



Pediatric systemic lupus erythematosus associated with autoimmune hepatitis and nephritic syndrome: A case report and review of the literature

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Abstract

Introduction: Systemic lupus erythematosus (SLE) is an autoimmune disease that can affect multiple organs. Associated pathologies such as hepatitis and lupus nephritis are not frequent in the child population. Nevertheless, they lead to severe consequences with the risk of liver failure and chronic kidney disease, increasing morbidity and mortality in pediatric patients.

Clinical case: An 11-year-old male patient with a clinical picture characterized by asthenia, hypoxia, epistaxis, pruritus, and marked jaundice, with four months of evolution, without an established diagnosis. Laboratory studies were requested that reported increased transaminases, proteinuria, ANAS, and AC. Positive DNA, imaging studies, and kidney and liver biopsy were also performed to clarify the diagnosis.

Evolution: Through a multidisciplinary clinical approach and paraclinical and pathological examinations, the diagnosis of SLE associated with autoimmune hepatitis and lupus nephritis was established. The patient remained in the pediatric intensive care unit with favorable evolution to treatment.

Conclusions: Pediatric SLE associated with autoimmune hepatitis and lupus nephritis is a rare clinical presentation, and very few cases have been reported worldwide. In its diagnosis, multidisciplinary clinical acumen, laboratory, imaging, and critical histopathological data should be highlighted to establish an opportune diagnosis with better prognosis and treatment and thus avoid fatal outcomes in pediatric patients.

Keywords: MESH: Systemic lupus erythematosus, autoimmune hepatitis, lupus nephritis, morbidity, and mortality indicators.

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Introduction

Pediatric systemic lupus erythematosus (PSLE) is an autoimmune disease with chronic inflammatory involvement in any part of the body, attributable to genetic and environmental factors. It develops self-destruction with organic damage simultaneously, sequentially, or alternately [1, 2]. Its diagnostic criteria have been reformed in the last 40 years to recognize new pathophysiological processes, but there still needs to be a diagnostic gold standard for the disease [3].

The incidence of PSLE ranges from 0.3 to 0.9 per 100,000 children per year, and the prevalence is approximately 3.5 per 100,000 children. The average age of onset is between 11 and 12 years, except in children under five years [4]. PSLE is more common in women, with a female:male ratio of 5:1. Morbidity is 20% in patients diagnosed since childhood and of the Hispanic race [5, 6].

As a chronic disease, it can affect multiple organs; however, the frequency of liver involvement is reported to be up to 8%, and one of the associated pathologies is autoimmune hepatitis (AIH) [7]. However, there are few reported cases of co-occurrence with PSLE worldwide [8, 9].

Currently, there is no specific approach for the diagnosis of AIH due to its clinical link with hepatotoxic drugs used in PSLE and viral complications. For this, the starting point is to rule out all related pathologies [10].

Zheng R et al. revealed that the main clinical and laboratory manifestations are rash, fever, fatigue, nausea, and jaundice, which occur in 12% of patients together with elevated alkaline phosphatase (AKP), serum ALT transaminase, and total bilirubin. In addition, lower white blood cell (WBC) counts ($2.92 \times 10^9/L$ vs. $5.48 \times 10^9/L$), platelet counts ($151 \times 10^9/L$ vs. $190 \times 10^9/L$), serum C3 levels, and C4 levels (0.34 g/l vs. 0.53 g/l; 0.06 g/l vs. 0.09 g/l) were observed. Other relevant data were the positive levels of anti-RNP antibodies, ANTI-SM, and the deposit of C1q in the liver [10].

At the same time, Czaja AJ et al. determined that ANA in autoimmune hepatitis is not detected or is slightly positive in 29% of cases, and immunoglobulin G (IgG) levels are expected in 25% of the patients studied [11]. At the histological level, no specific changes were reported; only steatosis, fibrosis, focal necrosis, and round cell infiltration in the portal area were observed. Hepatomegaly, cirrhosis, and liver atrophy can be found on ultrasound examinations [10].

On the other hand, renal involvement of PSLE occurs in 50% of patients. It is considered an indicator of morbidity and mortality, with lupus nephritis being one of the most severe consequences due to the risk of chronic kidney disease requiring dialysis in approximately 25% of patients [12, 13].

