19.5)
Seizures	20 (12.7)	175 (9.6)
Psychosis	7 (4.5)	67 (3.7)

Despite advances in therapy, the mortality associated with SLE remains considerable. In 1981, Wallace et.al. [21] reported survival data for 609 lupus patients (including 63 men) followed for a mean of 10 years. Comparative 5-, 10-, and 15-year survival rates for men and women with SLE were 77% vs. 89%, 75% vs. 80%, and 58% vs. 75%. Thereafter, many additional investigators noted decreased survival in male SLE. In 2006, Kasitanon et.al. [22] in their multivariate model, age at diagnosis of SLE > 50 years (hazard ratio = 5.9; $p < 0.001$) and male gender (hazard ratio = 2.4; $p = 0.004$) were associated with poorer survival. Death early in the disease course is often attributed to active disease and infection, while later mortality is often due to damage, corticosteroid-mediated injury, and cardiovascular disease.

Boodhoo et.al. [23] performed a meta-analysis where they included 16 studies with a total of 11,934 patients with SLE (10,331 women and 1,603 men). The average female to male ratio of all included studies was around 9.3:1. Their analysis, which compared clinical features between men and women with lupus, showed that alopecia, photosensitivity, and oral ulcers were significantly higher in female patients. Arthritis was also significantly less in the male patients. However, serositis and pleurisy were significantly higher in male patients. Cardiovascular diseases favored women. Likewise, it was shown that renal involvement was also significantly less in women. Pericarditis, seizures, and psychosis manifested similarly among male and female lupus patients. The hematological manifestations, as a whole, were similar between men and women. However, thrombocytopenia was significantly higher in male patients. Raynaud's phenomenon and neurological manifestations were similar between men and women. Regarding serological tests, anti-Sm antibodies favored women. Anticardiolipin antibodies also manifested similarly between male and female patients.

Lupus anticoagulant was significantly higher in women. Low C3 level was also significantly evident in women while low C4 level was similarly observed in both. Anti-dsDNA was significantly higher in male patients. Antinuclear antibodies (ANA) favored male patients, however the result was not statistically significant.

On the other hand, Ramírez-Sepulveda et.al. [24,25] studied a population consisting of 1226 patients with SLE, of whom 87% were women (n = 1060) and 13% men (n = 166). In the cohort, they first analyzed the frequencies of the ACR classification criteria items in female and male patients at the inclusion time point and observed significant sex differences in the frequencies of various clinical manifestations. Male patients were significantly more affected by serositis, both pleuritis and pericarditis. In addition, meeting the renal disorder criteria was significantly more frequent in men with SLE, as reflected in the higher frequencies of proteinuria and cellular casts. Men also presented the immunological disorder criterion more frequently. On the other hand, female patients more frequently presented the criteria of malar rash, photosensitivity, oral ulcers, and arthritis. However, female and male SLE patients did not differ in the number of ACR classification criteria fulfilled. Finally, Heydarinezhad P et.al [26] conducted a study that included 265 people with SLE who had met the revised classification criteria of the American College of Rheumatology (ACR). Of the total number of patients, 75% had arthralgia (n = 189 patients, 157 female and 32 male) and 49.3% had renal involvement (n = 113, female 94 and male 19). Skin involvement in the form of malar rash was observed in 52% (n=132 patients, 108 female and 24 male) and photosensitivity in 64% (n=162 patients, 133 female and 29 male) of the patients. Compromises of other organs such as cardiovascular, gastrointestinal, and arthritis were also present in the patients. Anti-dsDNA antibodies were present in 123 patients (52.1%) of which predominated in male patients (n = 25, with 62.5%) and ANA antibodies in 193 patients (81.1%) of which predominated in female patients. (n = 158, with 85%). Of the patients, 42% had increased erythrocyte sedimentation rate (ESR) and 16.5% were positive for C-reactive protein (CRP).

On the other hand, autoimmunity can be present in lupus patient for example Autoimmune thyroid disease (AITD) Myasthenia gravis (MG) Antiphospholipid syndrome (APS) Rheumatoid arthritis (RA) Sjögren syndrome (SS) Systemic sclerosis (SSc) (Table 2). Therefore, the diagnosis of both diseases and their cutaneous manifestations becomes more difficult.

