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"INTESTINAL PSEUDOOBSTRUCTION ASSOCIATED WITH EOSINOPHILIC ENTERITIS AS THE INITIAL PRESENTATION OF SYSTEMIC LUPUS ERYTHEMATOSUS IN CHILDREN"

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Case Report

Intestinal Pseudoobstruction Associated With Eosinophilic Enteritis as the Initial Presentation of Systemic Lupus Erythematosus in Children

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Systemic lupus erythematosus (SLE) is a multisystemic autoimmune inflammatory disease with a variety of presenting features and manifestations. Abdominal complaints in patients with SLE may pose a difficult diagnostic challenge. Intestinal pseudoobstruction (IPO) recently has been recognized as an uncommon complication of SLE (1–3). IPO reflects a dysfunction of the visceral smooth muscle or the enteric nervous system (2). The clinical presentation of this complication usually includes a subacute onset of abdominal pain associated with vomiting and constipation, as well as a distended, tender abdomen with hypoactive or absent bowel sounds (1). Only a few cases of IPO in SLE have been described in the literature (2–15). IPO is considered a severe manifestation of SLE (3). There have been recent reports associating eosinophilic enteritis with SLE in adults who presented with obstructive symptoms, but none in children (16,17). Eosinophilic gastroenteritis (EG) is a rare disorder defined by gastrointestinal symptoms due to eosinophilic infiltration of the gastrointestinal tract. We describe 2 cases of children presenting with IPO caused by eosinophilic enteritis as the first manifestation of SLE.

CASE 1

A 10-year-old boy was admitted to the National Institute of Pediatrics in Mexico City with a 1-week history of abdominal pain, constipation, bilious and fecaloid vomiting (6/day), and no fever. He had been treated by primary care physicians with antibiotics and analgesics without improvement. Physical examination revealed generalized abdominal tenderness and sluggish bowel sounds without rebound tenderness. Laboratory tests revealed Hb 16.6 g/dL, white blood cell count 14,800/μL, 84% neutrophils, 9% lymphocytes (total lymphocytes = 1332/μL), eosinophils 0%, platelets 470,000/mm^3, Na 120 mEq/L, K 4 mEq/L, and Cr 2 g/dL. The abdominal radiograph revealed distended intestinal loops with air-fluid levels and no air in the rectum. Because of concerns about either appendicitis modified by medications or a mechanical obstruction, a laparotomy was performed, revealing abundant serous liquid and a congestive small bowel. Clinical improvement was seen with conservative treatment. One day after discharge from the hospital, he was readmitted because of recurrence of vomiting and abdominal pain. Abdominal symptomatology continued. An ultrasound showed fluid in the right flank with bilateral hydronephrosis and dilated ureters. A second laparotomy was performed, which revealed an engrossed appendix, so he underwent an appendectomy. The histopathological studies revealed mural infiltration of eosinophils with few plasma cells and neutrophils in the appendix. Full-thickness biopsies of the small intestine and colon showed numerous eosinophils infiltrating, predominantly in the muscularis propria with diverse grades of fibrosis. Some areas had more than 20 eosinophils per high-power field and an infiltrated isolated myenteric plexus. Fibrosis in some fields was predominantly marked in the outer longitudinal layer (Fig. 1).

During his second admission, the patient developed generalized seizures and he was transferred to intensive care. The electroencephalogram showed diffuse slow waves with occipital spike activity. Brain CT scan did not show any abnormalities. Laboratory tests revealed complete blood count Hb 15 g/dL, white blood cell count 20,000 μL, 450,000 platelets, Cr 1.9 g/dL, and cylindruria with traces of protein in the urine. Immunologic evaluation revealed positive anti-nuclear antibody test (ANA) 1:160, CH50 76 (150–250), C3 36 mg/dL (55–128), C4 <5.3 mg/dL (15–52), immunoglobulin (Ig)G

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The authors report no conflicts of interest.