The pathology diagnosis is crucial in establishing the prognosis and treatment, and the current classification is the one proposed jointly by the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) (NG) in 2003 [13]. This classification has shown a good correlation between clinical and histological data. It must be emphasized that renal lesions in lupus nephritis are not static, and there may be transitions between the different classes either spontaneously or after treatment [12, 14].

Last, pediatric systemic lupus erythematosus syndrome associated with autoimmune hepatitis and lupus nephritis is a rare clinical presentation for which there are very few reported cases. For this reason, below, we describe the clinical case of a diagnostic association of PSLE.

Clinical case

Clinical history

An 11-year-old male patient with a history of hyperbilirubinemia due to ABO anti-A incompatibility. He presented a four-month history of asthenia and hypoxia, was diagnosed with Hepatitis An in a private health home, and was sent home with treatment based on Complex B. However, the condition persists and is accompanied by nausea, asthenia, dry skin, temperature rises predominantly at night, weight loss, epistaxis, pruritus, marked jaundice, and dyspnea (Figure 1).

Figure 1. Marked jaundice and areas of hypopigmentation on the face.



Physical exam

On admission, vital signs were normal for his age, and anthropometry with weight and low height were normal for his age with a standard deviation of -2. Generalized, dry, flaky jaundiced skin, areas of hypopigmentation on the face, thorax, abdomen, and upper and lower limbs. Eyes with icteric sclera and isochoric pupils. In the ab-

domen, a decreased, depressible, diffusely painful panniculus of the adipose tissue was observed, with air-fluid noises and hepatomegaly 4 cm below the rib cage. Glasgow 14/15 (ocular 4/4, verbal 4/5 and motor 6/6).

Complementary exams

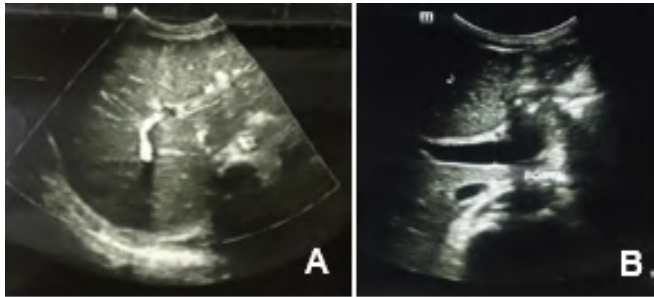
Laboratory: leukocytes: 22.9×10^3 u/ μ l lymphocytes: 2.5×10^3 u/ μ l; neutrophils: 94%; platelets: 111×10^3 u/ μ l; hematocrit: 17.3%; hemoglobin: 6.4 g/dL; creatinine: 3.44 mg/dl; urea: 111.5 mg/dl; OTT: 908.9 U/L; TGP: 88.8 U/L; GGT: 199 U/L; TP: 5.2 seconds; INR: 2.2; PCR: 13.2 mg/l; fibrinogen: 154 g/L; amylase: 275 U/L; lipase: 313 U/L; AST (TGO): 1025 U/L; ALT (TGP): 103 U/L; total bilirubin: 24.57 mg/dL; direct bilirubin: 20.62 mg/dL; indirect bilirubin: 3.95 mg/dL; total protein: 4.96 g/dL; albumin: 1.91 g/dL; globulin: 2.7 g/dL; serum iron: 129.8 ug/dL; transferrin saturation: 115%; ferritin: 5874 ng/mL; TORCH: negative. Ammonium: 41 ug/dl; Factor V: 121 U/dL. Due to the clinical picture and characteristics, immunological tests are requested (Table 1).

Table 1. Report of immunological tests.

Proof	Result	Reference value
C3	91	82 - 185 mg/dl
C4	36.5	18 - 49 mg/dL
ANA	Positive 1/640	<1/40
Ac. DNA	Positive (200)	0 - 7 IU/ml
Anti Smooth Muscle	Negative	$\leq 1 - 80$ IU/ml
Antimitochondrials	Negative (1.3)	$\leq 1 - 5$ IU/ml
Anti-RNP	Negative (1.9)	0 - 15 IU/ml
anti sm	Negative (1.3)	0 - 15 IU/ml
Ac. Anti-Ssa (Ro)	Negative (5.1)	
Anti Lkm 1	Negative (1.7)	
Anti-Scl 70	Negative (2.3)	

Doppler abdominal ultrasound: liver parenchyma with the anatomical situation and ultrasound texture within normal parameters, hepatic hilum with the portal vein of 12.9 mm caliber (reference value 10 mm), standard right and left branches (Figure 2).

