

Intractable colitis associated with chronic granulomatous disease in a young girl

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Received: 13 June 2014, Revised: 9 December 2014, Accepted: 6 January 2015

SUMMARY: Yaman A, Kuloğlu Z, Doğu F, İkinciogulları A, Ensari A, Çiftçi E, Kansu A. Intractable colitis associated with chronic granulomatous disease in a young girl. Turk J Pediatr 2015; 57: 189-191.

Chronic granulomatous disease (CGD) is an autosomal recessive or X-linked disorder caused by NADPH oxidase deficiency leading to an impaired ability of reactive superoxide anion and metabolite formation and recurring severe bacterial and fungal infections, with a high mortality rate. Diarrhea, colitis, ileus, perirectal abscess formation and anal fissures are reported gastrointestinal findings in these patients. We report a case of intractable colitis associated with CGD in a young girl.

Key words: chronic granulomatous disease, colitis, children.

Chronic granulomatous disease is a primary immune deficiency syndrome caused by X-linked or autosomal recessive mutations effecting the NADPH oxidase enzyme system. In addition to various infections, gastrointestinal involvement such as disrupted motility, obstruction and ulceration may be seen in up to 50% of patients.¹

Colitis associated with CGD resembles that of inflammatory bowel disease both histopathologically and clinically. The pathological mechanisms leading to colitis are not clearly defined, but increased antigen exposure due to diminished phagocytosis may be an important factor².

Here we present a case of a young girl with unusually early-onset CGD-associated colitis, which was aggressive and unresponsive to treatment.

Case Report

The patient was a young girl, aged 27 months. She was born at 36 gestational weeks weighing 2060 g, following an in vitro fertilization-induced twin pregnancy. She was diagnosed with CGD by nitroblue tetrazolium assay at 7 months of age after evaluation for

frequent lower respiratory tract infections and recurrent lymphadenitis. Co-trimoxazole and itraconazole prophylaxis were started. At the age of 8 months, she developed tuberculous lymphadenitis, regression of the lesion occurred during antituberculosis treatment. Her parents were nonconsanguineous. Her twin brother also had CGD. Her mother and father had both lost two siblings at young ages for unknown reasons.

Bloody diarrhea first began at the age of 2 years. Diarrhea occurred 7-8 times/day for 10 days, with occasional accompanying nausea and vomiting. Before referral to our unit, metranidazole was started in a local hospital, but no improvement was noted. Her weight was 12 kg (50%), and her height was 83 centimeters (10-25%). Except for pallor, weakness and perianal dermatitis, her physical examination was unremarkable. Laboratory investigations revealed hypoalbuminemia (3 g/dl, normal 3.8-5.4 g/dl), an elevated erythrocyte sedimentation rate (38 mm/hour, normal < 20 mm/hour) and CRP (20.2 mg/L, normal; < 3 mg/L). Stool examination revealed 1-2 fecal leukocytes and 2-3 red blood cells. Stool culture was negative, as were tests for bacteria, viruses, fungi and parasites. Colonoscopy showed pancolitis with

diffuse mucosal erythema, mucosal friability and extensive multiple hemorrhagic ulcers. Histopathological examination revealed severe diffuse active colitis characterized by focal ulceration, crypt distortion and cryptitis (Fig. 1). She was diagnosed with ulcerative colitis-

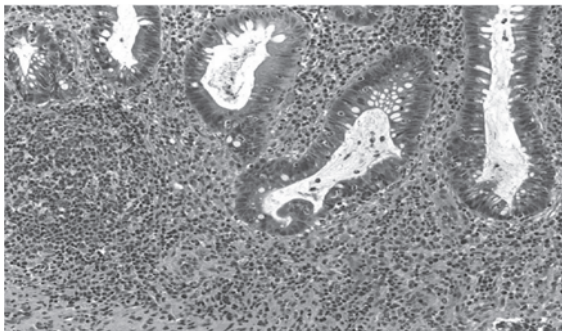


Fig. 1. Apparent crypt distortion, cryptitis and mixed inflammation in the lamina propria, forming lymphoid follicles (HE, x200).

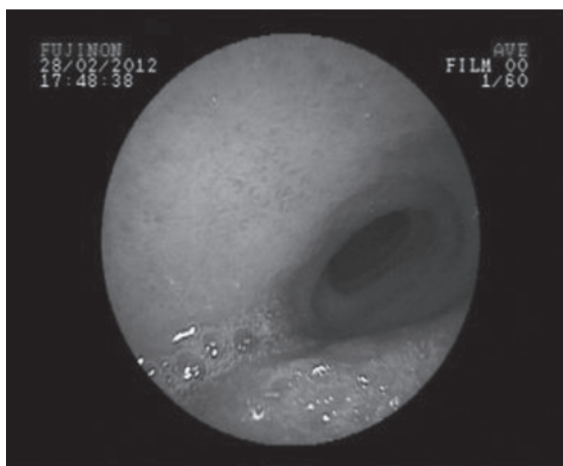


Fig. 2. Endoscopic appearance of the sigmoid colon.