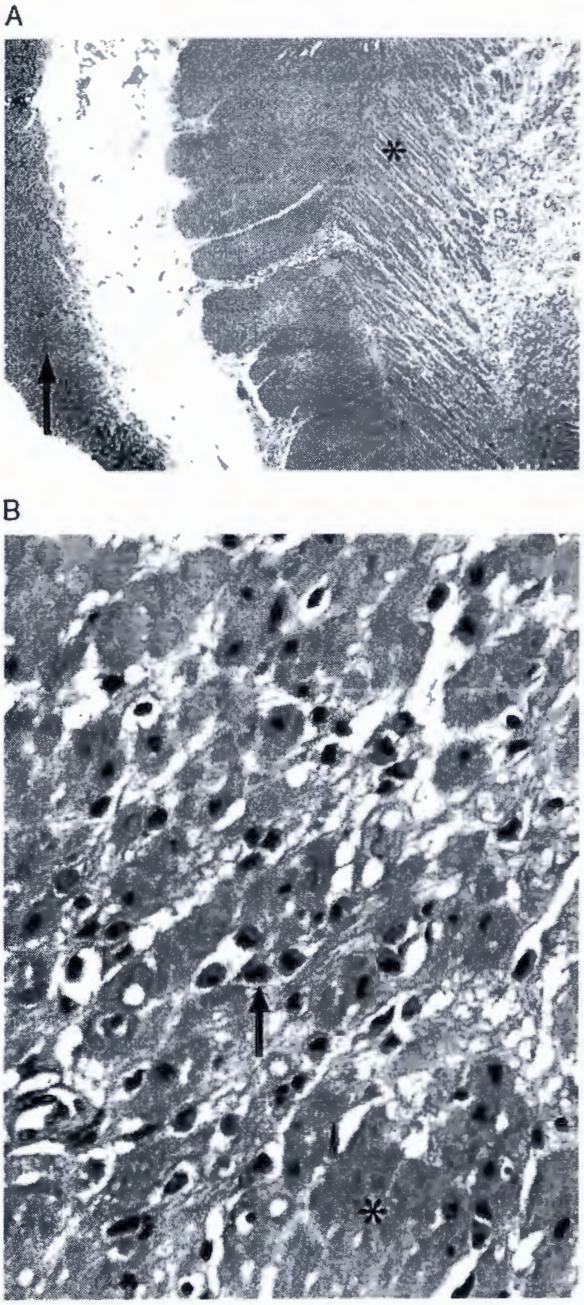

FIG. 1. A, Full-thickness colon biopsy; colonic mucosa (arrow) with lymphoid hyperplasia and inflammatory infiltrate in muscularis propria (*) and serosa layer (hematoxylin and eosin stain; original magnification ×10). B, Full-thickness small bowel muscularis propria (*) infiltrated by numerous eosinophils (arrow) (hematoxylin and eosin stain; original magnification ×40).

1430 mg/dL (886–1359), IgM 67 mg/dL (43–112), IgA 119 mg/dL (71–191), IgE 13 IU/mL (<54 IU/mL), negative ANCA, negative dsDNA, negative anti-Sm, IgM anti-β2 glycoprotein-I 47.8 U/MPL (0–20), and anticardiolipin 23 U/GPL (0–12). The diagnosis of SLE was made based upon the following criteria of the American College of Rheumatology: positive ANA, lymphopenia, seizures, serositis, and cylindruria (18). Treatment was begun with diazepam and phenytoin for control of the seizures. Aspirin, intravenous gammaglobulin, methylprednisolone pulses, and oral cyclophosphamide also were initiated with subsequent improvement of symptoms. He has been clinically followed for 2 years: abdominal symptoms have not recurred, the renal function has normalized, and prednisone has been tapered.

