

Rare clinical manifestations in systemic lupus erythematosus: a review on frequency and clinical presentation

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ABSTRACT

Objectives. The purpose of this study was to review the frequency and clinical presentation of the rarest clinical manifestations of systemic lupus erythematosus (SLE).

Methods. A list of 6 rare SLE manifestations were defined: gastrointestinal, liver, pulmonary, cardiac, ocular and neurological manifestations. Each topic was assigned to a couple of authors to perform a literature search and article review.

Results. In total, 149 articles were included in the literature review: 37 for gastrointestinal manifestations, 6 for liver manifestations, 27 for pulmonary manifestations, 50 for cardiac manifestations, 16 for ocular manifestations, 13 for neurological manifestations. Gastrointestinal disorders included several clinical presentations with variable frequency (from 0.5% to 10.7% of the cases); liver involvement included lupus-related hepatitis (9.3%) and autoimmune hepatitis (2.3%). The rarest pulmonary manifestations identified were shrinking lung syndrome, described in 1.5% of patients, while interstitial lung disease and lupus pneumonia were reported in 4% and 3% of patients, respectively. Myocarditis and pulmonary hypertension were also rarely described in SLE patients although ranging from 0.4–16% and 1–14% respectively, depending on the methodology used for its identification. Ocular manifestations in SLE included some rare manifestations (reported in less than 5% of patients) and lupus retinopathy that is described in 1.2–28.8% of patients depending on methods of ascertainment. Aseptic meningitis and chorea were also confirmed

as very rare manifestations being reported in less than 1% and in 0.3–2.4% of cases respectively.

Conclusion. The results of this literature review provide the basis for a better understanding of some less-known manifestations of SLE and for stressing the need for a higher awareness in diagnostic and therapeutic protocols regarding these rare disease aspects.

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with a multifaceted clinical picture and a variable course over time. Genetic, environmental, ethnic and socioeconomic factors account for a considerable heterogeneity in manifestations among SLE patients. Some clinical manifestations are rarely observed. The lack of standardised diagnostic and therapeutic protocols makes these rare manifestations a real challenge for the clinician. The purpose of this study was to review the frequency and clinical presentation of the rarest clinical manifestations in SLE.

The study responds to the ERN-ReCONNET call “rare inside rare” for papers focusing on rare rheumatologic conditions, as it is one of the specific tasks of ERN to disseminate knowledge and stimulate research on rare diseases and on rare disease manifestations that occur very infrequently and may otherwise be overlooked.

Methods

In June 2021 a list of rare SLE manifestations was drafted by all the authors based on their clinical expertise; after discussions, a final list of 6 topics was

formulated and each topic assigned to a pair of authors to perform a literature search and a narrative review.

Literature search

Between September and October 2021, independent MedLine searches were performed for each of the 6 topics selected; studies were searched by including MeSH terms, free text and subheadings “systemic lupus erythematosus” and each single rare manifestation. Searches were limited to articles written in English and published since 1980. The reference lists of retrieved articles were also screened to search for additional relevant studies to be included. The complete search strategies are available in Supplementary Table S1.

Inclusion and exclusion criteria and data collection

Studies were eligible for inclusion into the review if they were cross-sectional or had a longitudinal design and reported on prevalence and/or incidence of the specific rare clinical manifestations and their clinical characteristics. Case reports, narrative reviews and editorials were excluded while case series and systematic literature reviews were included. Manifestations due to associated antiphospholipid syndrome as well as treatments adverse events or comorbidities were not included. For each search, two reviewers screened independently the titles and abstracts of the retrieved articles and any discrepancies were resolved by consensus. The reviewers collected the data from the included studies using predefined extraction forms. By detailed full-text reading, additional potentially eligible articles were identified, and some others excluded. Finally, the results were synthesised and presented in summary tables. Treatments were not discussed.

Results

The main findings of the review are summarised in Table I while the results of the search are presented in detail in Supplementary Table S1. In total, 149 articles were included.