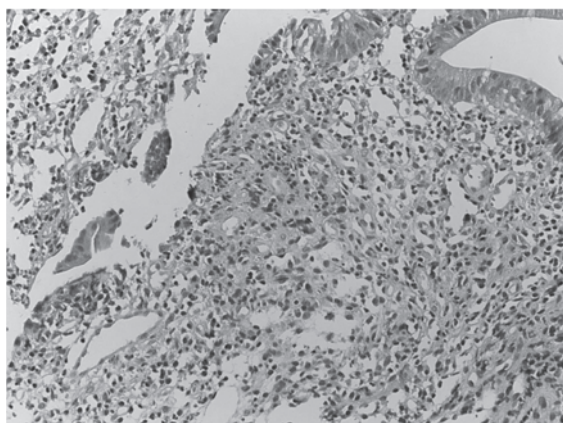


Fig. 3. Duodenal mucosa, showing histiocytic infiltration in the lamina propria (HE, x200).

like colitis associated with CGD; mesalazine (50 mg/kg/day) was initiated. Her symptoms resolved within two weeks.

After 3 months, watery and bloody diarrhea recurred in the patient following varicella infection. Although the infection was under control, her colitis worsened (25-30 movements per day), and she lost weight. All tests were negative for known infectious agents in stool and blood. Intravenous methylprednisolone, loperamide and octreotide infusion therapies failed to decrease stool volume and quantity. She became dependent on total parenteral nutrition. Shortly after, daily subcutaneous granulocyte colony-stimulating factor (G-CSF) (10 µg/kg/dose) was added to the treatment regimen but failed to improve the clinical picture. Upper and lower gastrointestinal endoscopies were repeated. Endoscopy showed all gastrointestinal mucosa to be hemorrhagic, fragile and ulcerated (Fig. 2). Histopathology revealed uniform findings throughout the upper and lower gastrointestinal mucosa, granuloma-like formation of epithelioid histiocytes in duodenal samples and infrequent pigmented histiocytes in the rectum. On the basis of these findings, she was diagnosed as CGD enterocolitis (Fig. 3). As medical therapies had failed and she had no available donor for hematopoietic stem cell transplantation, mesenchymal stem cell transplantation was planned. Unfortunately, the patient died during the planning process, due to candida sepsis.

Discussion

About half of patients with CGD show evidence of gastrointestinal system (GIS) involvement, which is an important cause of morbidity and mortality. No portion of the GIS is spared, although involvement of the esophagus is rare. Progressive dysphagia, disturbances in motility, esophagitis and epigastric pain are some of the upper gastrointestinal symptoms and findings. Eosinophilic gastritis, gastric abscess formation and gastric wall thickening causing obstruction have been reported¹. Duodenal biopsy revealed typical findings for CGD in our case; however, no esophagitis or upper gastrointestinal strictures were observed in upper GIS endoscopy. Among the symptoms of colitis, bloody diarrhea was predominant in our case, suggesting an association with

ulcerative colitis. The etiology, prevalence and inflammatory process of CGD colitis are unclear. Colitis and enteritis are observed in 17% of patients with CGD². Colitis in CGD resembles that seen in other types of inflammatory bowel disease (IBD); the disorders are often hard to differentiate. However, the mechanism of inflammation and the profile of inflammatory mediators in CGD colitis significantly differ from that in other IBD³. The etiology of colitis is obscure; increased antigenic exposure due to failure of phagocytosis is speculated to be the inciting factor. The severity of colitis is not related to patient age or duration of GIS symptoms. Apart from diarrhea, obstruction due to bowel wall thickening has been reported^{1,4}.

Endoscopically, it is difficult if not impossible to differentiate CGD colitis from other types. Patchy, swollen, fragile mucosa, a cobblestone appearance, pseudomembranes, pseudopolyps and petechial hemorrhages may be seen. Although macroscopic findings are similar to those of IBD, microscopy does show differences. The most typical histopathologic finding of CGD colitis is eosinophilic inflammation, along with large pigmented macrophages and a scarcity of neutrophils in the infiltrate. Degranulating eosinophils and granulomas may be seen in the lamina propria. The absence of neutrophils and the pigmented nature of the granulomas help to differentiate the findings from those seen in Crohn's disease⁵. In our patient, uniform histopathology throughout the gastrointestinal mucosa, granuloma-like formation of epithelioid histiocytes in the duodenal and rectal mucosa and the presence of pigmented histiocytes favored the diagnosis of CGD colitis. Barium studies of the GIS may show wall thickening, a cobblestone appearance, fistulae and strictures. Our case showed a normal GIS barium series, except for decreased colonic transit time.

No consensus exists regarding therapy of CGD colitis; however, many authors agree that immunosuppressive drugs should be withheld, considering the disturbed neutrophil function⁶. Sulfasalazine is recommended as first-line therapy⁷. In our case, remission of

the first attack of colitis was achieved with sulfasalazine, but this therapy was not effective in combatting the next attack. Case reports of successful implementation of G-CSF therapy exist in the literature, but the mechanism of the effect is not clear⁸. Our patient showed no improvement despite an adequate dosage and duration of G-CSF therapy. Allogenic stem cell transplantation is the definitive treatment option, but we failed to find a suitable donor for our patient. During the process of planning for mesenchymal cell transplantation, lethal candida sepsis developed.

In conclusion, we have reported a young girl with severe enterocolitis due to CGD, who did not respond to any therapy and eventually died. In view of the clinical and pathological similarities of CGD colitis to IBD, current treatment options are based on established IBD therapies; however, determination of the optimal treatment of colitis secondary to CGD is necessary.

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