Rom J Rheumatol 2025, 34(1):180-185 ISSN (print) 1843–0791, ISSN (online) 2069–6086

Revista Română de Reumatologie
Romanian Journal of Rheumatology

CASE REPORT

A Shared Fight: Two Lives, One Disease

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Abstract

Background. Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with complex and multifactorial etiology. While most cases are sporadic, familial clustering is increasingly recognized, particularly in early-onset forms. Childhood-onset SLE (cSLE) is associated with more severe disease and a higher genetic burden.

*Case Presentation***.** We report two cases of SLE involving a father and his daughter. The father presented in adulthood with antiphospholipid syndrome and pulmonary hypertension as initial manifestations, fulfilling the 2012 SLICC criteria for SLE. Over the course of his illness, he experienced multiple thromboembolic events requiring escalation of immunosuppressive and anticoagulant therapy. Seven years later, his daughter developed photosensitive skin eruptions beginning at the age of three, evolving into a full clinical picture of SLE by age eight, when she fulfilled the 2019 ACR/EULAR criteria. Immunologic investigations in both cases revealed distinct autoantibody profiles, highlighting phenotypic variability even within the same family.

Conclusion. Familial SLE, though relatively uncommon, provides valuable insights into the genetic and immunologic mechanisms underlying disease onset and progression. Early recognition and individualized management strategies are essential, particularly in pediatric populations and families with known autoimmune aggregation.

Keywords: systemic lupus erythematosus, antiphospholipid syndrome, childhood-onset lupus, pulmonary thromboembolism.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease primarily affecting women of childbearing age. However, this condition may also manifest during childhood and adolescence (referred to as childhood-onset SLE – cSLE), accounting for approximately 10-20% of cases [1]. Genetic factors play a significant role in the pathogenesis of SLE, as evidenced by the high concordance rate among monozygotic twins (>35%) and the elevated sibling risk ratio [2]. Familial aggregation demonstrates high heritability, with a 17-fold greater relative recurrence rate of SLE among first-degree relatives compared to the general population [2]. Familial cases account for approximately 10% of total SLE cases, and this model frequently illustrates the interaction between environmental and genetic factors [3]. To date, over 40 susceptibility loci have been identified, though further research is needed to establish clear associations between these loci and specific SLE phenotypes [4,5].

In the present article, we describe two cases of SLE (father and daughter), highlighting the variability and complexity of clinical presentations and immunological features among first-degree relatives with SLE with different ages of onset (adult and childhood-onset SLE).

Case Presentation

Father - Initial presentation

The father a non-smoker, with no prior medical or family history, presented to the emergency department at the age of 27 years with sudden-onset dyspnea, orthopnea, anterior chest pain, and cough. The physical examination revealed marked tachycardia, tachypnea, and hypoxemia (SpO_2 88%). Laboratory findings showed significantly elevated NT-proBNP levels. Electrocardiography confirmed sinus tachycardia without additional abnormalities.

Transthoracic echocardiography demonstrated right heart chamber dilation and severe pulmonary hypertension, with a systolic pulmonary arterial pressure (sPAP) of 88 mmHg. Emergency pulmonary CT angiography revealed filling defects in the brachial arteries, multiple bilateral pulmonary infarctions, and ground-glass opacities, leading to the diagnosis of bilateral pulmonary thromboembolism.

Considering the patient's young age and absence of comorbidities, antiphospholipid antibody testing was performed, showing triple positivity (with elevated anticardiolipin antibodies, anti-β2 glycoprotein I antibodies, and lupus anticoagulant

levels). The patient was subsequently referred to the rheumatology department for further investigation and management.

The rheumatological assessment identified a malar rash with photosensitivity, alongside inflammatory arthralgia and swelling of the small joints of both hands (consistent with inflammatory arthritis). Laboratory findings revealed anemia, thrombocytopenia and hepatocellular injury (elevated alanine aminotransferase: ALT; elevated aspartate aminotransferase: AST). The erythrocyte sedimentation rate (ESR) was elevated, while complement levels remained within normal range. The immunological evaluation confirmed positive antinuclear antibodies (ANA) and anti-double-stranded DNA (dsDNA) antibodies (Table 1).