Gastrointestinal manifestations

A total of 37 articles on rare gastro-

intestinal (GI) manifestations of SLE were included. The detailed description of all the included studies is shown in supplementary table 2.

Gastrointestinal (GI) manifestations were reported in 15–60% of SLE patients (1), many being nonspecific, including side effects of treatment, infections, functional disorders (9, 10) and celiac disease that are not discussed here (5, 11).

The rare GI manifestations discussed here, and their estimated prevalence ranges were: lupus enteritis (0.59–10.7%) (2, 3), intestinal pseudo-obstruction (0.5–4%) (3, 4), protein-losing enteropathy (0.5–7.5%) (5, 6), pancreatitis (0.1–5.5%) (4, 7) and acalculous cholecystitis (0.15–0.5%) (4, 8). Of note, the main pathogenic mechanisms include small-vessel vasculitis, smooth muscle dysfunction and lymphangiectasia (12). GI manifestations can be among the initial symptoms of SLE (13). Usual symptoms comprise abdominal pain, nausea, vomiting and diarrhoea.

Early detection and management of the rare GI manifestations are especially challenging due to lack of specific symptoms and the difficulty in their differentiation from infections and side effects of medications. A diagnosis of lupus enteritis was supported by computer tomography (CT) findings of thickened bowel wall, dilated bowel, “the target sign” indicating abnormal enhancement signal of the bowel wall and “the comb sign” depicting hypervascularity, stenosis, and oedema of the mesentery. In intestinal pseudo-obstruction, CT scanning reveals dilated fluid-filled bowel loops, thickened bowel walls, and multiple fluid levels without mechanical obstruction. Associated urological manifestations (*i.e.* lupus cystitis, ureterohydronephrosis) were common. Intestinal pseudo-obstruction should be considered in SLE patients with hypoalbuminaemia and symptoms of bowel obstruction.

Acute pancreatitis should be considered in patients with GI symptoms and elevated serum lipase (1).

It is noteworthy that some SLE disease activity scores such as the SLE Disease Activity Index (SLEDAI) do not account for GI manifestations, but GI

involvement might be associated with worse prognosis and pancreatitis is often considered a marker of disease severity in adult SLE (3, 14).

Liver manifestations

All causes taken into account, up to 25–60% of patients with SLE will present hepatic involvement during the disease course (15); in many cases it presents as non-specific liver enzymes abnormalities, possibly due to treatment adverse effects related or due to infections. These aspects are not discussed here as the review is focused on SLE-related liver manifestations.

Six articles on liver manifestations were included and a detailed description is reported in Supplementary Table S3.

In a Japanese study of 206 SLE patients, liver dysfunction was found in 59.7%, and associated with medications (30.9%), SLE itself (28.5%), fatty liver (17.9%), autoimmune hepatitis (4.9%), primary biliary cholangitis (2.4%), cholangitis (1.6%), alcohol (1.6%) or viral hepatitis (0.8%). Specific hepatic involvement by SLE is a highly controversial theme, and largely falls within the spectrum of autoimmune hepatitis, when related to an autoimmune mechanism (16).

Lupus hepatitis has been generally considered as a mild hepatopathy characterised by liver enzyme elevation along with systemic disease activity (17).

Among 242 Italian SLE patients, liver abnormalities were observed in 45 (18.6%). Only 14 cases (5.7%) were attributed to lupus hepatitis, which was generally subclinical with a fluctuating course and responded well to prednisone (18).

In a retrospective study of 504 Chinese SLE inpatients, 9.3% were diagnosed with lupus hepatitis with higher prevalence among patients with active disease than those with inactive disease ($p < 0.05$). Interestingly, liver immunopathological features showed deposits of complement (C1q) in 70% of patients with lupus hepatitis and none in patients with other liver diseases ($p = 0.011$) (19).

In a recent systematic literature review, 114 cases of lupus hepatitis have been reported, of which 30.7% were

Table I. Main findings of the literature review.

