

Hepatic and gastrointestinal manifestations in Mexican patients with juvenile systemic lupus erythematosus

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Abstract

Background: Systemic lupus erythematosus (SLE) is a multisystem disorder which can affect the gastrointestinal system (GI), symptoms can manifest in 50% of patients with systemic lupus erythematosus (SLE), these have barely been reviewed due to difficulty in identifying different causes [1]. The causes of abdominal pain in SLE patients are diverse, including lupus-related and non-lupus-related etiologies, as well as infections and medication side effects [2]. Children more often have lupus-related causes such as lupus mesenteric vasculitis, ascites peritonitis, and pancreatitis [2,3]. Liver manifestations, generally mild elevations in liver transaminases, have been reported in approximately 25-57.9% in paediatric-onset SLE (pSLE).

Methods: Retrospective study, with review of 63 medical records of patients diagnosed with paediatric-onset SLE (pSLE) according to ACR 1997 criteria treated at the UMAE Hospital Pediatría CMNO, during the period from 2018 to 2020.

Results: 63 patients were included, 49 (77.8%) girls and 14 (22.2%) boys, age range 5-17 years, mean 14 years (DS±2.9). Gastrointestinal involvement was recorded in 50.8% (n= 32) children. Lupus hepatitis, the most frequent digestive disorder (12.7%). Elevation of liver enzymes was detected in 31.7% with a higher elevation in patients with digestive disorders, in the case of AST (p= 0.001) and ALT (p= 0.024) Abdominal pain was the most frequent symptom, present in 38.1% (n= 24) patients, especially related to multiple medication 46% (n= 29), pancreatitis 7.9% (n=5), lupus enteritis 3.2% (n=2), intestinal pseud occlusion 1.6% (n=1) and ascites 1.6% (n= 1). A significant association was found (p= 0.03), among those patients with gastrointestinal affection and management with 4 or more drugs. Azathioprine was the drug most associated with abdominal pain (p= 0.07). Pancreatitis was associated with higher levels of disease activity by MEX SLEDAI score (p= 0.016). Of the manifestations not related to SLE, gastritis was the most frequent in 7.9% which was associated with a longer disease evolution time (p= 0.01).

The decrease in C4 was the only immunological parameter significantly associated in patients with lupus and digestive disorders (P = 0.033).

Conclusions: Gastrointestinal manifestations are common in paediatric-onset SLE (pSLE), but most of them are mild and due to adverse reactions to medications. Moderate elevation of liver enzymes occurred in 31.7% with significantly higher mean values of ALT and AST in patients with digestive disorders.

Background:

Systemic lupus erythematosus (SLE) is a multisystem disorder which can affect the gastrointestinal system (GI), symptoms can manifest in 50% of patients with systemic lupus erythematosus (SLE), these have barely been reviewed due to difficulty in identifying different causes [1]. The causes of abdominal pain in SLE patients are diverse, including lupus-related and non-lupus-related etiologies, as well as infections and medication side effects [2], children more often have lupus-related causes such as lupus mesenteric vasculitis, ascites, peritonitis, and acute pancreatitis (AP) [2,3].

Exist a limited number of studies, mostly case reports, to report GI involvement in pSLE, were identified only 3 large pediatric cohorts regarding this topic. Tahernia et al, published a retrospective study of 138 pediatric patients with SLE in Iran, as the main finding, liver involvement was found in 48.55% of children with abnormal liver enzyme levels. Abdominal pain was reported in 37%, mainly in the epigastrium (25%) [4]. Sonmez et al. in Ankara, Turkey, conducted a retrospective review of 69 medical records of children with SLE with gastrointestinal involvement, finding gastrointestinal manifestations in 27.5% of patients, the most frequent being autoimmune hepatitis (42.1%) and lupus enteritis (5.2%). [5]. In France, Richer et al. published a multicenter, retrospective study of 201 patients with SLE, 39 with gastrointestinal involvement were identified, with an overall prevalence of 19%. Gastrointestinal symptoms were present or occurred 1 month after diagnosis in 32% of patients. Abdominal pain was the most frequent symptom in 34 (87%) patients. They were mainly related to ascites (n= 14) and pancreatitis (n= 12); more rarely with events induced by treatment (n= 1) or infection (n= 1) and never with events unrelated to SLE [6].