Table 1. *Laboratory data*

	Patient's value	Normal range
Hemoglobin	10.7 g/dl	12-16
Platelets	88.000	150.000-400.000
ESR	88 mm/h	0-20
ALT	165 u/l	5-50
AST	56 u/l	5-34
ANA total	1:640	0.0
Anti dsDNA	>300u/ml	0.0-15.0

Father - Diagnosis

Under these circumstances, the diagnosis of SLE was established according to the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria, the patient fulfilling three clinical and three immunological criteria (Table 2).

Additionally, given the presence of vascular thrombosis accompanied by the persistence of triple positivity for antiphospholipid antibodies, the diagnosis of secondary antiphospholipid syndrome (APS) was confirmed at the time, the patient meeting the Sydney classification criteria (2006).

Table 2. *Clinical and Immunological Criteria Supporting the Diagnosis of SLE*

Clinical criteria	Imunological Criteria
Acute cutaneous Lupus	ANA
Arthritis	Anti-dsDNA
Thrombocytopenia	Antiphospholipid Ab

Father - Treatment

Treatment was initiated as follows:

- Intravenous methylprednisolone pulses, 1000 mg daily for 3 days, followed by oral prednisolone at a dose of 0.5 mg/kg/day;
- Oral vitamin K antagonist anticoagulation with warfarin, targeting an INR of 2–3;
- Hydroxychloroquine 400 mg daily.

During hospitalization, the patient developed edema, pain, and erythema of the right calf. The Doppler ultrasound of the venous system confirmed the diagnosis of deep vein thrombosis (DVT) involving the right iliac vein.

The following morning, the patient experienced sudden-onset dyspnea, accompanied by tachypnea, tachycardia, and hypoxemia. Pulmonary CT angiography excluded a new pulmonary embolism. Under oxygen therapy, respiratory distress improved. The clinical symptoms were attributed to right heart failure and fluid overload. A right heart catheterization was performed, confirming the diagnosis of pulmonary hypertension, likely of thromboembolic origin, based on pulmonary arterial pressure measurements. These clinical changes prompted a change in therapeutic strategy: monthly intravenous cyclophosphamide pulses were initiated at a dose of 1 g/m², and the INR target was adjusted to 3–4. Oral corticosteroid therapy and hydroxychloroquine were continued.

Father - Follow-up

Over the following period, the patient received a total of 11 intravenous cyclophosphamide infusions. Maintenance therapy was initiated with azathioprine, in combination with hydroxychloroquine and a vitamin K antagonist anticoagulant.

Approximately twelve years later, the patient experienced a new episode of deep vein thrombosis involving the left lower limb. At that time, anticoagulation therapy was switched to a non-vitamin K antagonist oral anticoagulant (NOAC), specifically apixaban, with favorable clinical evolution thereafter.

At the most recent follow-up, in 2025 (at the age of 39) the patient presented clinically stable with no active disease manifestations, with no new thromboembolic events and no significant laboratory abnormalities.

Daughter – early signs

At the age of 31, the patient welcomed the birth of his first daughter. The mother had no personal or family history of autoimmune diseases. At three years of age, the child developed skin lesions (described as "urticarial" in appearance, at the time) following prolonged exposure to sunlight (Figure 1). The lesions resolved with topical treatment and sun avoidance.

At the age of five, the patient developed a vasculitic-like eruption on both palms and the soles of her feet (Figure 2). The immunological investigations (including extended ANA panel, c-ANCA, p-ANCA, immunoglobulin profile, and complement fractions) revealed no pathological findings.

