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ORIGINAL ARTICLE

Gastrointestinal system manifestations in juvenile systemic lupus erythematosus

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Abstract Systemic lupus erythematosus (SLE) is an autoimmune disease which may involve gastrointestinal system (GIS). The aim of this study was to present GIS manifestations of pediatric SLE patients. The medical files of 69 children with SLE followed between January 2011 and January 2016 were reviewed. All fulfilled the Systemic Lupus International Collaborating Clinics criteria. All patients (≤18 years of age) with GIS manifestations were included. GIS manifestations were observed in 19 (27.5%) out of 69 SLE patients and present at the time of SLE diagnosis in 13 (68.4%). The GIS manifestations due to SLE were autoimmune hepatitis (AIH) (n = 8) and lupus enteritis (n = 1). Manifestations associated with SLE were hepatomegaly and hypertransaminasemia due to macrophage activation syndrome (MAS) (n = 3) and hepatic steatosis (n = 1). GIS manifestations as a result of the adverse events of drugs were as follows: toxic hepatitis (n = 3; associated with methotrexate and nonsteroidal anti-inflammatory drugs in one, methotrexate in another, and azathioprine in another patient), azathioprine-induced cholestatic hepatitis (n = 1), and gastritis associated with corticosteroid (n = 1). In one patient, acute appendicitis occurred as a coincidence. In this study, one of every five pediatric SLE patients had GIS-related manifestations. GIS involvement may occur as an initial manifestation of the disease.

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease which affects multiple organs such as skin, mucosa, musculoskeletal, renal, neurologic, cardiac, pulmonary, and gastrointestinal systems. Although childhood disease is similar to that in adults, the course and severity may differ. Severe involvements such as renal, neurological, and hematological are more common during childhood [1–3]. Early presentation of the gastrointestinal system (GIS) involvement in adults with SLE has been reported, while data in childhood is scarce [4–6]. The most frequent GIS symptom is abdominal pain with a frequency of 8–37% [7]. Abdominal pain may arise from different etiologies among children and adults [8–10].

GIS manifestations in SLE can occur as a disease manifestation, an association, or a result of the adverse effects of drugs. GIS findings are considerably variable and any part of GIS may be affected [7, 11]. When renal, hematologic, and neuropsychiatric findings become more prominent, GIS findings may be ignored, and the actual prevalence may be overlooked. Treatment of gastrointestinal and hepatic findings depends on personal experiences and uncontrolled observational studies, since we lack adequate trials. In this study, the aim was to report the pediatric SLE patients with GIS findings.

Material and methods

The medical files of 69 children with SLE who were followed at Department of Pediatric Rheumatology in Hacettepe University, Ankara, Turkey between January 2011 and

January 2016 were reviewed. The patients (≤18 years of age) who had gastrointestinal system involvement either at the time of SLE diagnosis or during the disease course were included in the study. All patients were fulfilling the Systemic Lupus International Collaborating Clinics (SLICC) criteria [12]. Demographic data, clinical manifestations, laboratory, radiological, endoscopic, and histopathological findings, treatment, and outcome were documented from patient charts retrospectively. The disease activity was evaluated with SLE disease activity index (SLEDAI) [13].

GIS involvement in juvenile SLE was categorized into four groups as GIS manifestations due to SLE, associated with SLE, due to drug-related adverse effects and coincidental features.

Autoimmune hepatitis (AIH) is a progressive inflammatory liver disease. AIH diagnosis was made according to International Autoimmune Hepatitis Group (IAHG) revised scoring system [14].

Drug-induced liver injury categorized as toxic hepatitis, cholestatic or mixed depending on biochemical abnormalities, and liver biopsy results and defined as liver damage between 1 week and 3 months after the drug use and resolution after drug withdrawal [15].

The diagnosis of lupus enteritis was made according to abdominal computed tomography (CT) findings such as dilated bowel and bowel wall thickening.