Methods:

In this observational study were collected from medical records 63 pediatric cases of pSLE attending in Pediatric Rheumatology Department at UMAE Pediatric Hospital CMNO in Guadalajara, México. The outcomes, frequency, and type of hepatic and gastrointestinal manifestations involvement were assessed as the main purpose of this study, but other functional gastrointestinal disorders were analyzed: constipation, dyspepsia and irritable bowel syndrome. In addition to the nutritional status of the patients. Information was collected from imaging studies performed: abdominal tomography and ultrasound. pSLE cases were diagnosed based on the presence of 4 of 11 American College of Rheumatology (ACR) criteria. ACR SLE classification criteria were revised and validated by Systemic Lupus International Collaborating Clinics (SLICC) group in 2012. According to SLICC, a person is classified as having SLE in presence of biopsy-proven lupus nephritis with ANA or anti-ds-DNA antibodies or 4 of diagnostic criteria, including at least one clinical and one immunologic criterion The clinical parameters analyzed were presence/absence of any gastrointestinal manifestations: related or not related to lupus and other functional digestive disorders (dyspepsia, constipation, irritable bowel); nutritional status of the patient, number of drugs consumed, imaging studies performed. Disease activity measured by Mexican SLE disease activity index score (Mex-SLEDAI).

Laboratory parameters included: SLE-specific antinuclear antibodies by ELISA, AST and ALT levels with a cut-off point >40 u/L, and GGT with a cut-off point >30 u/L. Hypoalbuminemia was considered a value (<3.5 gr/dl). The study was approved by the Local Investigation and Ethics in Research Committees of the Hospital (CLIS R-2020-1302-096).

Statistical analysis

The description of the data was presented as measures of central tendency (mean and median), as well as measures of dispersion (standard deviation or range) according to the distribution of the data. For the bivariate analysis of the continuous variables, the Student's T test was used, while for the qualitative

variables the Chi2 test. All analyzes will be performed using the IBM SPSS® v25.1. A p value less than 0.05 was considered statistically significant.

Results:

A total of 75 files were reviewed, of which 63 patient files met the inclusion criteria, 49 were girls (77.8%) and 14 boys (22.2%), with a male-female ratio of 1: 3.5. The ages ranged from 5 to 17 years, with a mean of 14 years and a standard deviation of 2.9 years. The majority adolescents in 77.8%.

Nutritional alterations were found in most of the patients (57.1%), overweight and obesity were the most frequent in one (41.3%); followed by growth retardation and malnutrition. Table 1. We found a significant association between patients with altered nutritional status and use of 4 or more drugs ($p= 0.03$), as well as higher levels of proteinuria ($p= 0.049$). Regarding the clinical presentation, gastrointestinal signs and symptoms were present in 50.8% ($n= 32$). The most frequent digestive symptom was abdominal pain in 38%. Hepatomegaly was the most frequent gastrointestinal sign unrelated to SLE, found in 4.8%, jaundice and ascites were less frequent, in 3.2 and 1.6%, respectively. **Table 2.**

A significant association was found ($p= 0.03$), among those patients with gastrointestinal signs and symptoms and management with 4 or more drugs, no statistical significance was found when correlated with time of disease evolution, antinuclear antibody positivity, complement levels or activity of the illness. Abdominal pain and digestive disorders were significantly associated with patients diagnosed with depression and higher levels of proteinuria with $p= 0.033$ and $p= 0.01$, respectively.

