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Exploring gastrointestinal manifestations in childhood onset systemic lupus erythematosus - Insights from a multicenter study

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Abstract

Objective: Systemic lupus erythematosus (SLE) constitutes an autoimmune disorder with potential involvement of the gastrointestinal system (GIS). Our objective was to assess the gastrointestinal (GI) manifestations in patients diagnosed with childhood onset SLE.

Methods: The study cohort consisted of 123 patients with childhood onset-SLE and GIS involvement from 16 referral departments of pediatric rheumatology. All participants met the Systemic Lupus International Collaborating Clinics criteria.

Results: Out of 123 patients, 78 (63.4%) exhibited GIS involvement at the initial SLE diagnosis, whereas the remaining 45 (36.6%) developed GI symptoms after a median duration of 12 (3–140) months. Eighty-two (66.7%) individuals experienced symptoms related to the GI tract, whereas the remaining patients received a diagnosis of GI involvement through laboratory assessments. The predominant initial GIS involvement symptom was abdominal pain, observed in 77 (62.6%)

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patients, followed by elevated hepatic transaminases in 70 (56.9%), hepatomegaly in 40 (32.5%), diarrhea in 26 (21.1%), and jaundice in 11 (8.9%) patients. The GIS involvement was associated with SLE in 82 (78.6%), while it resulted from drug-related adverse events in 35 (28.5%) patients or comorbidities in 6 (0.5%) patients.
Conclusion: GIS involvement should be considered in all childhood onset-SLE patients, especially in the presence of suggestive symptoms or elevated hepatic transaminases. It is also crucial to consider SLE in the differential diagnosis of GIS manifestations in children. Apart from GIS involvement directly associated with SLE, adverse events of drugs should be kept in mind.

Keywords
Systemic lupus erythematosus, gastrointestinal system, child, autoimmune hepatitis

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by multisystem involvement, encompassing the mucocutaneous, musculoskeletal, renal, neurologic, cardiac, pulmonary, and gastrointestinal (GI) systems.[1] While the clinical presentation of SLE in childhood bears a resemblance to that in adults, variations in disease progression and severity usually exist.[2] Notably, severe manifestations, including renal, neurological, and hematological features, demonstrate a higher frequency during childhood.[2,3] The early onset of GI system (GIS) involvement in adults with SLE has been documented; however, limited data are available regarding this occurrence in the pediatric population.[4]

Gastrointestinal manifestations in SLE encompass a spectrum that includes primary disease expression, concomitant associations, and manifestations resulting from the adverse effects of pharmacotherapy.[5] Symptoms may differ according to the involvement of anatomical segments within the GI tract and GIS involvement may occur either at the time of SLE onset/diagnosis or during the follow-up.[5] Among SLE patients, the predominant GIS symptom is abdominal pain, reported with a frequency ranging from 8% to 37%.[6] It is important to highlight that the underlying causes of abdominal pain may exhibit significant variations between pediatric and adult populations.[7] For instance, the most common reason for acute abdominal pain in adult-onset SLE patients is hepatobiliary disease while it is lupus mesenteric vasculitis in childhood onset-SLE patients.[7]

The primary objective of this study was to assess the prevalence, demographic attributes, clinical characteristics, and ultimate clinical outcomes related to GIS involvement in childhood onset-SLE.

Materials and method

The study cohort consisted of childhood onset-SLE patients from 16 referral departments of pediatric rheumatology. Patients aged 18 years or younger who exhibited GIS involvement either at the time of SLE diagnosis or during the course of the disease were eligible for inclusion.

All patients met the criteria established by the Systemic Lupus International Collaborating Clinics (SLICC). Data encompassing demographic information, clinical manifestations, laboratory findings, radiological and endoscopic assessments, histopathological analyses, treatments, and clinical outcomes were retrospectively extracted from patient records. Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).[8] SLICC damage index was used to assess the damage.[9]

The evaluation included an assessment of whether GI involvement was drug-related or associated with SLE.

The diagnosis of autoimmune hepatitis (AIH) was established using revised scoring system of the International Autoimmune Hepatitis Group (IAHG).[10]

In the presence of liver damage occurring between 1 week and 3 months after drug use, with resolution observed after the withdrawal of the drug, the liver injury is attributed to the drug.[11]

Ethical approvement for multicenter retrospective study was obtained from ethic committee and was performed in accordance with the ethical standards laid down Declaration of Helsinki.

