Case Report

Pediatric Gastrointestinal Sarcoidosis: Successful Treatment with Infliximab

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ABSTRACT

Gastrointestinal sarcoidosis is a rare disease with very limited data in children. Here we report the first pediatric case of successful treatment with infliximab. The first case was an 8-year-old Saudi girl who presented with fever, weight loss, and abdominal pain that was followed in a few months with hematemesis and development of hepatosplenomegaly. The second case was a 9-year-old Sudanese boy who manifested with vomiting, epigastric pain, and weight loss. On upper endoscopy, both cases demonstrated severe erosive nodular gastric mucosa. Gastric and esophageal biopsies had shown noncaseating granulomatous inflammation. The first case had histopathological evidence of granulomatous hepatitis, and both cases demonstrated lung nodularity on computed tomography chest. The boy had elevated angiotensin-converting enzyme level. Given the multisystem involvement with significant chest findings, tissue findings of granulomatous disease, and negative workup for other causes of granulomatous inflammation, both cases were diagnosed with active disseminated sarcoidosis, and treated with corticosteroids. The girl continued to be symptom-free for 4 years after tapering steroid therapy. The boy had relapses off steroids and the disease was brought into remission for 5 years off steroid therapy by infliximab. Pediatric GI sarcoidosis is a rare disease that exhibits heterogeneity in natural course. The chronic relapsing progressive form of the disease might benefit from infliximab therapy.

Key Words: Atrophic gastritis, children, gastrointestinal sarcoidosis, infliximab, Vitamin B12 deficiency

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Sarcoidosis is a multiorgan systemic disease characterized by the formation of non-necrotizing epithelioid granulomas in the affected organs, including skin, lungs, heart, nervous system, hilar lymph nodes, liver, eyes, and joints. Sarcoidosis occurs mainly in the 20- to 40-year-old age group. The prevalence is reported to be 1–40 per 100,000 in the United States.[1] Sarcoidosis of the gastrointestinal tract (GIT) is reported to be extremely rare. Several autopsy studies found no GI involvement,[2] while another reported gastrointestinal involvement in 2.5%.[2] In contrast, liver follows lymph nodes and lung in the frequency of involvement. About 50%–79% of livers are involved by biopsy and 67–70% by autopsy.[2] Treatment with corticosteroids results in symptomatic improvement in majority of patients. Other steroid-sparing agents that had been used in steroid-dependent or -resistant cases included chloroquine, azathioprine, methotrexate, and cyclophosphamide. Infliximab has been shown to produce clinical improvement and reduce the requirement for corticosteroids in a very small number of adult patients with sarcoidosis.[3]

We report two children with gastrointestinal (GI) sarcoidosis, added to the four cases of GI sarcoidosis already reported in the pediatric literature, and report the first pediatric case of successful treatment with infliximab.

CASE REPORTS

Case 1

An 8-year-old Saudi girl developed persistent daily fever, weight loss, and cough for two months. Her grandmother

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had pulmonary tuberculosis 15 months prior to the onset of symptoms. The family sought medical advice first in a local hospital where investigations revealed bilateral pneumonia, left-sided pleural effusion, and bilateral pulmonary nodules. There was a history of animal contact but no raw milk ingestion. She had normal bowel habits with no jaundice, dysphagia or any other GI symptoms. She had no neurological, rheumatological, ophthalmologic, or dermatological symptoms. Physical examination revealed a pale girl, at 10th percentile for weight and height, and hepatosplenomegaly. The laboratory examination was remarkable for anemia (hemoglobin 7.9 g/dL), erythrocyte sedimentation rate (ESR) of 120 mm/h, and an alanine aminotransferase of 75 U/L (normal, 0–35 U/L), serum calcium 2.6 mmol/L, and low albumin level 31 g/L. Abdominal computed tomography (CT) revealed hepatosplenomegaly and hypodense nonenhancing lesions throughout the liver (variable in size from a few millimeters to 3 centimeters), and multiple enlarged abdominal lymph nodes. Chest CT scan showed basal and peripheral nodular opacities. Tests for mycobacterium tuberculosis (MTB) including tuberculin skin test and serum QuantiFERON showed negative results. Liver biopsy showed noncaseating granulomas [Figure 1]. In light of the strong epidemiological exposure, antituberculous medications were initiated (combination of isoniazid, pyrazinamide, ethambutol, and refampicin). Despite compliance with treatment and proper dosing, the patient persisted to be febrile with further weight loss.