Functional digestive disorders appeared in 12.7%, constipation was the most frequent, followed by dyspepsia and irritable bowel syndrome **Table 4.**

Elevated aminotransferases were the most frequent biochemical alteration in liver function tests, in 31.7% of patients, taking into account ALT and AST with a cut-off point >40 u/L and GGT with a cut-off point >30 u/L. Hypoalbuminemia (<3.5 gr/dl) was common and occurred in 25.4%. **Table 3.**

A higher elevation in mean values of transaminases was demonstrated in patients with digestive disorders, in the case of AST and ALT with P less than 0.05, statistically significant. **Table 5.**

Hepatitis was the most frequent condition not related to SLE, in 14.3% of patients, classified as lupus hepatitis in 12.7% and drug-induced hepatitis in 1 patient. Prednisone was the drug most associated with hepatitis, although not significantly ($p= 0.17$).

Regarding digestive disorders and their relationship with gender, time of disease evolution, type of treatment and level of disease activity by MEX-SLEDAI, no significant association was found, however, azathioprine was the drug most associated with digestive disorders ($p= 0.07$) **Table 6.**

Significant association levels were found, with pancreatitis and disease activity level ($p= 0.016$) and gastritis with disease evolution time ($p= 0.01$).

The most frequently found antibodies were antinuclear antibodies (ANA) by indirect immunofluorescence homogeneous pattern in 93.7%, antiDNA_{dc} (58%), antiRNP (42.9%), anti SM (42.9%). Associations were made between antibodies and complement levels with digestive disorders, C4 was the only immunological parameter significantly associated in patients with lupus and digestive disorders (P = 0.033).

Regarding imaging studies, abdominal ultrasound was performed in 8 patients, with altered results in 5 of them, hepatic steatosis was present in 2 patients, followed by free abdominal fluid, alteration in hepatic echogenicity suggestive of chronic liver disease and thickening of the liver gut wall.

Abdominal tomography was performed on 2 patients, reporting thickening of the large intestine wall in one and changes in the caliber of hepatic vessels suggestive of portal hypertension in another. Likewise, 2 patients underwent endoscopy, altered only in one patient, reporting erosive gastritis. Colonoscopy was performed in 2 patients, without alterations and finally liver biopsy in only 1 patient, with a report of hepatic steatosis.

Discussion:

This retrospective study emphasises that abdominal manifestations are common in pSLE. The GI involvement in pSLE is variable. Sönmez et al., in a series of cases carried out in Turkey, described gastrointestinal involvement in 27.5%. Bader-Meuner et al., in 17% of children with SLE, and in this study it was found in 50.8% of children. [5, 7]

The most common symptom in the largest pediatric series is abdominal pain. The causes of abdominal pain in SLE patients are more frequent lupus-related etiologies, among which are: lupica enteritis (EL), protein-losing enteropathy (PLE), intestinal pseudo-obstruction (IPO), acute pancreatitis (AP). Its prevalence varies in variable ranges between 15.8–100% of cases. Richer et al. [6] reported that 87% of the causes of abdominal pain were due to acute pancreatitis, Sönmez et al. [5] and Tu et al. [8] to lupus enteritis in 5.2% and 31.6% respectively and in Hispanic children it was found in 38.1%, the most frequent cause was associated with the use of multiple medications. Gastrointestinal symptoms in Hispanic children with SLE were significantly associated with multiple medication (p = 0.033), without finding a correlation with disease activity levels, time of evolution or antinuclear antibody positivity. [6, 9]

Sönmez et al. reported autoimmune hepatitis as the most frequent disorder associated with SLE, in 42.1%. [5] In contrast, in our series no patient was found. Lupus hepatitis (LH) was the most frequent (12.7%), its evolution was subclinical with a course favorable to the use of steroids, none with progression to end-stage liver disease, and although the real prevalence of hepatitis autoimmune (AIH) with SLE in our patients is unknown, it was not necessary liver biopsy for diagnosis, since the evolution was satisfactory, unlike those reported by other authors in which there is overlap of both entities and therefore the need for histological study. [4, 5]