Figure 2. Doppler abdominal ultrasound images show normal liver parenchyma (A) and portal vein with a caliber of 12.9 mm (B).



Abdominopelvic Computed Tomography: saddle-shaped hepatic gland as an anatomical variant, size, morphology, and anatomy situation within normality. He presents an enlarged pancreas; the head measures 30 mm, body, and tail 35 mm (reference values, length 12.5 cm; diameters: head 2.2 cm, body: 1.8 cm, bottom: 1.6 cm) suggestive of an inflammatory process of the pancreas compatible with a picture of acute pancreatitis (Figure 3).

Figure 3. Abdominopelvic computed axial tomography images showing a saddle-shaped hepatic gland (A) and acute pancreatitis (B).



Renal biopsy was requested with a report of three cylinders, 26 glomeruli, glomerular sclerosis negative, partial sclerosis: negative, focal glomerulopathy pattern, type III for lupus glomerulopathy, tubular atrophy, thyroidization in the chronic process establishing histopathological diagnosis: grade I multifocal interstitial nephritis and grade I mild fibrosis (Figure 4). In addition,

a liver biopsy was performed with a report of active por-titis, parenchymal and extra parenchymal cholestasis, punched-out necrosis, fibrosis: F: 0, and zonal positive PAS (Figure 5).

Figure 4. Renal biopsy histopathology: proliferated mesan-gial glomerulus is observed, a red arrow (A). Renal biopsy his-topathology: kidney with atrophy and fibrosis is observed (B).

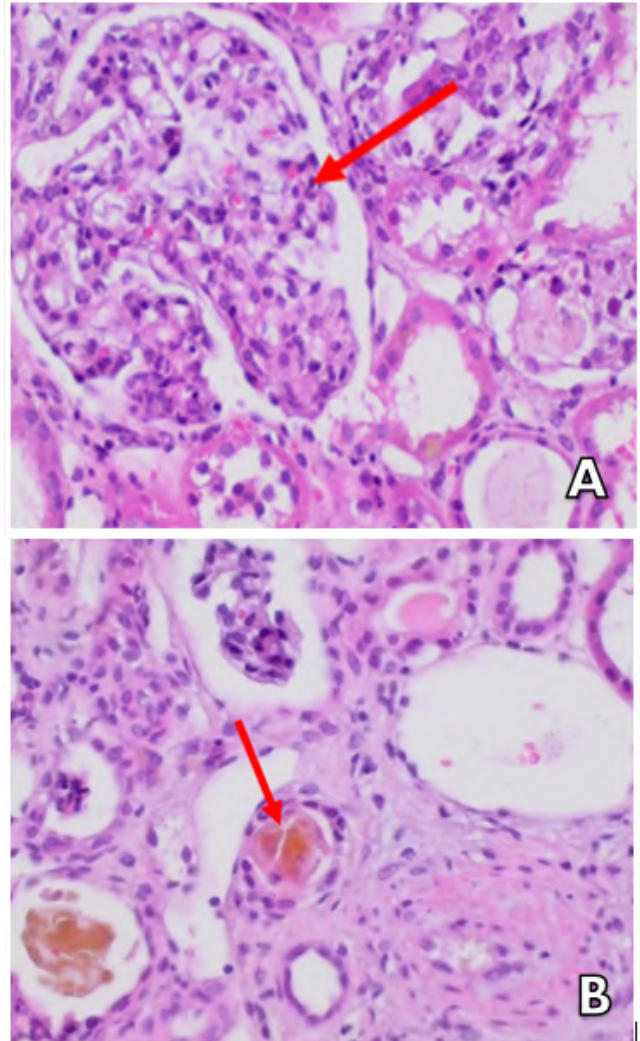
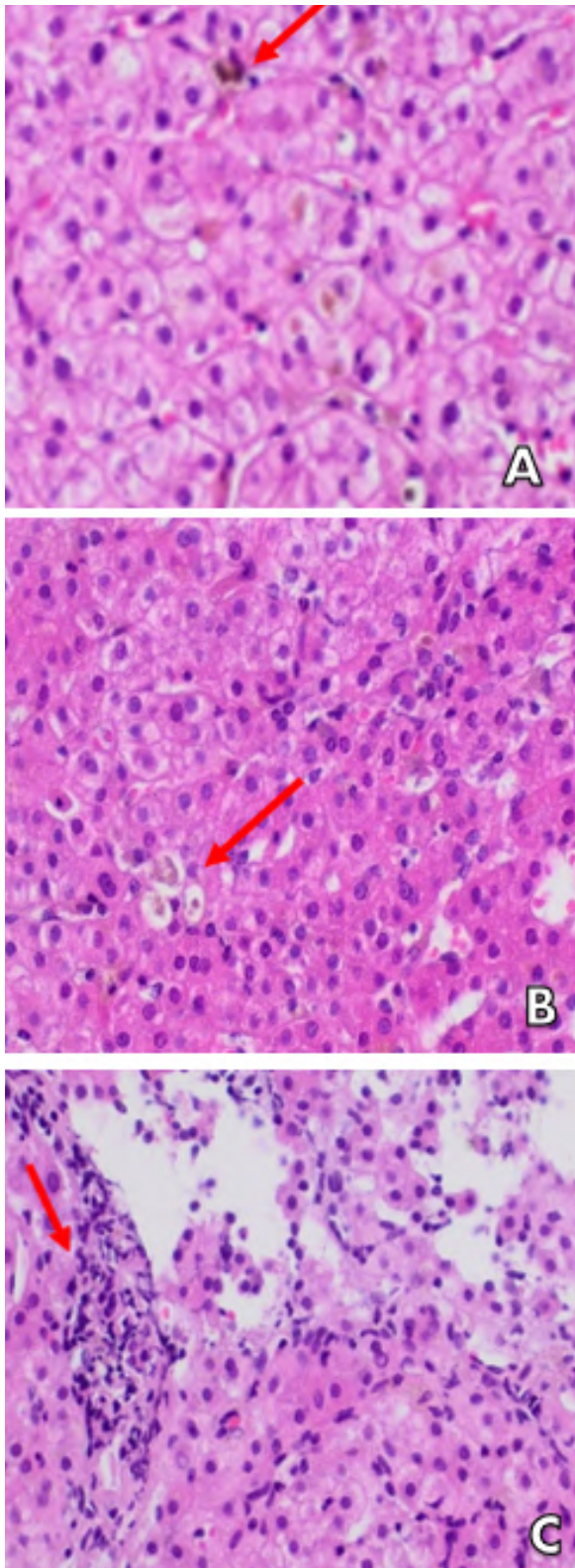