Three months later, the patient presented with repeated episodes of hematemesis and epigastric pain. Upper endoscopy revealed an erosive, hemorrhagic, nodular gastric mucosa over the entire stomach [Figure 2a]. Histopathology of biopsies revealed chronic noncaseating granulomatous inflammation and tests for MTB, and fungal infection on the gastric biopsies were negative. Tests for antibodies associated with inflammatory bowel disease (perinuclear antineutrophil cytoplasmic antibodies, antiouter membrane protein C, and anti-*Saccharomyces cerevisiae* IgA and IgG) showed negative results. Oxidative burst test for chronic granulomatous disease was negative. Serum angiotensin-converting enzyme (ACE) level was 45 U/L (normal, 29–110 U/L).

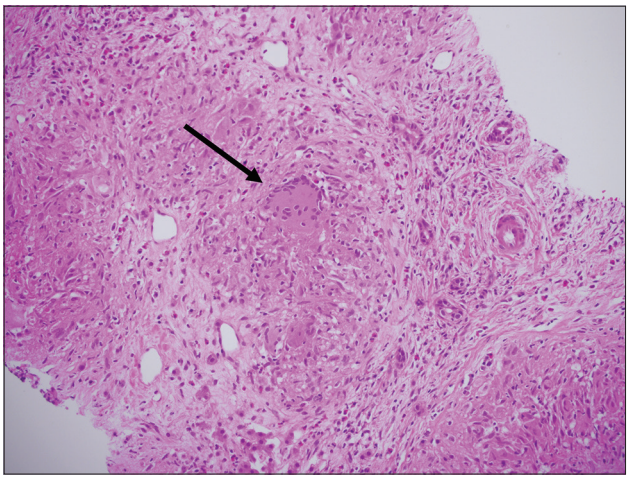

Figure 1: Epithelioid noncaseating granulomas with giant cells in the liver sample (arrow)

Given the multisystem involvement with significant chest findings, tissue findings of granulomatous disease from the liver and upper GIT, together with exclusion of other causes of granulomatous inflammation, the patient was diagnosed with active disseminated sarcoidosis, and intravenous corticosteroids (methylprednisolone 2 mg/kg/day) and omeprazole were started. Ten days after steroid therapy, a repeat of upper endoscopy showed dramatic improvement in the esophageal and gastric appearance [Figure 2b], and a colonoscopy showed no colonic involvement and normal terminal ileum. Biopsies from the esophagus, stomach, and duodenum showed dramatic reduction in the inflammation and disappearance of the granulomatous changes. The corticosteroids were tapered over 3 months. At 6 months after diagnosis, chest and abdomen CT showed resolution of the hepatosplenomegaly, and clearance of the hypodense lesions. During the four years after the diagnosis, the child has remained in remission with normal growth and development.

Case 2

A 10-year-old Sudanese boy presented with frequent episodes of vomiting associated with epigastric pain and weight loss for 6 months. He had no respiratory, neurological, rheumatological, ophthalmologic, or dermatological symptoms. Physical examination showed a pale child with weight and height both below the 3rd percentile for age. Laboratory investigations were remarkable for anemia (hemoglobin 9.8 g/dL), ESR 114 mm/h, serum calcium 2.26 mmol/L, and low albumin level 28 g/L. Endoscopy revealed an erosive, friable, and nodular gastric mucosa over the entire stomach. Histopathology of biopsies revealed chronic noncaseating granulomatous inflammation [Figure 3]. Special stains and cultures for

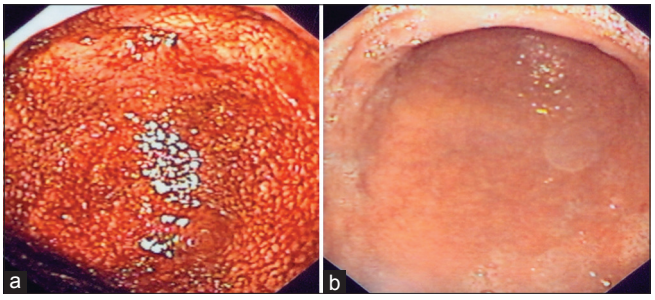

Figure 2: (a) Hemorrhagic erosive gastric mucosa on upper gastrointestinal endoscopy. (b) Healing of the gastric mucosa 10 days after steroid therapy