Globally, the estimated prevalence of LE ranges between 0.2% and 14% among all SLE patients [16] and accounts for 29–65% cases of acute abdominal pain [10], in our review it was found in only 3.2% of our patients. Intestinal wall edema and ascites are important for diagnosis, and imaging studies are necessary for a definitive diagnosis. The two patients with lupus enteritis were the only ones who underwent imaging studies and responded satisfactorily to treatment with steroids and alkylating agents. Patients with lupus and severe abdominal pain require a thorough investigation as elevated disease activity is related to the presence of intra-abdominal vasculitis. [11]

Reported prevalence of AP in pSLE ranges between 2.6% and 6% (12–16). In the cohort described by Bader-Meunier et al., AP was the most common cause of abdominal pain [5]. In our study, it occurred in 7.9% of patients and it was confirmed that it is significantly associated with lupus activity, in our case by the MEX-SLEDAI score ($p = 0.016$). [7, 11]. Figure 1. Likewise, we corroborate that the association between the administration of steroids or azathioprine and the development of pancreatitis cannot be proven significantly.

Mild elevation of transaminases occurs in up to 57.9% of patients, most of the time asymptotically, in our case it was the most frequent biochemical alteration in 31.7% of patients and a greater elevation was demonstrated in mean values of transaminases in patients with digestive disorders, however, to attribute it to SLE, it is due to hepatotoxicity due to drugs, autoimmune hepatitis, viral hepatitis and fatty liver. [4, 11]

In our study, 58.7% of patients presented some type of nutritional impairment, in contrast to other studies conducted in adults, where it is described in less than 10% of patients. Possibly this difference is due to the fact that the disease is more serious and has greater renal involvement in children, since we significantly correlated those patients with altered nutritional status and higher levels of proteinuria ($p = 0.049$), on the other hand, they were not significantly associated with the time of evolution or the activity of the disease. [7]

Although gastrointestinal manifestations are frequent, functional digestive disorders have hardly been studied in children with SLE, in our study they occurred in 12.7% of patients, constipation being the most frequent, it is likely that medications alter gastrointestinal homeostasis, such as glucocorticoids and non-steroidal anti-inflammatory drugs, and these are potential risk factors for its development.

In our study, associations were made between antibodies and complement levels with digestive disorders, only the decrease in C4 was the only immunological parameter significantly associated in patients with lupus and digestive disorders ($p = 0.033$).

Abdominal ultrasound shows abnormalities in up to 79% of patients with gastrointestinal manifestations, increased echogenicity of the liver parenchyma is the most common alteration in more than 50% of patients. [5]. On the contrary, hepatic steatosis was the most frequent alteration in our patients, and ultrasound alterations in general were described less frequently than those described in other series (62.5%). Figure 2.

Abdominal tomography has been described as abnormal in 5.5% of patients, the most common finding being thickening of the intestinal wall. In our study, only 2 patients underwent abdominal tomography, due to the severity of their symptoms, reporting thickening of the wall of the large intestine. Figure 3, in one and changes in the caliber of hepatic vessels suggestive of portal hypertension in another. Abdominal tomography should be mandatory in children with lupus who have unexplained abdominal pain to rule out findings suggestive of ischemic bowel disease.[6]

Liver biopsies performed on patients with SLE mainly report autoimmune hepatitis (42%), hepatocellular damage (10%), toxic hepatitis (5%) and cholestatic hepatitis (5%). [4] In our series, only 1 patient underwent liver biopsy, with a report of hepatic steatosis. Hepatic steatosis is rarely described in children with SLE, secondary to lupus per se or corticosteroid therapy. Histopathological approach is necessary in children with SLE and elevated transaminase levels unexplained by other causes, due to the high frequency of autoimmune hepatitis and associated histopathological alterations [5].