The study was approved by the ethics committee of Hacettepe University and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All these patient files were evaluated retrospectively and all patients were anonymous. When the patients admitted to the hospital, the parents gave a general consent approving anonymous data use for academic purpose.

Statistical analyses were performed using the SPSS software version 21. Descriptive analyses were presented using proportions, medians, minimum, and maximum values as appropriate. Kruskal-Wallis test was conducted to compare non-normally distributed numeric variables between independent groups. The Mann-Whitney *U* test was performed to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. A p value of less than 0.05 was considered to show a statistically significant result.

Results

Out of 69 pediatric SLE patients, 19 (27.5%) had GIS involvement (Table 1). The median (minimum-maximum) age at SLE diagnosis was 120 (60–192) months and the median age at GIS involvement was 156 (60–204) months. GIS manifestations were present at the time of SLE diagnosis in 13 (68.4%)

Table 1 Juvenile systemic lupus erythematosus patients with gastrointestinal manifestations

	All patients (n = 19)	Patients with GIS manifestations due to SLE (n = 9)	Patients with GIS manifestations associated with SLE (n = 4)	Patients with GIS manifestations due to drug adverse events (n = 5)	Other (n = 1)
Gender (female/male)	15/4	7/2	4/0	3/2	1/0
Abdominal pain	3 (15.7)	1	0	2	0
Oral ulcers	8 (42.1)	5	2	1	0
Diarrhea	1 (5.2)	1	0	0	0
Gastritis	1 (5.2)	0	0	1	0
Ascites	0 (0)	0	0	0	0
Peritonitis	0 (0)	0	0	0	0
Serositis	1 (5.2)	0	0	1	0
Enteritis	1 (5.2)	1	0	0	0
Hepatic transaminasemia	11 (57.8)	5	3	3	0
Hepatomegaly	5 (26.3)	4	1	0	0
Jaundice	4 (21)	3	0	1	0
Surgical abdomen	1 (5.2)	0	0	0	1
Hypocomplementemia	11 (57.9)	7	3	1	0
ANA	19 (100)	9	4	5	1
Anti-dsDNA	17 (89.5)	9	3	5	0
ENA	8 (42.1)	3	2	3	0
SLEDAI at the time of GIS manifestations	8 (1–26)	8 (4–16)	7 (1–8)	5 (2–26)	12

ANA antinuclear antibody, *anti-dsDNA* anti-double stranded DNA, *ENA* extracted nuclear antigen antibody, *GIS* gastrointestinal system, *SLE* systemic lupus erythematosus, *SLEDAI* systemic lupus erythematosus disease activity index

patients. The median time period between the diagnosis of SLE and GIS involvement was 0 (0–96) months. We compared the clinical characteristics, laboratory features, and SLEDAI scores of patients with and without GIS involvement. Petechia, hypocomplementemia, and ENA positivity were more frequent in SLE patients with GIS involvement than patients without GIS involvement (15.8 vs 0%, $p = 0.022$; 94.7 vs 65.2%, $p = 0.014$; and 52.6 vs 17.3%, $p = 0.004$, respectively).

The initial symptoms or findings of GIS involvement were increase in hepatic transaminases ($n = 11$; 57.9%) hepatomegaly ($n = 5$; 26.3%), jaundice ($n = 4$; 21.1%), abdominal pain ($n = 3$; 15.8%), and diarrhea ($n = 1$; 5.2%). GIS involvement was associated with skin manifestations in 18 (94.7%) patients (14 with malar rash, 3 with alopecia, and 3 with petechia), oral ulcers in 8 (42.1%), arthritis in 11 (57.9%), renal involvement in 5 (26.3%) (one with class II, one with class IIIA, and 3 with class IV), cardiac involvement in 3 (15.8%), and neurologic involvement in 3 (15.8%) patients.