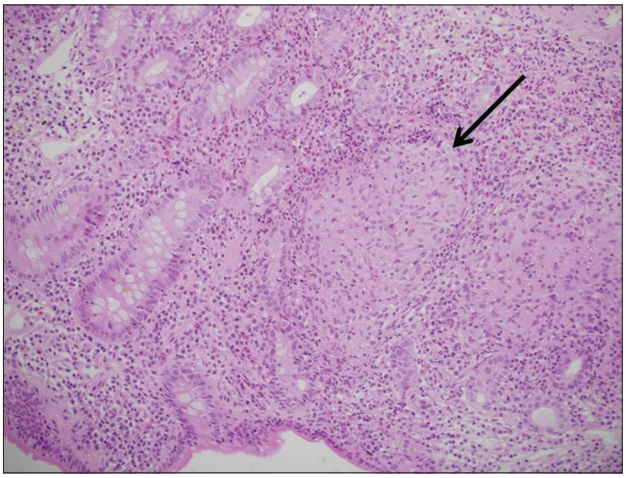

Figure 3: Noncaseating granuloma in gastric biopsies from Case 2 (arrow)

acid-fast and fungal microorganisms showed negative results. Colonoscopy was normal including terminal ileum. CT scan of the chest and abdomen demonstrated multiple, small, centrolobularly distributed nodules within the acini of both lungs and enlarged mesenteric lymph nodes. Ophthalmological examination showed evidence of uveitis. ACE level was elevated at 135 U/L. Similar to Case 1, extensive investigations for infectious, immunologic, and inflammatory conditions associated with GIT granulomatous inflammation were negative.

The combination of tissue findings of granulomatous disease from upper GIT, elevated ACE, systemic involvement, and negative workup for infectious disease suggested systemic sarcoidosis with significant GI involvement. The patient received corticosteroids at 1 mg/kg/day and omeprazole, resulting in resolution of GI symptoms and normalization of activity markers and ACE level. Tapering of corticosteroids over 3 months led to relapse of the disease. Again, remission was induced by a course of steroids supplemented by mesalamine (Pentasa 50 mg/kg/day) and azathioprine (up to 2.5 mg/kg/day) to maintain remission. Throughout the 4-year follow up, the course of the disease was punctuated by several relapses on tapering of corticosteroids and later development of vitamin B_{12} deficiency anemia: hemoglobin 10.6 gm/dL, macrocytosis (MCV 102, normal 80–91 fL), hyperchromasia (MCH 34.5, normal 20–31 pg), low serum vitamin B_{12} 119.2 pmol/L (normal 162–638 pmol/L). Red blood cell folate level was normal at 16.2 nmol/L (normal, 10.4–42.2 nmol/L). Antigastric parietal cell antibodies were negative. The patient received weekly injections of vitamin B_{12} (1 mg weekly) for 6 weeks that raised the level to 231.8 pmol/L with correction of anemia and normalization of his peripheral blood picture.

Considering the steroid dependency of the disease and the short stature of the patient, he was commenced on infliximab 5 mg/kg administered intravenously at 0, 2 and 6 weeks and then every 8 weeks. The patient reported a significant subjective general improvement as well as resolution of his GI symptoms. ESR and ACE concentration returned to normal. A repeat of endoscopy after the 6th dose of infliximab infusion demonstrated loss of gastric folds pattern and loss of normal vascular pattern; otherwise there were no more erosions or friability. Biopsies from the gastric mucosa showed a marked reduction of inflammation, atrophic gastric glands, and absence of granulomas. At 5 years posttreatment with infliximab, the patient remains in remission off corticosteroids.

DISCUSSION

Our report is unique in several aspects. First, we report the first successful use of infliximab in the treatment of steroid-dependent pediatric GI sarcoidosis. Second, the evolution of erosive active gastritis in Case 2 to atrophic chronic gastritis and subsequent development of vitamin B_{12} deficiency has never been reported in the pediatric literature. Third, our two cases are the youngest children with pediatric GI sarcoidosis yet reported. We conducted a search in the English medical literature using the terms "Gastrointestinal" and "Sarcoidosis" coupled with either "children," "pediatric," or "childhood" in various combinations in PUBMED, MEDLINE, EBMASE, and OVID search engines (1966–2013). This strategy was supplemented by a manual search of the bibliographies from all retrieved publications. Four cases of pediatric GI sarcoidosis were found in the literature[4–7] and are summarized in Table 1.

The main difficulty in establishing the diagnosis of GI sarcoidosis is differentiation from Crohn's disease (CD) However, there are several distinctive features that favor the diagnosis of sarcoidosis over Crohn's disease [Table 2]. Although both diseases can have ocular, dermatological, GI, and joint manifestations; lung involvement is common in sarcoidosis and rare in CD. Serum ACE level can be elevated in approximately 55% of children with sarcoidosis[8] but is not elevated in CD. Granuloma in sarcoidosis is usually present in the intramucosal rather than submucosal layer together with lack of intestinal crypt involvement or deformity; lack of overall mucosal architectural distortion and acute inflammation; and prominence of giant cells rather than a loose aggregation of mononuclear histiocytes. Furthermore, Schaumann bodies and birefringent calcifications are commonly observed in sarcoidosis, but rarely in CD.[1,8] Finally, demonstration of granulomas in another extra-intestinal organ strongly supports a diagnosis of sarcoidosis.