Statistical analyses

Statistical analyses were executed using SPSS software version 21. The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Descriptive statistics were utilized, including proportions, means, medians, standard deviation, minimum, and maximum values as relevant.

Results

A total of 123 patients enrolled in the study. Of them, 101 (82.1%) were girls and 22 (17.9%) were boys. The mean

current age of patients was 18.8 ± 5.5 years. The mean age at diagnosis was 12.5 ± 3.5 years. The median time of follow-up was 44.5 (6–168) months. The clinical findings of patients were depicted in Table 1.

Seventy-eight (63.4%) patients presented with GIS involvement at the time of diagnosis, while the remaining 45 (36.6%) patients experienced GI symptoms after a median of 12 (3–140) months. Eighty-two (66.7%) patients suffered from GI-related symptoms while the remaining patients were diagnosed with GI involvement based on laboratory values. The most common initial symptom/sign of GIS involvement was abdominal pain in 77 (62.6%) patients, followed by elevated hepatic transaminases in 70 (56.9%), hepatomegaly in 40 (32.5%), diarrhea in 26 (21.1%), and jaundice in 11 (8.9%) patients.

At the time of diagnosis, the median (min-max) SLEDAI was 13.5 (2–76), whereas it was 11.5 (2–76) when GI complaints or findings occurred. Ninety patients had active SLE at the time of GIS involvement. Among them, 82 individuals had SLE-related manifestations, 35 had drug-related GI involvement, and 6 had comorbidities (Table 2). At the time of GIS involvement, erythrocyte sedimentation rate (ESR) was elevated in 64 (52%) patients and hypocomplementemia was present in 68 (55.3%) patients (Table 3).

Abdominal ultrasonography was performed on 93 (75.6%) patients, revealing abnormalities in 67 (72.0%) of them. The most common abnormality was hepatomegaly (n = 32), followed by hepatosteatosis (n = 20), splenomegaly (n = 12), increased parenchymal echogenicity in liver suggestive of chronic liver disease (n = 10), gallstones (n = 6), portal hypertension (n = 5), ascites (n = 3), intestinal wall edema (n = 3), bile sludge (n = 2), enlargement of intrahepatic bile ducts, and appendicitis (n = 1). Abdominal computed tomography (CT) revealed abnormalities in one patient, indicating dilated bowel and bowel wall thickening. Twenty-nine patients underwent abdominal magnetic resonance imaging (MRI), with abnormalities detected in 12 patients, including hepatomegaly (n = 4), increased liver parenchymal echogenicity (n = 3), splenomegaly (n = 3), cavernous changes in the portal area (n = 3) pericholecystic edema (n = 2) expansion of the intrahepatic bile ducts (n = 1). Endoscopy was performed on 26 patients, revealing gastritis in 19 individuals and esophageal varices in three patients. Colonoscopy was performed on five patients, and colitis was detected in three of them.

Liver biopsy was performed in 26 patients. The findings were as follows: chronic hepatitis (n = 22), toxic hepatitis (n = 1), hepatosteatosis (n = 1), cholestatic hepatitis (n = 1), and active hepatitis (n = 1).

The GIS manifestations resulted from drug-related adverse effects in 35 (28.5%) patients or comorbidities in 6 (4.9%) patients.

Thirty-one (25.2%) patients were diagnosed with autoimmune hepatitis, 16 (13%) with hepatic steatosis, 14 (11.3%) with lupus hepatitis, 5 (4.1%) with peritonitis, 5 (4.1%) with pancreatitis, 3 (2.4%) with portal hypertension, 3 (2.4%) with cholecystitis, 2 (1.6%) with viral hepatitis, 1 (0.8%) with mesenteric vasculitis, 1 (0.8%) with sclerosing cholangitis, and 1 (0.8%) with lupus enteritis. The median (min-max) AIH score was 6 (3–13) in patients with AIH.

Table 1. The clinical findings of patients with juvenile systemic lupus erythematosus who had gastrointestinal involvement.