The laboratory findings and SLEDAI have been evaluated at the time of GIS involvement. The median (minimum-maximum) erythrocyte sedimentation rate (ESR) was 40 (4–81) mm/h (normal range 0–20), and the median C-reactive protein (CRP) was 0.54 (0.1–10.8) mg/dL (normal range 0–0.8). ESR was high in 13 (68.4%) and CRP was high in 3 (15.8%) patients. The median SLEDAI was 8 (1–26). There was hypocomplementemia in 11 (57.9%) patients. Antinuclear antibody (ANA) was positive in all; anti-double stranded DNA (anti-dsDNA) was positive in 17 (89.5%), and extracted nuclear antigen antibody (ENA) was positive in 8 (42.1%) patients (anti ribonucleoprotein in two, anti SSA in four, anti-centromere in one, anti-Smith in two patients). Antiphospholipid antibodies and anti-ribosomal P antibody were negative in all of 19 evaluated patients.

Abdominal ultrasonography (USG) demonstrated abnormalities in 15 out of 19 evaluated patients, including hepatomegaly ($n = 6$), increase in liver parenchymal echogenicity ($n = 13$), splenomegaly ($n = 4$), and appendicitis ($n = 1$). Abdominal CT was abnormal in one patient, showing dilated bowel and bowel wall thickening. Abdominal magnetic resonance imaging (MRI) was abnormal in six out of seven patients evaluated. The findings in MRI were as follows: hepatomegaly ($n = 5$), increased liver parenchymal intensity ($n = 5$), and expansion of the intrahepatic bile ducts ($n = 2$). Endoscopy was performed in only one patient who had the diagnosis of gastritis. Colonoscopy was normal in one evaluated patient.

Liver biopsy was performed in 12 (63.1%) patients. The findings were as follows: interface lobular hepatitis with lymphoplasmacytic infiltration and rosette formations consistent with AIH ($n = 8$), toxic hepatitis ($n = 1$), hepatocellular damage ($n = 2$), and cholestatic hepatitis ($n = 1$).

The GIS manifestations were due to SLE in nine patients, associated with SLE in four patients, and were due to drug-related adverse effects in five patients, and were interpreted to be a coincidental finding in one patient. The median (min-max) SLEDAI scores for these three groups were 8 (4–16), 7 (1–8), and 5 (2–26), respectively, and did not differ significantly ($p = 0.36$).

The GIS manifestations due to SLE were autoimmune hepatitis (AIH) ($n = 8$; 42.1%) and lupus enteritis ($n = 1$; 5.2%). AIH was diagnosed in 8 patients according to the IAHG revised scoring system [14] at the same time with the diagnosis of SLE. All patients with AIH had specific histological findings for AIH such as interface hepatitis, piecemeal necrosis, rosette formation, and portal plasma cell infiltration, in addition to meeting the criteria for SLE. They had typical SLE features as follows: malar rash in 8, photosensitivity in 8, renal involvement in 4, cardiac involvement in 2, and neurologic involvement in 2 patients. The AIH score was 18 (15–22) in patients with AIH. One of these eight patients was positive for anti-smooth muscle antibody, while all but one had positive anti-dsDNA and three had positive ENA. None of the patients had anti-ribosomal P antibody. The patients were followed up for a median (min-max) of 24 (16–33) months.

None of the patients developed complications such as cirrhosis, portal hypertension, and hepatocellular carcinoma during the follow-up. All of them responded to the therapy, and hepatic transaminases returned to normal after treatment.

SLE associations were hepatomegaly as well as hypertransaminasemia related to MAS ($n = 3$; 15.7%) and hepatic steatosis ($n = 1$; 5.2%). GIS involvements as a result of the adverse events of drugs were as follows: toxic hepatitis ($n = 3$; 15.7%; associated with methotrexate and nonsteroidal anti-inflammatory drugs [NSAIDs] in one patient, methotrexate in another patient, and azathioprine in another patient), azathioprine-induced cholestatic hepatitis ($n = 1$; 5.2%), and gastritis associated with corticosteroid ($n = 1$; 5.2%). After the cessation of these drugs, GIS symptoms/findings improved. In one patient, acute appendicitis occurred as a coincidental manifestation.