Figure 5. Hepatic histopathology: hepatic cholestasis (A). Punched liver necrosis (B), Portitis (C).



Resolution

The patient was admitted to Child Intensive Care in critical condition, where a team of multidisciplinary health professionals approached him. He received life support therapy, and the rheumatology treating physician indicated intravenous boluses of methylprednisolone for five days, azathioprine, chloroquine, and prednisone. Peritoneal dialysis was performed for ten days until the renal injury was stabilized, followed by antihypertensive treatment with losartan and amlodipine.

It was established by the Pediatric Intensive Care Unit and Rheumatology services after the diagnostic approach and response to the therapy described above: Pediatric Systemic Lupus Erythematosus associated with autoimmune hepatitis and interstitial nephritis. After a month of hospitalization, the patient was discharged in favorable condition and followed up by an outpatient nephrology and rheumatology consultation.

Discussion

Patients with systemic lupus erythematosus at an early age have greater organic involvement, affecting the kidney, nervous system, or liver. Liver involvement in SLE can lead to severe and even fatal diseases, as reported by Runyon et al. In a study in which the records of 238 patients with SLE were reviewed, 43 patients met strict criteria for the existence of liver disease, and 33 patients presented cirrhosis, active chronic hepatitis, granulomatous hepatitis, persistent chronic hepatitis, and steatosis. Of the nine patients who underwent serial liver biopsies, four showed disease progression, and three died of liver failure [9].

Likewise, Beisel et al. describe hepatic alterations in patients diagnosed with SLE; for this reason, they present the case of six patients who, at the time of diagnosis of AIH, reported arthralgia, abdominal discomfort, skin involvement, and fatigue, with the presence of serological markers, such as ANA, anti-dsDNA, or elevated IgG; their study highlights liver

biopsy as a crucial point in distinguishing AIH in SLE. The treatment used was based on immunosuppressive strategies with good results. Nevertheless, the aggressive histological process of AIH reveals a 5-year survival rate of less than 25% in untreated patients versus 80% in those treated with corticosteroids [15].