Table 2: SLE associated with other diseases.

Autoimmune thyroid disease (AITD)	Both AITD and SLE share common mechanisms, including genetic factors involving both HLA (e.g., HLADRB1*0301) and non-HLA genes (e.g., CTLA4, PTPN22) influencing the risk of acquiring the disease, clinical subphenotypes such as articular involvement and constitutional symptoms, and even environmental factors such as smoking [27].
Myasthenia gravis (MG)	SLE and MG are autoimmune states which have presentational similitude. Both conditions test serologically positive for anti-nuclear antibodies and require exceptional differential diagnostic acumen to segregate one from the other. Biochemical factors such as variation in CXC (an α chemokine subfamily), CXCL13, and granulocyte-macrophage colony-stimulating factor levels are assumed to play a pivotal role in the pathogenesis of SLE and MG [28].
Antiphospholipid syndrome (APS)	APS is defined by the occurrence of venous and arterial thrombosis, often multiple, and pregnancy morbidity (abortions, fetal deaths, premature births), in the presence of antiphospholipid antibodies, namely lupus anticoagulant (LA), anticardiolipin antibodies (aCL), or anti-b2-glycoprotein-I antibodies (ab2-GPI). The APS can be found in patients having neither clinical nor laboratory evidence of another definable condition (primary APS) or it may be associated with other diseases, mainly SLE. The "Euro-Phospholipid" project came to enlighten this field. In its baseline study, 53.1% had primary APS, 36.2% had APS associated with SLE, while 5.0% had APS associated with lupus-like syndrome [29].
Rheumatoid arthritis (RA)	Both RA and SLE are caused by a dysregulation of the innate and adaptive immune systems, including clonal expansion of auto-reactive lymphocytes, production of auto-antibodies and elevated production of multiple cytokines and other inflammatory mediators. Research into the underlying cause of both diseases focusses heavily on dysregulated T- and B-cell responses [30].
Sjögren syndrome (SS)	SS is a chronic autoimmune disorder, characterized by lymphocytic infiltration and malfunction of the exocrine glands, resulting in dry mouth and eyes. SS can present either alone (primary SS) or in the context of a underlying connective tissue disease such as systemic lupus erythematosus (SLE; secondary SS).1 The first report of SS occurring in SLE (SLE-SS) in 1959 was followed by case series reports on the combined disease. The prevalence of SS in SLE is estimated to be 17.8%, which is within the reported range 8.3% to 19% [31].
Systemic sclerosis (SSc)	SSc is a chronic, and complex connective tissue disease (CTD) that is characterized by microvascular endothelial cell damage and progressive fibrosis of the skin and visceral organs (lungs, heart, and kidney). Predominantly occurs in young and middle-aged women. Approximately 6.8% to 14.7% of SSc patients have overlapping systemic lupus erythematosus (SLE), called SSc-SLE overlap syndrome [32].

Comment

According to the clinical data generated during the last decades, it is probable that there are at least some specific characteristics of male SLE, for which, in summary, those found in the consulted bibliography are mentioned. Chronic discoid lupus and photosensitivity as far as skin findings are concerned, there is less joint involvement in these patients, however, severe systemic findings predominate, such as serositis, pleuritis, central nervous system involvement with the presence of seizures, thrombotic events, and a variety of lupus nephropathy (acute proliferative glomeruonephritis). serologically there is no consensus such as clinical manifestations, however the presence of anti-dsDNA anti-Sm antibodies and anticardiolipin antibodies is also frequently found.

Although several reasons for the sex discrepancies in SLE are proposed, there are no convincing data to explain them and a satisfactory hypothesis is desired. The clinical trend of male SLE cases is not fully established up to now because the disease is rare. Therefore, understanding sex-dependent differences in the epidemiology, clinical course, and outcomes in SLE is essential to raise awareness of a more severe course in male patients and thereby provide timely care for these patients.

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