Topic	Number of studies included in the review	Prevalence
Gastrointestinal involvement	37	<ul style="list-style-type: none"> • Lupus enteritis 0.59 -10.7% • Intestinal pseudo-obstruction: 0.5- 4% • Protein-losing enteropathy: 0.5 -7.5% • Pancreatitis: 0.1-5.5% • Acalculous cholecystitis: 0.15-0.5%
Liver involvement	6	<ul style="list-style-type: none"> • Lupus hepatitis: 5.8-9.3% • Autoimmune hepatitis: 2.3%
Pulmonary manifestations	27	<ul style="list-style-type: none"> • Interstitial lung disease: 4% • Shrinking lung syndrome: 1.5% • Lupus pneumonia: 3%
Cardiac manifestations	50	<ul style="list-style-type: none"> • Myocarditis: 0.4-16% • Pulmonary arterial hypertension: 1-14%
Ocular manifestations	16	<ul style="list-style-type: none"> • Episcleritis/scleritis: 1.7-3.1% • Anterior uveitis: 0.6-0.8% • Lupus retinopathy 1.2-28.8%:
Neurological manifestations	13	<ul style="list-style-type: none"> • Aseptic meningitis >1% • Chorea: 0-3-2.4%

the initial manifestation of SLE. The most frequent concomitant active disease manifestations were haematological (60.8%), mucocutaneous (59.5%), articular (48.1%) and renal (46.8%). Overall, hepatitis improved with corticosteroids, with or without immunosuppressants. The mortality rate of lupus hepatitis was 1.75%. In addition to ANA, the most frequent positive autoantibodies in patients with lupus hepatitis were: anti-dsDNA (70%), anti-SSA (59.7%), anti-ribosome P (51.4%) and anti-RNP (48.1%) (15).

In a work by Ohira *et al.* the positive rate of anti-ribosomal P antibody was significantly higher in patients with lupus hepatitis (68.8%) than in patients with SLE complicated by autoimmune hepatitis (20%) and in patients with autoimmune hepatitis alone (0%) (20). However, more recently, anti-ribosomal P antibodies have also been found in autoimmune hepatitis patients without evidence of SLE, suggesting a common underlying mechanism targeting the liver in both diseases (17).

The term “lupoid hepatitis” was firstly used in the 1950s to refer to the association between autoimmune hepatitis and lupus. In SLE patients with abnormal liver enzymes, the incidence of autoimmune hepatitis is around 5–10%. The differentiation between lupus hepatitis and autoimmune hepatitis is

challenging, and anti-liver autoantibodies and liver biopsy may be essential to distinguish between them (21). Histological examination of autoimmune hepatitis shows specific changes, such as interface hepatitis, resetting of hepatocytes, emperipolesis and fibrosis which are absent in lupus hepatitis.

Out of 675 patients with SLE followed at the University College London Hospital from 1978 to 2015, 4.3% presented an associated autoimmune gastrointestinal disease; 2.3% had SLE, autoimmune hepatitis overlap syndrome including 1.9% with a positive anti-dsDNA antibody. The principal manifestation was elevation of liver enzymes. In addition, 87.5% of these overlap patients had arthritis, 50% skin rash and 37.5% mouth ulcers.

In contrast, the association of primary biliary cholangitis with SLE is extremely rare. In the above study, only two female SLE patients developed primary biliary cholangitis. Both were diagnosed with SLE before primary biliary cholangitis onset and had positive dsDNA antibodies (2).

Pulmonary manifestations

During the disease course, up to 50% of SLE patients will develop lung pathology with pleuritis (with or without effusion), the most common SLE-related manifestation. Infections are

another frequent cause of respiratory symptoms in SLE patients and they should be taken into consideration in the differential diagnosis. The rare pulmonary manifestations addressed by this review include interstitial lung disease (ILD), shrinking lung syndrome and acute lupus pneumonia.

Twenty-seven articles were included in the literature review and results are detailed in Supplementary Tables S4.1, 4.2 and 4.3.