Features	*N* (%)
Fever, *n* (%)	50 (40.7)
Fatigue, *n* (%)	93 (75.6)
Weight loss, *n* (%)	53 (43.1)
Lymphadenopathy, *n* (%)	33 (26.8)
Photosensitivity, *n* (%)	57 (40.3)
Malar rash, *n* (%)	65 (52.8)
Oral ulcer, *n* (%)	52 (42.3)
Nasal ulcer, *n* (%)	1 (8.9)
Alopecia, *n* (%)	26 (21.1)
Petechiae, *n* (%)	23 (18.7)
Arthritis, *n* (%)	67 (54.5)
Serositis, *n* (%)	24 (19.5)
Neurologic involvement, *n* (%)	17 (13.8)
Pulmonary involvement, *n* (%)	5 (4.1)
Cardiac involvement, *n* (%)	11 (8.9)
Renal involvement, *n* (%)	47 (38.2)
• Class I	6
• Class II	10
• Class III	0
• Class IV	20
• Class V	3
• No biopsy	3
• Acute tubular necrosis	1
SLE-related gastrointestinal manifestations, *n* (%)	82 (66.7%)
Drug-related gastrointestinal involvement, *n* (%)	35 (28.5%)
Comorbidities, *n* (%)	6 (4.8%)

GIS involvements due to the adverse events of drugs were as follows: toxic hepatitis (n = 11; 31.4%) associated with hydroxychloroquine (n = 4), azathioprine (n = 2), methotrexate (n = 5), steroid-related gastritis (n = 19; 54.3%), duodenitis (n = 2; 5.7%), esophagitis (n = 1; 2.9%), and gastroesophageal reflux (n = 1; 2.9%). Appendicitis (n = 1), Celiac disease (n = 1), inflammatory bowel disease (n = 3), and Wilson disease (n = 1) were detected as comorbidities.

Patients with AIH mainly received corticosteroids and azathioprine for treatment. Other treatments were summarized in Table 4. Due to inadequate response to the combination of corticosteroids and azathioprine, mycophenolate mofetil was added to the treatment in 12 patients, and rituximab was administered to 5 patients. At last control, three patients had portal hypertension and ten had increased parenchymal echogenicity suggestive of chronic liver

Table 2. The types of gastrointestinal involvement in patients with childhood onset systemic lupus erythematosus.

Diagnosis	*N* (%)
SLE-related manifestations	82 (78.6)
Autoimmune hepatitis	31 (25.2)
Hepatic steatosis	16 (13)
Lupus hepatitis	14 (11.3)
Peritonitis	5 (4.1)
Pancreatitis	5 (4.1)
Portal hypertension	3 (2.4)
Cholecystitis	3 (2.4)
Viral hepatitis	2 (1.6)
Mesenteric vasculitis	1 (0.8)
Sclerosing cholangitis	1 (0.8)
Lupus enteritis	1 (0.8)
Drug-related involvements	35 (28.5)
Toxic hepatitis	11 (31.4)
Steroid-related gastritis	19 (54.3)
Duodenitis	2 (5.7)
Esophagitis	1 (2.9)
Gastroesophageal reflux	1 (2.9)
Comorbidities	6 (0.5)
Appendicitis (*n* = 1)	1
Celiac disease	1
Inflammatory bowel disease	3
Wilson disease	1

disease while none of them exhibited damage to other organs (SLICC damage scores were 0 in all). Dietary modifications were advised to the patients with hepatosteatosis. For patients experiencing drug-related GI symptoms, discontinuation of the drug, along with the use of proton pump inhibitors and H2 receptor antagonists, led to the improvement of the symptoms. The patient with appendicitis underwent an appendectomy. A gluten-free diet was applied to the patient with Celiac disease. Patients with inflammatory bowel disease were treated with mesalazine concomitant to medications related to SLE. The patient with Wilson disease was treated with a diet low in copper and medications that increase copper excretion.

Discussion

Herein we summarized the clinical and laboratory findings of childhood onset-SLE patients manifesting with GIS involvement. The most common symptom was abdominal pain (*n* = 77, 62.6%) in patients and the most common diagnosis was autoimmune hepatitis (*n* = 31, 25.2%).

GIS involvement may occur at any stage of childhood onset-SLE. For instance, in a study conducted by Bader-Meuner and colleagues,[12] it was revealed that 17% of childhood onset-SLE patients exhibited GIS involvement as their initial presentations, with abdominal pain as a

Table 3. The laboratory findings of patients with childhood onset systemic lupus erythematosus and gastrointestinal involvement.