Conclusion:

Gastrointestinal manifestations in Hispanic children are mostly mild and secondary to the use of multiple medications, and hepatic non related of SLE,

Most SLE GI manifestations our children responded well to glucocorticoids and immunosuppressants

In view of the limited available data, further studies in children are needed to better explore the prevalence, prognosis and treatment recommendations for GI involvement in pSLE.

Limitations:

Among the limitations of our study were incomplete data in the clinical records, so it was not possible to include the total number of SLE patients treated at our reference center. In addition, it was not possible to perform imaging studies on all patients who presented some gastrointestinal symptom, because most of the symptoms were mild, including liver disease. Therefore, the performance of a histological study was not justified.

Abbreviations:

Systemic lupus erythematosus (SLE)

Paediatric-onset SLE (pSLE)

Gastrointestinal system (GI)

Paediatric-onset SLE (pSLE).

American College of Rheumatology (ACR)

Systemic Lupus International Collaborating Clinics (SLICC)

Protein-losing enteropathy (PLE)

Intestinal pseudo-obstruction (IPO)

Enteritis lupica (EL)

Acute pancreatitis (AP).

Autoimmune hepatitis (AIH)

Lupus hepatitis (LH)

Mexican SLE disease activity index score (Mex-SLEDAI)

Antinuclear antibodies (ANA)

Declarations:

Availability of supporting data: the statistical analysis and the databases are available and updated if required by the publisher.

Competing interests: the authors declare that they have no conflicts of interest.

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Authors' contributions: The main author is responsible for the design of the study, revision and editing of the database for its final statistical analysis. Third year resident of pediatrics: review of the literature, collection of sociodemographic information, elaboration of databases of the patients included in the study.

Co-author review of the literature and research protocol, revision and final edition of the manuscript.

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Tables:

Tables 1-6 are not available with this version

Figures

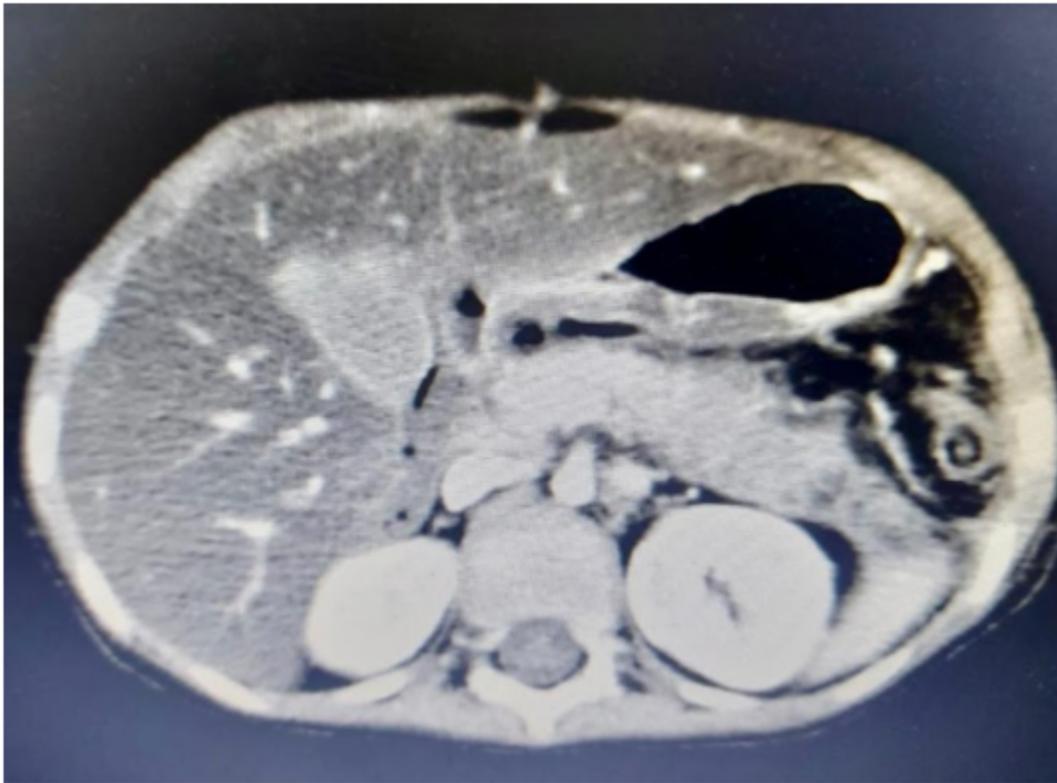


Figure 1

Computerized axial tomography in a 15-year-old boy with Balthazar C pancreatitis; to the onset of systemic lupus.