When analyzing the serological findings for active SLE, the positivity of the AC. DNA and ANCA are sensitive and specific [9]. Alvarez et al. revealed that 70% of patients with AIH present significant ANA or SMA, and 3% have anti-LKM-1, while 20% do not have any of these antibodies [16]. For Lohse et al., biopsy is the starting point in detecting and differentiating the causes of liver disease in PSLE [17].

Therefore, Zheng R et al. revealed that at the histological level in patients with AIH, no specific changes were reported; only steatosis, fibrosis, focal necrosis, and infiltration of round cells in the portal area and in ultrasound examinations were observed. Hepatomegaly, cirrhosis, and liver atrophy may be found [10].

The present case with a diagnosis of PSLE presented changes in liver enzymes since admission, accompanied by asthenia, epistaxis, jaundice, and hepatomegaly. Reports of immunological tests describe ANAS positivity, AC. Positive DNA and when the clinical condition improves, the liver biopsy performed pieces: active portitis, parenchymal and extra parenchymal cholestasis, punched-out necrosis plus fibrosis, which is consistent with previously published studies, although the literature investigated is not exclusive to pediatrics and goes back several times. Autoimmune hepatitis persists but is not associated with PSLE due to insufficient reported cases.

On the other hand, the patient was admitted to intensive care for children with renal injury with a creatinine value of 3.44 mg/dl and whose renal biopsy revealed grade I multifocal interstitial nephritis and mild grade I fibrosis requiring peritoneal dialysis and later antihypertensive therapy.

In contrast to those previously described, in the research by Casado Picón et al., data were obtained from 16 patients with an age at onset of SLE of 10.6 ± 2.9 years and the beginning of lupus nephritis (LN) diagnosed by biopsy. Patients received bolus cyclophosphamide treatment, with 11.1% developing end-stage renal disease after ten years [18].

Estévez del Toro et al. determined the predictive factors for LN development in patients with SLE, participating 595 patients with SLE without LN. Clinical follow-up was carried out for six years, and from the data, 124 patients with LN were found. Among the associated factors, an albumin/globulin ratio (AGR) below one was established with low levels of C3 and high levels of anti-dc DNA antibodies [19].

Therefore, renal involvement is joint in patients with SLE, as described by Shen et al.: renal biopsy evaluation offers prognostic information. It indicates severe active and chronic histological changes to establish the risk of developing chronic renal failure [20].

However, despite the meticulous investigation of the world literature, pediatric systemic lupus erythematosus associated with autoimmune hepatitis and nephritic syndrome as a triad in the same patient under the same condition has not been described. There are very few cases of PSLE with autoimmune hepatitis reported worldwide; in contrast, its most common presentation is PSLE with lupus nephritis.

Conclusions

Pediatric systemic lupus erythematosus associated with autoimmune hepatitis and lupus nephritis is a rare condition in the pediatric population, highlighting the importance of a multidisciplinary team to make an insightful diagnosis based on clinical manifestations, laboratory data, and imaging. It is crucial to perform liver and kidney biopsies whose histological results allow early adjustment of treatment and prevent the progression of the disease with fatal consequences.

Abbreviations

pSLE: pediatric systemic lupus erythematosus; AIH: autoimmune hepatitis; HLA: human leukocyte antigen; IgG: immunoglobulin G; C4a: complement factor 4a; LN: lupus nephritis; AGR: albumin/globulin ratio.

Supplementary information

No supplementary materials are declared.

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Author contributions

Jonathan Maximiliano Tipán Barros: bibliographic review and writing of the manuscript

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César Francisco Patiño Rocha: review and critical analysis of the article

Tatiana Maribel Tipán Barros: case writing, a compilation of paraclinical tests and biopsies.

Freire Ochoa Jennifer Andrea. Physician: bibliographic review, critical analysis of the article, and final correction of the manuscript

All authors read and approved the final version of the manuscript.

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Availability of data and materials

The data were collected from the medical files provided by the Vicente Corral Moscoso Hospital, Cuenca – Ecuador L. They are not publicly available due to

the confidentiality of the participant, but they are available through the corresponding author under a justified academic request.

Statements

Ethics committee approval and consent to participate

Not required for clinical cases.

Publication Consent

The authors have the informed consent of the patient's mother for the publication of the clinical case, as well as for the images presented for academic purposes, safeguarding the confidentiality of the minor.

Conflicts of interest

The authors declare they have no conflicts of interest.

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