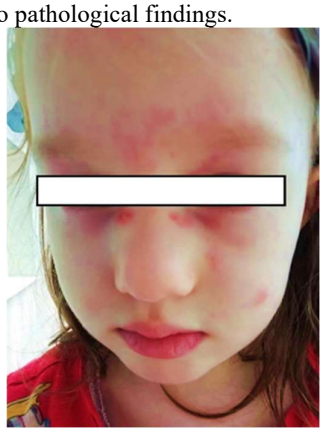

Figure 1. *Skin lesions following prolonged sun exposure*

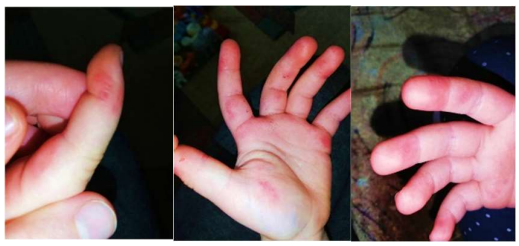

Figure 2. *Vasculitic-like eruption*

Daughter - Diagnosis

At the age of 8 years, the patient developed erythematous plaques with polycyclic borders, non-pruritic, disseminated over the upper limbs, trunk, and face, accompanied by vasculitic-like lesions on the palms (Figure 3). The patient was admitted to the pediatric department for further diagnostic evaluation. The laboratory investigations revealed significant hepatocellular injury, while a potential myositic process was excluded based on normal levels of creatine kinase and lactate dehydrogenase. The patient tested positive for total ANA, anti-dsDNA antibodies, and anti-SS-A antibodies (Table 3). Additionally, complement analysis showed a decreased C4 fraction. Antiphospholipid antibodies and antibodies specific for autoimmune hepatitis were negative. A skin biopsy was performed, revealing histopathological features indicative of SLE cutaneous lesions. Imaging studies showed no evidence of serositis at the pulmonary, cardiac, or abdominal levels.

Table 3. *Laboratory data*

	Patient's value	Normal range
ALT	230 u/l l	10-29 u/l
AST	169 u/l	20-40 u/l
C4	6 mg/dl	12-36 mg/dl
ANA total	6.4 u/ml	0-1.2 u/ml
Anti dsDNA	48.8 u/ml	0-25 u/ml
Anti SS-A	45.4 u/ml	0-15 u/ml

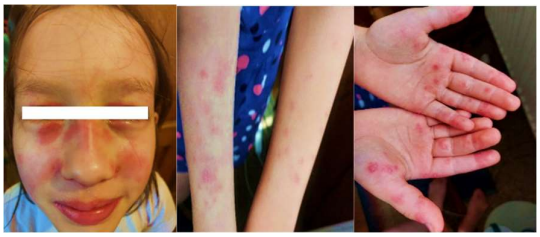

Figure 3. *Vasculitic-like lesions on the palms*

The patient was diagnosed with SLE according to the 2019 ACR/EULAR classification criteria, with positive ANA (entry criterion) and a total score of 13 points for the additive criteria.

Daughter – Treatment

Treatment was initiated with intravenous methylprednisolone pulses (500 mg daily for 3 days), followed by oral corticosteroid therapy at a dose of 0.5 mg/kg/day (prednisolone equivalent) with progressive tapering. Azathioprine (2 mg/kg/day) and hydroxychloroquine (5 mg/kg/day) were also initiated.

Daughter - Outcome

The patient showed a favorable response to therapy, with significant improvement in hepatocellular injury, normalization of the C4 complement fraction, and no adverse effects related to the medication.

Discussions

The occurrence of SLE in both a father and his daughter highlights the issue of familial aggregation in autoimmune diseases. While SLE is generally considered a sporadic condition in most cases, growing evidence points to a substantial genetic contribution to disease susceptibility.

A 2018 meta-analysis comprising six studies included a total of 733 familial SLE cases and 1,405 sporadic cases. The objective was to evaluate the association between clinical manifestations and laboratory parameters by comparing familial and sporadic SLE. The results showed that familial SLE was less frequently associated with photosensitivity, lupus nephritis, and thrombocytopenia [6]. In the cases described in the present work, photosensitivity was a shared feature. However, thrombocytopenia (observed in the father) was absent in the daughter, and neither patient developed lupus nephritis.

In another study, Sinicato et al. examined familial SLE characteristics in a cohort of 392 patients, including 112 with childhood-onset and 280 with adult-onset disease. Recurrence rates were reported at 19.4% among first-degree relatives, 5.4% among second-degree relatives, and 3.0 % among third-degree relatives. No significant phenotypic differences were found between multicase and single-case families. The authors concluded that familial aggregation is more prevalent in childhood-onset SLE, suggesting a significant genetic predisposition [7].