In light of the reviewed literature and our two cases, GI sarcoidosis seems to behave in two identifiable forms: an

Table 1: Summary of the pediatric cases of gastrointestinal sarcoidosis reported in the English medical literature

Reference	Age (year)/sex/ ethnicity	Clinical presentation	GIT involvement	ACE	Treatment
Noël *et al*.[4]	15/Male/Afrco-American	Proptosis, diarrhea, early satiety, weight loss, vomiting, duodenal stenosis	Stomach, duodenum	Elevated	Steroids
Brunner *et al*.[5]	12/Female/Turkish	Abdominal pain and skin rash over the legs	Stomach	Elevated	Steroids and MTX
Boyum *et al*.[6]	11/Female/American	Poor growth, diarrhea, abdominal pain-protein-losing enteropathy	Esophagus, colon	Normal	Steroids and MTX
Hourigan *et al*.[7]	15/Male/Afrco-American	Epigastric pain, hematemesis, and melena due to bleeding duodenal ulcer	Stomach, duodenum	Elevated	Steroids
Present paper	8/Female/Saudi	Weight loss, epigastric pain hematemesis, hepatosplenomegaly	Esophagus, stomach, duodenum, liver	Normal	Steroids
	10/Male/Sudaneese	Vomiting, epigastric pain, weight loss	Esophagus, stomach, duodenum	Elevated	Steroid dependent, infliximab

ACE: Angiotensin-converting enzyme, GIT: Gastrointestinal tract, MTX: Methotrexate

Table 2: Features that differentiate between gastrointestinal sarcoidosis and Crohn's disease

Differentiating features	Gastrointestinal sarcoidosis	Crohn's disease
Predominant age of involvement	Young adulthood (rare in children)	Pediatric/ adolescence and young adulthood
Organ involvement		
Lung	Common	Rare
Liver (granulomatous hepatitis)	Common	Rare
Stomach	Most common	Uncommon
Laboratory		
Elevation of ACE	Common	None
Positivity of ASCA	Rare	Common
Histological		
Noncaseating granuloma	Intramucosal layer	Submucosal layer
Intestinal crypt involvement or deformity	Uncommon	Common
Mucosal inflammation	None-to-mild	Moderate-to-severe
Schaumann bodies birefringent calcifications	Common	Rare

ACE: Angiotensin converting enzyme, ASCA: Anti-Saccharomyces cerevisiae antibodies

acute form that responds dramatically to a tapering course of corticosteroids without further relapses, similar to that in Case 1, and a chronic relapsing progressive form that is steroid dependent or refractory necessitating a secondline therapy, similar to that in Case 2. In the latter form, if the disease is not controlled early, granulomatous inflammation will eventually diminish, and progressive fibrosis can occur.[9] The occurrence of pernicious anemia-like picture in Case 2 was probably secondary to the development of atrophic gastritis and progressive glandular loss that led to a state of achlorhydria and subsequent vitamin B_{12} malabsorption. Normal terminal ileum and negative antiparietal antibodies in Case 2 further support our postulation that achlorhydria was the underlying cause of Vitamin B_{12} deficiency.

In sarcoidosis, tumor necrosis factor-alpha (TNF-α) has been demonstrated to play an essential role in the formation of non-caseating granulomas, with macrophages being the main source of TNF-α. Tumor necrosis factor-alpha facilitates macrophage-CD4 + cells interactions, leading to inflammation and granuloma formation.[9] Also TNF-α was shown to act synergistically with interleukin-1 to stimulate synthesis of cytokines such as transforming growth factor-beta which is involved in fibrogenesis.[9] Therefore, there is a rationale for the blockade of TNF-α, using infliximab. In this report, we have demonstrated that infliximab could be used effectively in the treatment of steroid-dependent pediatric GI sarcoidosis. The optimal dose, duration of therapy, and stage at which infliximab therapy should be initiated in patients with GI sarcoidosis is yet to be determined in a large prospective multicenter study.

CONCLUSION

Pediatric GI sarcoidosis is a rare disease that exhibits heterogeneity in natural course. The chronic relapsing progressive form of the disease might benefit from infliximab therapy.

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Conflicts of interest
There are no conflicts of interest.

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