Two patients with MAS received corticosteroid and cyclosporine-A, while one got corticosteroid and intravenous immunoglobulin (IVIG). Seven out of eight patients with AIH received corticosteroids and azathioprine for treatment. One of these patients who had cholestatic hepatitis received ursodeoxycholic acid in addition to the immunosuppressive treatment given for SLE. One AIH patient was treated with only corticosteroid. Appendectomy was performed in the patient with appendicitis. Corticosteroid treatment was given to the patients with lupus enteritis. Proton pump inhibitor was prescribed to all patients receiving corticosteroid. Dietary modifications were advised to the patient with hepatosteatosis.

The GIS manifestations improved in all patients with the treatment.

Discussion

Systemic lupus erythematosus is a heterogeneous disease with diverse system involvement. The SLICC criteria set was used for diagnosis since 2012 [12]. The SLICC criteria are made up of 11 clinical plus 6 immunological criteria and four criteria must be present in order to fulfill the requirements for a clinical diagnosis with at least one being clinical and one immunological. These criteria were initially developed for adult patients. Subsequently, this criteria set was found to be 98.7% sensitive and 85.3% specific in a multicenter study, including our pediatric SLE patients [16]. Although GIS involvement is not rare at the time of SLE diagnosis, GIS manifestations are not included in the SLICC criteria [12]. Only serositis is included [12]; whereas, this feature is less often in children when compared to adults [3].

Although it is known that the onset and course of SLE during childhood can be distinctive and more severe than adults [17–20], studies related to GIS involvement are limited. The most common gastrointestinal symptom is abdominal pain in both childhood and adulthood, but various etiologies can cause abdominal pain. Tu et al. [10] demonstrated that the etiologies of acute abdominal pain were different between the childhood-onset group and the adult-onset group, and the most common etiology was lupus mesenteric vasculitis in childhood; on the other hand, hepatobiliary disease, peptic ulcer, and malignancy were only seen in adults as causes of acute abdominal pain.

Bader-Meuner et al. [6] reported that 17% of juvenile SLE patients had GIS involvement as an initial manifestation. According to their study, the most common symptom was abdominal pain which was related to pancreatitis, intestinal pseudo-obstruction, cholecystitis, lupus peritonitis, and other causes such as diarrhea, vomiting, and GIS bleeding [6]. Richer et al. [21] showed that 82% of SLE patients with GIS involvement had GIS symptoms at diagnosis of SLE, and abdominal pain was again the most common symptom. Fawzy et al. found the prevalence of GIS involvement in pediatric SLE patients as 42.5%, and the most common symptom was again abdominal pain. Of note, in this study, Giardia infestation was more common in patients with GIS symptoms when compared to the patients without GIS symptoms [22]. In our study, most of the patients (almost 70%) with GIS involvement had symptoms at the time of SLE diagnosis, and the most common initial finding was elevated levels of hepatic transaminases. Abdominal pain was the first symptom in only 15.8% of our patients.

GIS involvement in SLE can occur as an association, as a disease manifestation, or as a result of drug adverse effects or infections.