Kuo et al. conducted a large-scale population-based study involving over 23 million individuals, of whom almost 18,300 had a confirmed diagnosis of SLE. The heritability of SLE was estimated at over 40%. The relative risk of developing SLE was markedly elevated among twins, siblings, as well as for patients who had parents with SLE. Furthermore, the relatives of SLE patients exhibited an increased risk of developing other immune-mediated diseases, including Sjögren's syndrome, systemic sclerosis, and rheumatoid arthritis [2]. Notably, in this case, the daughter with cSLE had positive anti-SSA antibodies, but no sicca symptoms.

Two major genetic contributors have been identified in SLE: high-penetrance single-gene mutations and common low-effect variants. The first category involves mutations strong enough to cause monogenic SLE, while the variants included in the second category are insufficient to trigger disease alone but may contribute additively or synergistically to disease susceptibility. Monogenic cases are rare, accounting for only 1–3% of all SLE diagnoses across age groups. In contrast, the majority of patients carry common genetic variants that increase the risk of developing SLE [8]. Genetic predisposition appears to play a more substantial role in pediatric-onset SLE

compared to adult-onset disease. Joo et al. calculated the Genetic Risk Score (GRS) in a cohort comprising both childhood-onset SLE (cSLE) and adult-onset SLE (aSLE) patients. The GRS was significantly higher in patients with childhood-onset disease, further supporting the substantial genetic contribution to early-onset SLE [9]. We reported the cases of two patients with SLE within the same family, one aSLE (father) and one cSLE (daughter), pointing to potential genetic risk factors being implicated in the appearance of SLE in the daughter. However, the mother did not have a personal or family history of autoimmune diseases, while the father was the first one in his family to be diagnosed with a chronic immune-mediated condition.

Type I interferon (IFN-I) signaling remains significant in cSLE and aSLE alike. The genetic analysis of a cohort of over 340 cSLE patients from the United Kingdom investigated pathogenic variants underlying disease susceptibility. Rare, likely deleterious mutations were detected in more than 5.5% of cases. Over 90% of these mutations were located in genes involved in the IFN-I signaling pathway. While monogenic forms of the disease remain uncommon, the significant genetic burden in cSLE emphasizes the presence of numerous common risk variants contributing to disease development [8,10]. Raupov et al. conducted a study to evaluate the role of IFN-I signaling and identify genetic variants associated with cSLE. The study included 80 patients, of whom 60 had IFN-I scores assessed. Elevated IFN-I activity was found in 77% of tested individuals. Rare SLE-associated genetic variants were identified in 56.9% of patients. Of those with high IFN-I activity, 84% also carried variants associated with SLE susceptibility. Most of these variants (74%) were involved in IFN pathway modulation. The authors proposed that IFN-I scoring could be a valuable tool for selecting candidates for targeted genetic testing in future studies [11]. The overexpression of interferon-stimulated genes (ISGs) constitutes an early and characteristic molecular signature in SLE pathogenesis. Baechler et al. analyzed 48 patients with SLE and 42 healthy controls, demonstrating more pronounced involvement of the central nervous system, renal structures, and hematopoietic compartments in patients with high ISG expression [12]. Similarly, a 2019 study reported more severe cutaneous and musculoskeletal manifestations among ISG-positive patients [13]. Serologically, elevated levels of anti-dsDNA, anti-ENA antibodies, and B-cell activating factor (BAFF) have been consistently associated with increased ISG expression [14,15].

cSLE presents several notable differences compared to adult-onset cases. The discrepancies arise from diverse clinical manifestations, immunological features, as well as different organ involvement and mortality rates. cSLE is reported in approximately 15–20% of cases and is associated with substantial organ damage and increased mortality [16–18]. The estimated incidence ranges from 0.36 to 2.5 per 100,000 children, with a prevalence between 1.89 and 34.1 per 100,000 [19–21]. Ethnic differences in disease expression have also been observed. A recent study from the United Kingdom showed that Black African/Caribbean children with cSLE exhibited distinct clinical and laboratory features when compared to their Caucasian and Asian counterparts. Renal involvement was notably more rare Caucasians and Asians compared to the Black African/Caribbean subgroup [21].