Eighteen articles provided information on ILD, of which 12 addressed its prevalence (22-33). The included studies reported a total of 367 cases of SLE-related-ILD over a cohort of 9034 SLE patients, representing 4% of lupus patients. The 9 studies addressing the clinical presentation (25, 26, 32, 34-39), described 142 SLE-ILD. SLE-ILD was diagnosed using CT scan in 7 studies, X-ray *plus* pulmonary function tests in one study, and lung biopsy in another study. Ground glass opacities and septal thickening were the most common lesions (56% and 46%, respectively), with non-specific interstitial pneumonia (NSIP) and organising pneumonia (OP), the most common CT patterns (26% and 17.6%, respectively) although notably 21% were defined as unclassifiable (Suppl. Table S2). ILD was more common in patients developing SLE after the age of 50. In the most extensive study published on this topic (39), ILD developed concomitantly or after SLE diagnosis in most cases (87%), the overall 5-years survival rate was 85.3%, and the NSIP+OP pattern was predictive of good outcome.

Twelve articles were focused on shrinking lung syndrome, 5 on its prevalence (31-33, 42, 43) and 9 on its clinical presentation (34, 40-47). Shrinking lung syndrome was reported in 91 (1.5%) out of 6054 SLE patients. Its characteristics are summarised in Supplementary Table S2. The presence of a restrictive pattern in pulmonary function tests was considered necessary for diagnosis in 11 studies, in combination with dyspnoea (8 studies), diaphragm elevation on chest X-rays (5 studies), and normal diffusion capacity of carbon monoxide (DLCO) (2 studies), after the exclusion of ILD or other

lung diseases (6 studies). Interestingly, pleuritic chest pain was widespread among patients with SLS (75–93% of patients), suggesting the potential pathogenic role of pleural inflammation, as suggested by Henderson *et al.* (46) based on the prevalence of pleural alteration in 16–75% of cases.

Lastly, 4 studies were retrieved centred on acute lupus pneumonia, 2 reporting on its prevalence (22, 29) and 2 on its clinical presentation (36, 48). A total of 124 (3%) patients were described in a cohort of 4068 SLE patients. Acute lupus pneumonia was defined by the presence of lung infiltrates on X-ray or CT scan in the absence of active infections. A characteristic CT scan finding of acute lupus pneumonia was the presence of isolated ground-glass opacity (*i.e.* without any sign of fibrosis) which, along with the presence of fever differentiate it from ILD. However, this finding is not specific for acute lupus pneumonia, thus possible differential diagnoses (*i.e.* infectious diseases) should be always considered.

Cardiac manifestations

The heart is one of the most frequently affected organs in SLE. Any part of the heart can be affected, including the pericardium, myocardium, coronary arteries, valves, and the conduction system with different pathogenetic mechanisms. Pericarditis and coronary artery disease are the most common cardiac manifestations. The rare cardiac manifestations addressed by this review are myocarditis and pulmonary arterial hypertension (PAH). A total of 18 and 32 articles were included in this review for myocarditis and PAH, respectively, and the results are presented in Supplementary Tables S5.1 and 5.2.

Myocarditis in SLE is a rare but potentially severe manifestation which may be characterised by chest pain, heart failure, arrhythmias and, in some cases, sudden death.

The majority of papers on SLE-associated myocarditis are case reports or small case series, involving a total of 80 patients in 64 papers, which were not included in this review. Most of the 18 articles considered (49–66) included controlled, case-control, pro-

spective and retrospective studies. Two articles reported data on *post-mortem* analysis (62, 66) and two on endomyocardial biopsy (52, 61). The diagnosis was made by clinical, biochemical, echocardiographic and, in most recent papers, cardiac magnetic resonance imaging features. Prevalence ranged between 0.4–16% considering all retrieved studies (51, 53–55, 64, 65), and between 0.4–6.1% considering studies published after 2000 (51, 53–55). Myocarditis is usually associated with pericarditis but also with extra-cardiac active disease (*i.e.* lupus nephritis) (56, 57) and a high mortality rate (51, 53, 56, 62). Early diagnosis can improve outcomes and the use of cardiac magnetic resonance imaging may help the early detection of subclinical myocarditis, even in patients with moderate disease activity (49, 50, 58, 59).

