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Cyclosporine Treatment of Intractable Colitis in Chronic Granulomatous Disease

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INTRODUCTION

Chronic granulomatous disease (CGD) is a genetically determined disorder characterized by a relative inability of the patient's phagocytic cells to kill catalase-producing bacteria and fungi.⁽¹⁾ This decrease in intracellular killing leads to a marked increased susceptibility to infection. Gastrointestinal manifestations, such as colitis, have also been seen in CGD.⁽²⁾ Typically, CGD patients with colitis are treated with steroids and antimicrobials, although this therapy is not uniformly successful.⁽²⁾ Recently, cyclosporine has been used successfully to treat a single CGD patient with colitis who failed to respond to steroids.⁽³⁾ We report another patient with CGD and intractable colitis who was successfully treated with cyclosporine, thereby providing additional evidence that cyclosporine may be effective therapy in such patients who are resistant to the usual modes of therapy.

CASE REPORT

An 8-year-old male was diagnosed at birth to have X-linked CGD. Infections during his first few years of life included staphylococcal cervical node infections, candidal pneumonia, cellulitis, and perianal abscesses. Gastrointestinal symptoms developed at age 3 years with a progressive increase in bloody diarrhea. Stool cultures were repeatedly negative. Colonoscopy at age 4 revealed chronic inflammation, and biopsies revealed focal inflammatory disease with pigmented macrophages typically seen in CGD inflammatory bowel disease (Figure 1). He was started on mesalamine 5-aminosalicylic acid enemas with minimal relief of the diarrhea. He was then started on prednisone at 1 mg/kg per day with initial improvement of his symptoms. Over the next few years, he had multiple hospitalizations for recrudescence of his colitis. He was treated with different regimens of prednisone, metronidazole, and 6-mercaptopurine and eventually was maintained on 6-mercaptopurine at 1 mg/kg per day and prednisone at 0.75 mg/kg every other day. Because of the multiple hospitalizations and immunosuppressive therapy, his growth velocity was initially slightly delayed by age 4, but returned to normal around age 6. However, his height and weight remained below and parallel to the 3rd percentile. His bone age was mildly delayed with normal growth hormone and somatomedin levels.

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At 8-and-a-half years of age, he presented with cramping abdominal pain, watery diarrhea (8–10 times per day), anorexia, and rectal bleeding. Erythrocyte sedimentation rate was increased to 82 mm/hour, and stools for culture were negative on several occasions. He was hospitalized after 1 week of failing to respond to an increase in the prednisone dose to 1.5 mg/kg per day. During the hospitalization, he had two abdominal CT scans that revealed inflammatory colitis most prominent in the transverse colon and rectosigmoid. Rectal biopsies confirmed active chronic colitis typically seen in CGD.

After 1 week of failing to respond to 3 mg/kg per day of intravenous solumedrol and intravenous antibiotics, he was started on a 7-day course of intravenous cyclosporine at 4 mg/kg per day divided every 12 hours. The cyclosporine levels were monitored using a standard radioimmunoassay and maintained between 100 and 200 ng/ml. The medication was tolerated well and associated with a dramatic response in 48 hours; gross bleeding ceased and bowel movements diminished to twice daily and became more formed. He was then observed off cyclosporine for 4 days and advanced to regular diet with only a mild increase in stool frequency and no significant bleeding.

He was discharged home on oral prednisone at 1.5 mg/kg per day, 6-mercaptopurine, and metronidazole. Follow-up at 1 month demonstrated continued control of his bowel symptoms, with stool frequency decreased to two to three formed stools per day. On the regimen of prednisone tapering to 1 mg/kg per day, a reduction in sedimentation rate to 20 mm/hour was noted.

Two months after discharge, he was treated for a right lower lobe pneumonia with oral cefuroxime and trimethoprim/sulfamethoxazole. His gastrointestinal symptoms continued in good control with one to two formed soft stools and no evidence of bleeding. At 11 months after treatment with intravenous cyclosporine, he has been doing well and weaned to 0.5 mg/kg every other day of prednisone and prophylactic metronidazole. His sedimentation rate returned to normal at 15 mm/hour, and he was able to tolerate an unrestricted diet.

DISCUSSION

Gastrointestinal manifestations of CGD include gastric outlet obstruction, colitis, appendicitis, hepatic abscesses, salmonella enteritis, and cholecystitis.⁽⁴⁾ Colitis affects about 15% of patients with CGD and presents with chronic, bloody diarrhea that can be difficult to manage. Endoscopy biopsy typically shows focal inflammation with pigmented macrophages such as seen in our patient.⁽⁴⁾ The usual therapy for colitis in CGD includes corticosteroids and antimicrobial agents.⁽²⁾ However, some of these patients can be particularly refractory to typical medical management. Cyclosporine has been used to treat colitis in patients without CGD,^(5,6) but has not been frequently reported as therapy in patients with CGD.

One previous patient with CGD and intractable recrudescing inflammatory bowel disease was recently treated with intravenous cyclosporine at 4 mg/kg per day with rapid improvement in 3 days.⁽³⁾ Within days of completing 7 days of cyclosporine therapy, he developed *Paecilomyces variotti* pneumonia, which was successfully treated with amphotericin B. His bowel symptoms remained in good control at a follow-up visit at 9 months, and symptoms were controlled on daily metronidazole and mesalamine. With our patient, the response was equally rapid and dramatic. Although our patient did develop pneumonia, it was 3 months after his cyclosporine treatment, and therefore it is difficult to determine whether this infection was related to the medication or a manifestation of his underlying CGD. While surgical therapy such as total colectomy with ileostomy is another

option,⁽²⁾ the use of cyclosporine may be reasonable before such irreversible treatment is employed.⁽³⁾

When dealing with an already immunosuppressed patient such as this CGD patient, the benefits of potent therapy that diminishes T-cell function, such as steroids, 6-mercaptopurine, or cyclosporine, must be weighed against their potential risks. The brief course of intense cyclosporine therapy provided marked improvement; however, one must also weigh the risk of increasing susceptibility to infections in an immunocompromised host. In conclusion, this case demonstrates a second instance in which cyclosporine produced rapid and dramatic improvement for intractable colitis in a patient with CGD. Cyclosporine may therefore be considered as an option to irreversible colectomy in the CGD patient with intractable colitis unresponsive to typical medical therapy.

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FIG. 1. Photograph showing biopsy of colon with chronic inflammatory cells. The pigmented cells in the center of the photo are clustered pigmented macrophages. These findings are typical of colitis in chronic granulomatous disease.