CASE 2

A 15-year-old girl was referred to our hospital with a 4-month history of abdominal pain, loose stools, and vomiting. She had undergone 2 previous surgeries, an appendectomy in another facility and an adhesiotomy. During this time, she lost 25 kg of weight. On admission, physical examination revealed a distended abdomen, sluggish bowel sounds, and no rebound tenderness. She underwent an esophagogastroduodenal endoscopy, which revealed candidal esophagitis. An upper gastrointestinal series was performed, which suggested a mechanical obstruction in the lower portion of the duodenum, and a laparotomy was performed. Full-thickness intestinal biopsies were taken. She was started on parenteral nutrition and intravenous fluconazole. Laboratory tests showed Hb 11.9 g/dL, white blood cell count 4000/μL, lymphocyte count 1400, 354,000/mm^3 platelets, Cr 0.4 g/dL, UA with proteinuria 500 mg/dL and cylindruria, 24-hour proteinuria 1.73 g/day, negative HIV, positive ANA 1:160, CH50 57 (150–250), negative anti-dsDNA, positive anti-Sm 30 U (<20 U), positive anti-ribonucleoprotein 200 U (<20 U), IgE 77.8 IU/mL (<100 IU/mL), IgG 1190 mg/dL (822–1070), IgM 148 mg/dL (39–79), and IgA 254 mg/dL (85–211). An echocardiogram revealed mild pericarditis with pericardial effusion. Stool studies ruled out enteric infection. A percutaneous renal biopsy showed a lupus nephropathy class III (focal proliferative glomerulonephritis) with an activity index of 4 of 12 and chronicity index 2 of 12. Scanty mesangial deposits of IgG, IgA, IgM, C1q, C3, and fibrinogen were found with immunofluorescence studies. Esophageal biopsy showed an ulcer consisting of fibrin and numerous neutrophils and eosinophils; the epithelial remnant showed regenerative changes. The muscularis propria of the esophagus also showed inflammatory involvement, predominantly by eosinophils. Small intestinal and colonic full-thickness biopsies demonstrated similar inflammatory changes previously described with a more florid acute peritonitis and mild perivasculitis (Fig. 2).

The presence of proteinuria, cylindruria, serositis, lymphopenia, positive ANA, and anti-Sm antibodies in this patient led to a diagnosis of SLE (18). While in the hospital, she developed ataxia, which was considered to be a clinical manifestation of SLE, so methylprednisolone

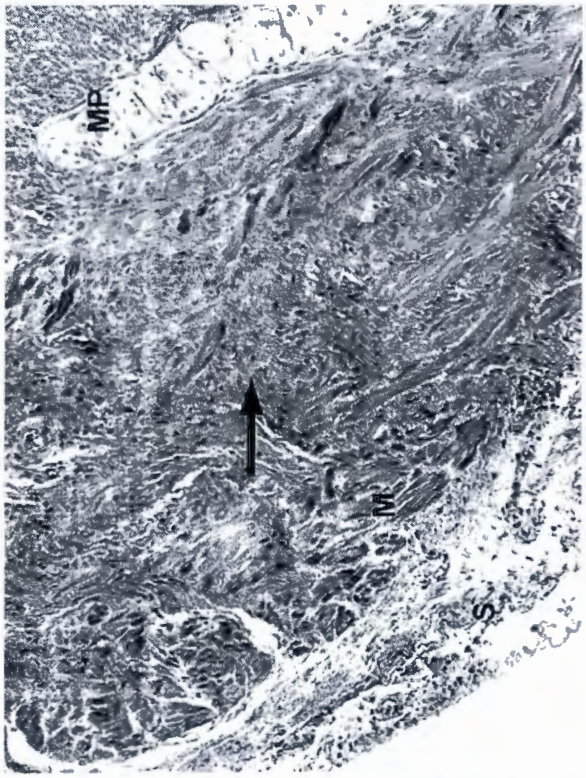

FIG. 2. Full-thickness small bowel biopsy. Dense fibrosis (in blue, arrow) in muscularis propria (M). Inflammatory infiltrate is composed of eosinophils. Also shown are serosa (S) and myenteric plexus (MP) (trichrome Masson stain; original magnification ×10).

pulses were administered, with resolution of the neurological symptoms. She was discharged home without gastrointestinal symptoms while taking oral cyclophosphamide and prednisone. She has been studied for more than 1 year; she is stable with no further intestinal flares.