Pulmonary arterial hypertension (PAH) is associated with SLE and can ultimately lead to death. Patients typically present with progressive exertional dyspnoea and fatigue and diagnosis is often delayed.

Prevalence of PAH in different SLE cohorts varies between 1–14% (68–70, 74, 76, 78, 82, 84, 86, 90, 92, 94, 97, 98) and a 5-year survival rate of 70–80% has been reported (69, 72, 77, 83).

The gold standard for diagnosing PAH remains right ventricular catheterisation, however, several ultrasound techniques offer non-invasive alternative for screening as well as for follow-up after diagnosis (67, 73, 75, 85).

Several disease-related factors have been associated with the presence PAH in SLE. Raynaud's phenomenon (88, 89, 91, 97), history of serositis (70, 74, 79, 84) and antiphospholipid antibodies (78, 88, 90, 91) have been reported as risk factors in various studies. The presence of anti-RNP has been identified as an additional risk factor (70, 79, 84, 89), although its presence seemed to be protective in one cohort (77).

Ocular manifestations

Ocular manifestations in SLE are very heterogeneous, and the disease can affect multiple ocular structures including the periorbital, adnexa, eyes and optic nerves. Globally, ocular involve-

ment can be detected in approximately one-third of patients with SLE including manifestations related to organ damage or concomitant Sjögren's syndrome; it could represent the first manifestation or appear during the follow-up and may sometimes be sight threatening if not promptly and adequately treated. Ocular adverse events related to the use of treatments were not the focus of this review, therefore posterior subcapsular cataracts, secondary open-angle glaucoma and aminoquinolines-related maculopathy will not be discussed (99).

Sixteen articles were included in this literature review; a detailed description of the included studies is reported in Supplementary Table S6.

Anterior ocular structures are frequently affected, and keratoconjunctivitis sicca represents the most frequent manifestation, especially in the context of secondary Sjögren's syndrome. Scleritis and episcleritis occur rarely in SLE. In an Italian retrospective study episcleritis/scleritis was found in 3/98 (3.1%) of SLE patients: one case of anterior diffuse, one case of anterior nodular and 1 case of bilateral necrotising scleritis (100). More recently, in a population-based retrospective study from Taiwan, scleritis/episcleritis were reported in 8/521 (1.7%) of SLE patients and in 13/5194 (0.2%) of the control population (101).

Another rare manifestation affecting the anterior segment is uveitis. In a multicentre cohort study of Brazilian juvenile SLE patients, 7/872 (0.8%) cases of uveitis occurred, being the first symptoms of the disease (in 6 of cases) or occurred within 6 months of SLE onset. Severe ocular sequelae occurred in two patients, whereas another one died due to complications of SLE (102). Again, in a prospective Portuguese study in adult SLE patients, anterior uveitis was found in 1/161 patients (0.6%) (101).

Posterior segment involvement, namely lupus retinopathy, choroidopathy and optic neuropathy is particularly concerning given the potential for a devastating impact on visual prognosis and their association with poor systemic disease control.

Lupus retinopathy frequency ranges widely in various studies (1.2–28.8%), mostly depending on the population studied (all SLE patients or patients with visual disturbances alone) and the activity of the disease (99, 100, 102–111). The most common feature is microangiopathy with the presence of soft exudates (cotton-wool spots), described in 41/45 lupus retinopathy cases in a cross-sectional Indian study (108) and in 34/41 patients with lupus retinopathy in a similar Canadian one (110). Less frequent is the occurrence of central retinal artery and/or vein occlusion, with the exception of the paper by Montehermoso *et al.*, where venous or arterial occlusive events occurred in 46% of LR cases (107). Another type of rare retinal manifestations is optic neuropathy, with variable presentations including acute retrobulbar optic neuropathy and ischaemic optic neuropathy (107, 110, 112).