Laboratory findings	At the time of diagnosis	At the time of gastrointestinal involvement
Leukocyte[a] mm^3	5500 (1400–23400)	5900 (1400–26700)
Hemoglobin[a], g/dL	11.5 (5.4–16.1)	11.5 (6–16.1)
Platelet[a],/mm^3	180500 (2000–475000)	203000 (10000–475000)
Urea,[a] mg/dL	22 (7–206)	12 (7–14)
Creatinine[a], mg/dL	0.5 (0.05–3.08)	0.4 (0.05–0.87)
Alanine aminotransferase[a], U/L	38 (6–1060)	58 (6–1775)
Aspartate aminotransferase[a], U/L	39 (9–1190)	53 (11–2095)
Erythrocyte sedimentation rate[a], mm/h	26 (3–113)	26 (3–113)
Complement 3[a], g/L	0.61 (0.01–1.23)	0.77 (0.01–1.84)
Complement 4[a], g/L	0.11 (0.01–1.67)	0.11 (0.01–0.9)
Anti-nuclear antibody positivity, *n* (%)	123 (100)	123 (100)
Anti-double-stranded DNA (anti-dsDNA) positivity, *n* (%)	72 (58.5%)	72 (58.5%)
Extracted nuclear antigen antibody (ENA) positivity, *n* (%)	52 (42.3%)	52 (42.3%)
Anti-ribonucleoprotein positivity, *n*	21	21
Anti-SS-A positivity, *n*	17	17
Anti-SS-B positivity, *n*	9	9
Anti-centromere positivity, *n*	4	4
Anti-smith positivity, *n*	12	12
Antiphospholipid antibody positivity, *n* (%)	15 (12.2%)	15 (12.2%)

[a]median (minimum-maximum).

Table 4. Therapies administered for gastrointestinal involvement in patients with childhood onset systemic lupus erythematosus.

Drugs	*N* (%)
Mycophenolate mofetil	12 (9.8)
Steroids	54 (43.9)
Azathioprine	24 (19.5)
Rituximab	5 (4.1)
Intravenous immunoglobulin	2 (1.6)
Proton pump inhibitors	60 (48.8)
H2 receptor antagonists	8 (6.5)
Ursodeoxycholic acid	26 (21.1)

predominant symptom. In another study by Richer et al.,[13] 82% of childhood onset-SLE patients experienced GI symptoms at the time of diagnosis, with abdominal pain being the most frequently reported symptom. A previous study from our country documented 19 patients with childhood onset-SLE who presented with GI involvement.[5] Among these 19 patients, 13 (68.4%) exhibited GI symptoms at the onset of the disease while the others did so during the course of the disease. Pavli et al.[14] highlighted that patients with SLE may experience disease flare with acute GIS involvement such as lupus peritonitis, lupus enteritis, mesenteric vasculitis. Consequently, they emphasized that clinicians should be alert about these rare involvements.[14] In the present study, 78 (63.4%) patients presented with GIS involvement at the time of diagnosis, while remaining ones experienced GI symptoms during the course of the disease.

Previous researches showed that abdominal pain emerged as the predominant symptom in childhood onset-SLE patients with GIS involvement.[12,13,15] However, a previous report from our country documented that the most common feature was elevated hepatic transaminases.[5] In the aforementioned study, GI manifestations were directly attributed to disease in nine patients, while these were associated with SLE in four patients. Five patients had GI complications attributed to drug-related adverse events. Furthermore, one patient developed appendicitis which seemed to be coincidental rather than directly related to the disease.[5] In the present study, the most common symptom was abdominal pain (n = 77, 62.6%). Furthermore, GIS manifestations resulted from drug-related adverse effects in 35 (28.5%) patients or comorbidities in six (4.9%) patients.

Although hepatic involvement is rare, it is closely associated with an increased risk of mortality in SLE.[16] Hepatic involvement may be due to several different causes such as primary SLE involvement (lupus hepatitis), autoimmune hepatitis (AIH), viral hepatitis, fatty liver or drug-related side effects.[4] Elevated transaminases are the most common warning sign of hepatic involvement in SLE. Elevated liver enzyme levels may be observed in 25–59% of SLE patients over the course of the disease.[17] In various studies, drug-induced hepatic dysfunction was observed in 21%–31% of SLE cases.[17] Between 18% and 26% of SLE patients were diagnosed with non-alcoholic steatohepatitis, while viral hepatitis was identified in 0.8% to 14% of patients.[17] Furthermore, in 28% to 42% of patients, the cause of liver dysfunction remained unclear, with the possibility attributed to SLE itself.[17] Most of the available data comes from studies involving adults, and there is a restricted number of studies about pediatric population. In a study from Iran evaluating 138 childhood onset-SLE patients, the authors reported that 48.5% presented with elevated transaminases with varying degrees.[18] However, the etiological factors contributing to elevated liver enzymes were not comprehensively elucidated. Balbi et al.[19] evaluated 847 patients with childhood onset-SLE, biopsy-proven AIH was detected in seven of them. In a single-center study conducted in our country, 11 SLE patients were reported with hypertransaminasemia as an initial finding of GIS involvement, of which eight were diagnosed with AIH. In the present study, 70 (56.9%) patients presented with elevated hepatic transaminases, 31 patients were diagnosed with AIH, 16 with hepatic steatosis, 14 with lupus hepatitis, 11 with toxic hepatitis, and two with viral hepatitis.