Peak disease onset typically occurs between 12 and 14 years of age, with onset before the age of 5 being exceptionally rare. This highlights the atypical nature of the presented case (the daughter), particularly due to the very early onset and absence of disease-specific autoantibodies at the moment of the first clinical symptoms (first cutaneous lesions at the age of three). Studies have shown that specific autoantibodies may be absent especially in patients younger than five, probably in the context of an immature immune system at this age [8].

A Canadian cohort study, which included 67 cSLE and 131 aSLE patients, reported significantly higher disease activity scores in children (16). According to the literature, cSLE may present with more severe disease, greater organ involvement, and poorer treatment responses compared to aSLE [22,23]. Notably, our pediatric patient has shown significant improvement undergoing treatment.

Phenotypic heterogeneity is also notable within the pediatric population. A 2020 UK-based cohort study involving 418 patients with cSLE reported considerable variability in clinical presentation and laboratory findings. Adolescents exhibited a more severe disease course along with a classic immunologic profile at onset. These findings reinforce the hypothesis that pathogenic mechanisms in SLE may vary according to the age at onset [24].

SLE is a disease that predominantly affects female patients. This sex distribution can be attributed to several factors, including genetic and hormonal influences. Epidemiological studies report a female-to-male ratio ranging from 8:1 to as high as 15:1 [25,26]. The influence of sex hormones has been demonstrated in multiple studies, and gender differences in disease expression may, in part, be attributed to hormonal factors [27]. Significantly lower androgen levels have been inversely correlated with disease activity in male SLE patients compared to healthy male controls [28,29]. Clinically and serologically, male SLE patients tend to present with a more aggressive disease course, characterized by rapid and severe organ involvement and poorer prognosis. Serositis, renal involvement, and seizures are also reported to occur more frequently in male patients [30]. Our male patient did not exhibit serositis, nephritis or neurological involvement. However, he presented with severe APS-related clinical changes (massive pulmonary thromboembolism) that preceded the confirmation of SLE diagnosis.

Secondary APS may be present in patients with SLE and is associated with increased mortality in these

cases. Although the available evidence is limited and most cohorts are small, no significant sex-related differences have been identified regarding the antiphospholipid antibody profile or their associations [31]. From a clinical perspective, male patients have been reported to exhibit a higher prevalence of arterial events such as myocardial infarction and lower limb thrombosis [32]. This observation is consistent with the case described in the present work, in which the male patient developed lower limb thrombosis (albeit not at the initial presentation). However, a notable particularity in his case is the occurrence of pulmonary thromboembolism, a complication described more frequently in female patients according to the literature [33] Interestingly, these differences may also be influenced by individual risk factors and therefore cannot be solely attributed to sex-related discrepancies [34].

Conclusions

These two familial cases of SLE (illustrating both the pediatric and the adult-onset forms) highlight the complex interplay between genetic predisposition and clinical heterogeneity in autoimmune diseases. The divergent clinical trajectories of the father and daughter reflect the influence of age, sex, and immunological profile on disease expression and prognosis.

Current evidence supports a strong genetic component in SLE, particularly in childhood-onset patients who have first-degree relatives with autoimmune diseases. The presence of persistent interferon pathway activation, as well as elevated genetic risk scores in pediatric populations, further emphasizes the need for age-stratified genetic and immunologic evaluation.

Sex-related differences in disease expression, with more aggressive phenotypes sometimes observed in males (while there is a clear predominance of female SLE cases in study cohorts), suggest that both hormonal and genetic factors may modulate immune responses and influence disease course. These insights point toward a future of more personalized care in SLE, guided by genetic, immunologic, as well as demographic profiles.

Finally, the present case reports highlight the importance of clinical vigilance (in the context of familial aggregation) and the potential value of early immunological screening in first-degree relatives of patients with SLE. The enhanced understanding of the genetic and molecular basis of familial SLE may pave the way for earlier diagnosis, targeted therapies, and improved long-term outcomes in this challenging and multifaceted disease.

Acknowledgements

The authors would like to thank all the medical staff involved in the diagnosis and management of the patients.

Conflicts of Interest: The authors declare no conflicts of interest.

Patient Content

The authors obtained informed consent from the father for the publication of the present work (including images).

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Received: 09.02.2025

Accepted: 27.02.2025