DISCUSSION

Gastrointestinal manifestations of systemic lupus erythematosus are common and can involve any organ of the abdomen (1). Intestinal abnormalities in SLE include dysmotility, vasculitis, and malabsorption (1). IPO has recently been recognized as an uncommon complication of SLE and can be the presenting feature. There are only a few small case series describing this complication (2–15). Laparotomy with bowel biopsies is a useful diagnostic tool. In the literature, intestinal histopathological findings have shown that vasculitis is not the cause of this complication, but rather it is a myopathy secondary to inflammatory infiltration.

EG is a rare disorder defined by gastrointestinal symptoms due to eosinophilic infiltration of the gastrointestinal tract (19). The diagnosis of EG is confirmed by a characteristic biopsy and/or eosinophilic ascitic fluid in the absence of infection by intestinal parasites (19). A correlation exists between the depth of intestinal wall invasion and the extent of clinical symptoms. Disease of the mucosa is associated with malabsorption and protein-losing enteropathy; infiltration of the muscularis propia results in obstructive symptoms and involvement of the serosa produces ascites. EG is classified according to 2 different subtypes, primary and secondary. The primary subtype includes the atopic, nonatopic, and familial variants. The secondary subtype can be divided into eosinophilic disorders (hypereosinophilic syndrome) and noneosinophilic disorders, which include infection, inflammatory bowel disease, vasculitis (Churg Strauss syndrome), celiac disease, and scleroderma (19). Our 2 patients can be classified in the secondary subtype of the disease. There have been recent reports associating eosinophilic enteritis with SLE in adults (16,17). In these reports, eosinophilic enteritis manifested as symptoms and signs of IPO, particularly when the muscularis layer was affected. Barbie et al (16) reported a 37-year-old woman with a history of purpura and a 2-month history of nausea, vomiting, diarrhea, and abdominal pain. Gastric antrum and small bowel biopsies revealed similar changes as in our cases. Because gastric antrum involvement occurs in more than 95% of cases, the authors diagnosed a classic presentation of eosinophilic gastroenteritis (mural type). Sunkureddi et al (17) described a 47-year-old woman with SLE and several months of nausea, vomiting, diarrhea, and abdominal pain. Complete blood counts revealed discrete eosinophilia (500–700/mm^3). She responded to hydroxychloroquine and prednisone (17).

The diagnosis of eosinophilic enteritis was made in our patients based on the clinical and histopathological findings. The colon was severely inflamed, contributing to the abdominal pain and weight loss observed in both patients. As in Barbie and colleagues's report (16), peripheral eosinophilia was not documented, but its presence could be a diagnostic clue. In all of the cases (including ours), the clinical course was chronic and the diagnosis delayed.

Hill et al (13) reported on a 38-year-old woman with intestinal pseudoobstruction and segmental resection of the ileum and colon; histopathological studies showed changes similar to our case: myocite loss and fibrosis with mixed infiltrate. Eosinophils were present but they did not predominate. Isolated submucosal vasculitis with fibrinoid necrosis also was described, but there were no alterations in the mesenteric vessels. Her final diagnosis was an intestinal smooth muscle myopathy. In another report, Perlemuter et al (2) described extensive fibrosis of the muscularis layer with a decreased number of smooth muscle cells and normal innervation of the digestive wall. Polymorphic cellular infiltration of the mucosal and submucosal layers was present, but no eosinophilic infiltration was described. It is important to note that in both