The majority of data concerning GI manifestations in SLE is heterogeneous and retrospective, primarily presented in the form of case reports or case series involving adults. Most recently, in a prospective cohort from India including 2503 SLE patients with 490 (19.6%) having childhood onset-SLE, the authors showed that 243 (9.7%) patients presented with GI manifestations.[20] Among these 243 patients, ascites (162, 6.5%) was the most prevalent manifestation, followed by enteritis (41, 1.6%), pancreatitis (35, 1.4%), and hepatitis (24, 0.9%). However, data on children was not provided separately. The frequency of pancreatitis was reported as 2.6% in another multicenter cohort from Brazil evaluating 852 childhood onset-SLE patients. The most common form of pancreatitis was acute in 91% attributed to glucocorticoid treatment and active severe disease.[21] In the current study, pancreatitis occurred in 4.06% (n = 5) of participants, in three cases related to active disease and one case attributed to gallstones. Serositis is a common feature of SLE, but the actual prevalence of SLE-related peritonitis remains unknown.[22] Man et al.[22] reported that approximately one-third of episodes of serositis involved peritonitis or ascites. Five patients in our study cohort were presented with peritonitis. Furthermore, other rare manifestations such as portal hypertension, cholecystitis, mesenteric vasculitis, sclerosing cholangitis, and lupus enteritis were also observed in less than 3% of the cohort.

Medina and colleagues[23] examined 51 adult SLE patients presenting with acute abdominal symptoms and found that a higher disease activity was linked to intra-abdominal vasculitis or thrombosis, while a lower disease

activity was associated with acute abdomen unrelated to SLE. Interestingly, three of their patients with low SLE disease activity were diagnosed with acute appendicitis. In the present study, 82 patients who had SLE-related manifestations were active at the time of GI involvement. The main goal of the SLE treatment is to achieve low disease activity during the follow-up. Lupus low disease activity is defined as having a SLEDAI score ≤4 with no activity from major organ systems, a Physician's Global Assessment of ≤1 with no new activity, a prednisone dose ≤7.5 mg/day, and standard doses of antimalarials, immunosuppressives, and biologics.[24] The disease activity is typically assessed using SLEDAI, but unfortunately, the SLEDAI score is unable to capture GI activity[8] It may be insufficient to solely rely on the evaluation of disease activity, especially in cases where GI findings are prominent, potentially causing delays in achieving the goal of low disease activity. In the present study, 20 patients who had SLE-related manifestations were inactive at the time of GI involvement. Moreover, the prevention of damage in chronic diseases is equally important as the control of the disease's activity. The SLICC Damage Index serves as a metric for assessing the cumulative organ damage attributable to the disease and its corresponding treatments. Although this scoring system has been validated for children, it does not address damage on liver.[25] In the present study, three (4.7%) patients had portal hypertension and ten had increased parenchymal echogenicity suggestive of chronic liver disease. However, none of the 14 patients with chronic liver changes exhibited damage to other organs (SLICC damage scores were 0 in all).

The strength of the present study lies in its multicenter and nationwide design. Considering the rare prevalence of childhood onset-SLE, the cohort size is quite large, and our results provide significant insights to the GIS involvement in childhood onset-SLE patients. Limitations of this study include its retrospective design and the absence of a comparison of childhood onset-SLE patients with and without GIS involvement.

In conclusion, abdominal pain as a symptom and elevated transaminases as a laboratory feature may be red flags to recognize GIS involvement in childhood onset-SLE. Also, since a significant number of patients present with GIS features, it is crucial to consider SLE in the differential diagnosis of GIS manifestations in children. The inclusion of GIS involvement as a new diagnostic criterion may be warranted, given its potential prevalence that might be higher than currently recognized.

Declaration of conflicting interests

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Ethical statement

Ethical approval

The study complies with the Declaration of Helsinki that the Ethics Committee of Kocaeli University has approved the research protocol and that written informed consent has been obtained from the subjects (or their legally authorized representative).

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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