It has been demonstrated that lupus retinopathy can be more frequently found in patients with active SLE, as demonstrated in the study of Seth *et al.*, where lupus retinopathy was associated with a higher SLEDAI, and the presence of neuropsychiatric lupus, lupus nephritis and autoimmune haemolytic anaemia (108). Notably, Klinkoff *et al.* demonstrated that retinopathy improved in association with disease control in 5/7 patients with lupus retinopathy (105). The presence of antiphospholipid antibodies is an additional risk factor for thrombotic retinal events (107). Microangiopathy is usually associated with better outcomes than thrombotic events. In the study of Stafford *et al.* none of the 34 patients with microangiopathy presented a chronic visual loss, a sequela that occurred in the 5 cases of central retinal artery, vein occlusion and ischaemic optic neuropathy (110).

Unilateral or bilateral blurred vision without severe visual loss is the common presenting sign of choroidopathy: Nguyen *et al.* reported 3 new cases and revised 28 cases (47 eyes involved). In all the reported cases Choroidopathy was associated with systemic disease activity (LN was present in 64% of cases) (113). More recently, Braga *et*

al. evaluated choroidal thickness in 15 SLE patients with previous LN, 15 SLE without LN and 15 controls, all without a history of ocular involvement. LN patients displayed significantly increased diffuse thickness, allowing the authors to suggest a relationship between LN and choroidal changes (114).

Neuropsychiatric manifestations

Neuropsychiatric (NP) involvement in SLE (NPSLE) is one of the most challenging features of SLE. In 1999 the American College of Rheumatology (ACR) published an attempt to standardise the terminology and define NP manifestations in SLE (115). NPSLE ranges from mild cognitive symptoms to severe CNS manifestations and generally leads to a significantly increased mortality rate (116). The prevalence of NPSLE is biased by different definitions of NPSLE in different studies. A robust estimate is that up to half of SLE patients develop NPSLE during their disease (117).

The NPSLE syndromes that can occur are not specific for SLE, and thus, it remains a challenge to differentiate symptoms caused by SLE from symptoms of other origins. Several attempts have been made to define algorithms that can help differentiate between NPSLE and non-SLE NP symptoms (118). However, no individual biomarker or measure exists that defines definite NPSLE.

NPSLE manifestations including aseptic meningitis, movement disorders, myelopathy, and demyelinating syndromes and acute encephalitis, all occur in less than 0.5–4% of SLE patients (119). Aseptic meningitis and movement disorders are addressed by this review. A total of 13 articles are included (5 for aseptic meningitis and 8 for movement disorders, respectively) and the details are reported in Supplementary Table S7.

Aseptic meningitis is observed in <1% of SLE patients. The possibility of ibuprofen-related meningitis or meningoencephalitis should also be considered in SLE patients taking ibuprofen, especially and if it is recurrent (118). The clinical presentation is not different from infectious meningitis except that improvement may be very quick.

However, SLE patients with aseptic meningitis, are younger, have lower leucocyte counts (both total leucocyte count and neutrophil count are generally higher in infectious meningitis in both plasma and cerebrospinal fluid) and higher glucose concentration in the cerebrospinal fluid (120–124).

Chorea is the only movement disorder included in the NPSLE nomenclature by ACR (117). Data on the prevalence of this manifestation in SLE are scarce, only two studies reported a prevalence ranging from 0.3 to 2.4% of patients (125–130). Chorea in SLE has been associated with the presence of antiphospholipid antibodies (aPLs) (126, 127) and with an increased risk of thrombosis (125, 126). Some studies support a humoral autoimmune pathogenesis and the need for immunosuppressive therapy (118, 128). Whereas other studies describe chorea as a less severe NPSLE symptom than other NPSLE manifestations (129).

Discussion

Rare clinical manifestations of SLE represent a clinical challenge because of difficulties in recognition and diagnosis, differential diagnosis and treatment. There are no specific therapeutic protocols for many of them, and their clinical management is based on literature data referred to other clinical manifestations or on data related to the same manifestations in different clinical settings.

Indeed, available guidelines and recommendations for disease assessment and management provide very little guidance on some uncommon manifestations of this disease. Moreover, although the impact of the single rare manifestations could be considered residual in the context of the disease, taken together these manifestations represent a significant burden for the patients' community and for the society.