In this study, AIH was present in eight patients and lupus enteritis in one patient as a GIS manifestation of SLE. AIH is a chronic liver disease characterized by elevated levels of transaminase, inflammatory liver histology including interface hepatitis, piecemeal necrosis, rosette formation, portal plasma cell infiltration, and presence of autoantibodies such as ANA, anti-smooth muscle antibodies (SMA), anti-liver kidney microsomal antibodies (LKM), and increased levels of immunoglobulin G [23, 24]. The scoring criteria proposed by the IAIHG may help for the diagnosis of AIH and also anti-ribosomal P antibody may be a useful marker to differentiate lupus hepatitis from AIH [25]. Anti-ribosomal P antibody was negative in all of our patients with AIH. AIH is classified into two types according to seropositivity: AIH type I is associated with SMA and/or ANA, whereas AIH type II is associated with LKM autoantibody. The most common one is type I [14, 26]. SLE and AIH often share some features of autoimmune disorders, including hypergammaglobulinemia, polyarthralgia, and the presence of ANA, anti-dsDNA antibodies. The exact etiology of AIH and juvenile SLE remains unknown; however, a shared immunogenetic susceptibility is suggested. Although rare, overlap of AIH and SLE was previously described in the literature [27]. The boundary between an autoimmune liver disease accompanying SLE and a clear-cut AIH may not be clear; however, we have decided to depend on whether they met the accepted IAIHG criteria and the SLICC criteria to define them as AIH and SLE, respectively. The real prevalence of AIH and SLE is unknown. Irving et al. [28] showed that the incidence of AIH was significantly higher in children than adults (9.8 vs 1.3%; $p < 0.001$). In this study, incidence of AIH is 11.6% (42.1% of the patients with GIS involvement), similar to previous data. The prognosis of the AIH was good in our patients, and all responded to immunosuppressive treatments. In children with SLE who have elevated liver transaminase levels, AIH must be considered if toxic and infectious factors are absent [29, 30].

Lupus enteritis is a rare complication of SLE; however, its actual incidence is unknown. It could have been underdiagnosed, since its major physical indicator is abdominal pain which is a common and nonspecific symptom. CT findings such as bowel wall edema, mesenteric abnormalities, and ascites are important for diagnosis and are responsive to steroid therapy [31].Our patient received corticosteroid treatment and was in clinical remission at his last visit.

SLE-associated GIS manifestations were in the form of MAS and hepatic steatosis in our study. MAS is a severe, potentially life-threatening complication of rheumatic diseases which is characterized by prolonged fever, pancytopenia, and hepatosplenomegaly. Its association with SLE is relatively rare and the incidence is about 0.9–4.6% [32]. Hepatic

steatosis is common in SLE patients. It may be due to SLE per se or the corticosteroid therapy [32, 33].

GIS involvement can also occur as a result of drug adverse effect or infections. The drugs such as NSAIDs, methotrexate, azathioprine, and hydroxychloroquine used in the treatment of SLE can cause hepatotoxicity [34–36]. In this study, five patients had GIS involvement due to drug side effects, and in all of them, symptoms improved after drug withdrawal.

There was no association between SLEDAI and the type of GIS involvement (as SLE disease manifestation, SLE-association, or drug adverse effect) in this study. However, in a previous study, Medina et al. evaluated 51 adult patients with SLE as well as acute abdomen and demonstrated that higher disease activity was associated with intraabdominal vasculitis or thrombosis, while lower disease activity was associated with non-SLE-related acute abdomen [37]. Acute appendicitis was the diagnosis in three of these patients who had low SLE disease activity [37].

In our study, hypocomplementemia and ENA positivity were more frequent in SLE patients with GİS involvement than the ones without GIS involvement. Xu et al. [38] had also shown that decreased C3 and CH50 were independent predictors of GIS involvement in SLE. No specific autoantibody had been identified as being associated with GI involvement in SLE [39]. Clotet et al. [40] demonstrated that positive ENA antibodies distinguished a certain subset of SLE with renal disease, positive Coombs test, and anticoagulant serum factors. Alba et al. [41] showed that ENA positivity was a factor associated with lupus nephritis. However, there was no previous study on ENA and GIS involvement in SLE. According to our results, ENA may also be associated with GIS involvement in SLE.

In conclusion, in this study, one out of every five pediatric SLE patients had GIS involvement during SLE course and GIS involvement occurred as an initial manifestation in some of these patients. It is important to keep SLE in mind in the differential diagnosis of GIS manifestations in children. Furthermore, GIS involvement may be considered as a new item in the criteria, since it is probably more common than appreciated.

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Compliance with ethical standards The study was approved by the ethics committee of Hacettepe University and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All these patient files were evaluated retrospectively and all patients were anonymous. When the patients admitted to the hospital, the parents gave a general consent approving anonymous data use for academic purpose.

Disclosures None.

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