Figure 2

Abdominal ultrasound: showing increased hepatic echotexture due to moderate-grade hepatic steatosis with hepatomegaly in a 15-year-old girl with lupus.

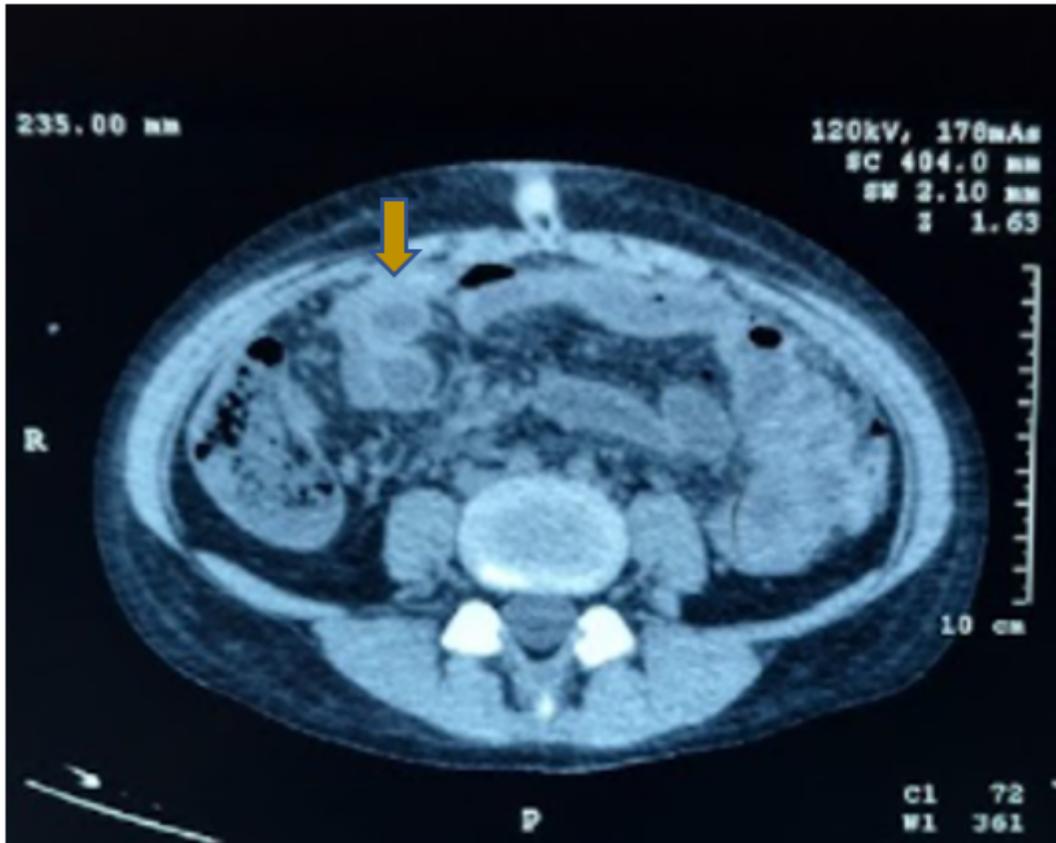


Figure 3

Abdominal contrast-enhanced computed tomography: demonstrating multiple segments of focal bowel wall thickening, diffuse bowel wall enhancement with peripheral rim enhancement (target sign).