The first step toward a better management of these rare conditions is an accurate knowledge of their frequency and clinical presentation, leading to the ERN-ReCONNET call for papers entitled "rare inside rare" aimed at promoting collaborative research projects and at disseminating knowledge around rare

and complex connective tissue diseases. Here, we reviewed the literature on rare clinical manifestations of SLE focusing on their frequency and clinical aspects.

We restricted our review on six topics chosen based on expertise of the participating European health care providers interested in SLE within the ERN-ReCONNECT network.

This study highlights that the literature on these manifestations is sparse and heterogeneous, mainly based on small and/or retrospective studies; the quality of the evidence is particularly weak for liver manifestations, lupus pneumonitis, ocular manifestations, aseptic meningitis and movement disorders. For these manifestations, case definitions adopted are also very variable, leading to wide ranges of frequencies.

Instead, for interstitial lung disease and cardiac manifestations large prospective cohort are available; moreover, especially for PAH, the methods adopted for case definitions were homogeneous across studies (right heart catheterisation). As far as gastro-intestinal involvement is concerned, we found several studies on this topic; however, due to the wide range of possible manifestations and the different methods of ascertainment adopted, the overall frequency of this involvement resulted heterogeneous and each single manifestation (*i.e.* lupus enteritis, pancreatitis) should be considered separately. Similarly, literature is heterogeneous for ocular involvement which includes a large variety of syndromes with difficulties in distinguishing lupus-related manifestations to comorbid condition (*i.e.* Sjögren's syndrome) or drug-related adverse events. In the majority of the cases the disease manifestations that were selected for this review were confirmed to be uncommon in SLE. Literature data on movement disorders and aseptic meningitis are scarce but they are confirmed as very rare disease manifestations being reported in less than 3% of cases. Among pulmonary findings, shrinking lung and lupus pneumonitis were confirmed as extremely rare manifestations; data on ILD are more robust, however, the prevalence of ILD resulted highly variable (up to 41%) depend-

ing on the method of ascertainment (clinical or X-ray vs. CT).

PAH and myocarditis were confirmed as very rare disease manifestations in SLE; nevertheless, they are still associated with a potentially fatal outcome. Thus, their early recognition and treatment are crucial. Interestingly, prevalence of myocarditis was lower in more recent studies; this probably means that the available improved diagnostic and therapeutic tools contribute to the apparent decrease of prevalence of this condition.

Conversely, some manifestations were more frequent than expected, *i.e.* gastrointestinal involvement.

However, the spectrum of possible gastrointestinal manifestations is very wide, and the literature includes both rare syndromes (*i.e.* acute pancreatitis or lupus enteritis) and unspecified gastrointestinal symptoms with a significantly higher frequency. However, in the latter, difficulty in differentiating SLE-related gastrointestinal symptoms from infections and side effects of medications could be responsible for their unexpected higher prevalence. Similarly, while unspecified liver dysfunctions are frequently observed in SLE (up to 59%), SLE-related hepatitis and primary biliary cirrhosis are quite uncommon.

The paper has some limitations. First of all, this is not formally a systematic literature review because it lacks some essential steps (*i.e.* study quality assessment and risk of bias evaluation). Moreover, a large number of authors took part in this review and the six topics were reviewed by six different couples of authors, leading to possible heterogeneity in the literature search, in data analysis and in the reporting of the results.

However, the working group tried to search and assess the available literature according with some pre-defined rules and methods derived from the systematic literature review methodology (*i.e.* articles flows, clear search strategies, detailed summary tables). Thus, we think that the result offers a very comprehensive and accurate literature scan on these manifestations.

In conclusion, the results provided by

the review are important for a better understanding of some less-known manifestations of the disease and for stressing the need of the development of diagnostic and therapeutic protocols that also include these rare disease aspects. This literature review highlights that there is a critical knowledge gap regarding some rare manifestations of SLE; this should serve as a stimulus for future studies on the rarer aspects of this disease.

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