TABLE 1. *Clinical features, pathological findings, treatment, and outcomes of children with intestinal pseudoobstruction (IPO) and systemic lupus erythematosus (SLE)*

Author	Age, y/sex	Positive serology	Systemic involvement	Urological involvement	Histopathologic findings	Treatment	Outcome
Case 1	10/M	ANA, β2, GP-I, low CH50	CNS (seizures), nephritis, lymphopenia	Hydronephrosis	Eosinophilic gastroenteritis	Steroids, cyclophosphamide	Good
Case 2	15/F	ANA, RNP, Sm, low CH50	CNS (ataxia), neuropathy, nepritis, lymphopenia	None	Eosinophilic gastroenteritis	Steroids, cyclophosphamide	Good
Munyard et al (4)	15/F	dsDNA	NR	NR	NR	Steroids	Good
Tanaka et al (15)	11/F	ANA, low C3 and C4	Autoimmune anemia, thrombocytopenia	Hydroureter, hydronephrosis, interstitial cystitis	NR	Steroids, cyclophosphamide, azathioprine, cyclosporine	Steroid dependent, recurrent
Bader-Meunier et al (21)	2 patients NR	NR	NR	NR	NR	NR	NR
Richer et al (22)	1 patient NR	NR	NR	NR	NR	NR	NR

ANA = anti-nuclear antibody test; CNS = central nervous system; IPO = intestinal pseudoobstruction; NR = not reported; RNP = anti-ribonucleoprotein antibodies test; SLE = systemic lupus erythematosus.

of our cases the eosinophilic infiltrate markedly predominated. Although eosinophils are not usually involved in the pathogenesis of SLE, a Th2 cytokine imbalance has been noted (20). IgE levels and peripheral eosinophils counts were normal in both of our patients, with a particular intestinal Th2 cell–mediated damage. IPO in SLE is usually relieved with high-dose steroids and immunosuppressive therapy. Treatment with these medications has been advocated in severe cases of EG (19). Other therapeutic modalities for IPO include octreotide and erythromycin to improve small bowel motility.

Interestingly, 63% of patients with IPO have concomitant ureterohydronephrosis, as identified in our first patient (9). The high association of IPO and ureterohydronephrosis suggests a possible common smooth muscle dysmotility (9). Interstitial cystitis, an uncommon manifestation of SLE, has been repeatedly associated with intestinal manifestations, but we could not document it in our patients. However, Alarcon-Segovia et al (21) reported involvement of the urinary bladder due to interstitial cystitis in 11 of 35 necropsies of patients with SLE who had no lower urinary tract symptoms.

Five prior cases of IPO as a manifestation of SLE have been reported in the pediatric population (Table 1.). In these cases, the histopathological findings were not reported. Munyard and Jaswon (4) described a 15-year-old Indonesian girl who presented with IPO as the first symptom of SLE and was successfully treated with corticosteroids and hydroxychloroquine. Tanaka et al (15) described an 11-year-old patient with suspected SLE who later developed IPO. This patient also had bilateral hydroureters with mild hydronephrosis and a contracted bladder. She was corticosteroid dependent with poor response to immunosuppressant treatment. In a large multicenter retrospective study from France involving 155 children with SLE, 2 presented with IPO as the initial manifestation (22). Recently, the same authors described a patient with intestinal occlusion among a group of 39 patients with childhood-onset SLE and abdominal manifestations (23).

In summary, IPO has been recognized as a rare but important complication of SLE, and it can be the presenting feature of the disease. Eosinophilic enteritis was the cause of IPO in our 2 pediatric cases. We consider visceral eosinophilic myopathy to be an alternative name for this rare entity because it reflects a more detailed histopathology. It also could be a way to separate it from the clinical syndromes that eosinophilic gastroenteritis embraces. Furthermore, SLE should be considered in the differential diagnosis in individuals presenting with IPO to achieve appropriate early medical treatment.

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