CASE REPORT | INFLAMMATORY BOWEL DISEASE

Chronic Granulomatous Disease Mimicking Colonic Crohn’s Disease Successfully Treated with Infliximab

Armando Peixoto, MD1,2, Rosa Coelho, MD1,2, Tiago Maia, MD3, António Sarmento, PhD4, Fernando Magro, PhD1,2,5,6, and Guilherme Macedo, PhD1,2

1Department of Gastroenterology, Centro Hospitalar São João, Porto, Portugal
2WGO Porto Training Center, Porto, Portugal
3Department of Pathology, Centro Hospitalar de São João, Porto, Portugal
4Department of Infectious Diseases, Centro Hospitalar São João, Porto, Portugal
5Department of Pharmacology and Therapeutics, Faculty of Medicine, University of Porto, Porto, Portugal
6MedInUP, Center for Drug Discovery and Innovative Medicines, University of Porto, Porto, Portugal

ABSTRACT

Chronic granulomatous disease (CGD) is a genetically induced disease caused by mutations in one of the components of the NADPH-oxidase in phagocytes, characterized by life-threatening bacterial and fungal infections and granuloma formation. Treatment includes prevention of infectious complications and immunomodulation. However, a standard strategy is not yet defined. The authors report an X-linked CGD female carrier who presented during adulthood with diarrhea and colorectal ulcers, with high impairment of quality of life. Induction with infliximab 5 mg/kg (weeks 0, 2, and 6) with infectious prophylaxis was initiated. She continued infliximab 5 mg/kg every 8 weeks with complete symptomatic response at 15 months.

INTRODUCTION

Chronic granulomatous disease (CGD) is a rare primary immunodeficiency disease caused by a defect in a subunit of NADPH oxidase; 70% of cases are X-linked and associated with CYBB mutation, with defective production of gp91phox. This mutation leads to decreased macrophage capacity to eliminate bacteria and fungi. Female carriers can present with gastrointestinal (GI) symptoms similar those seen in inflammatory bowel disease. Treatment of symptomatic carriers includes prevention of infectious complications and immunomodulation, although a standard strategy is not defined.

CASE REPORT

A 41-year-old woman presented with chronic diarrhea for 3 years associated with significant weight loss. An ileocolonoscopy showed multiple well-defined rectal ulcers (Figure 1). Biopsies revealed reactive hyperplasia of the superficial and cryptic epithelium with extensive ulceration translated by the presence of exudate, as well as epithelioid granulomas with nucleated giant cells (Figure 2). Histiocytes containing brown pigment in the cytoplasm were observed in the lamina propria. Biopsies from the colon showed mild chronic inflammatory changes with an epithelioid granuloma. Immunohistochemistry for cytomegalovirus, periodic acid-Schiff, and Ziehl-Neelsen stains were negative. Abdominopelvic computed tomography enterography showed only circumferential thickening of the rectum.

After reviewing the patient’s medical history, we found that one of her children had died at the age of 9 years with a septic complication due to CGD. A cellular immunity and oxidative burst of granulocytes study showed a shortfall
in the production of oxidative metabolites in 35% of granulocytes, therefore establishing the diagnosis of CGD carrier linked to chromosome X.

A repeat colonoscopy was performed due to her high risk for recurrent infections. A rectal ulcer biopsy was positive for Nocardia through polymerase chain reaction (PCR). After excluding cerebral disease, she was started on cotrimoxazole for 3 months, followed by continuous weekly prophylaxis. Forty-two days after colonic biopsies were performed, a positive cultural result for mycobacterium tuberculosis (TB) was depicted. Standard anti-TB therapy was started, consisting of isoniazid, rifampicin, ethambutol, and pyrazinamide; symptoms persisted after 12 months of treatment.

Three months after the end of antibiotics, a new colonoscopy revealed that the ulceration had extended to the proximal colonic segments. Histological evaluation showed similar histological findings to what was described initially, including pigmented histiocytes and epithelioid granulomas (Figure 3). Biopsies for Mycobacteria and Nocardia were negative; however biopsies were now positive for herpes simplex 1 PCR and Aspergillus PCR. There was no evidence of herpes viremia. Blood cultures for fungi were also negative. The patient was treated with valacyclovir and subsequently maintained prophylaxis with itraconazole. After controlling these infections, she continued to complain of diarrhea (>10 bowel movements per day) with further weight loss. The patient was reluctant to start systemic steroids, so a multidisciplinary meeting led to the initiation of infliximab 5 mg/kg with cotrimoxazole and itraconazole prophylaxis.

After 15 months of infliximab 5 mg/kg every 8 weeks, she had decreased her bowel movements to 3 per day and gained 5 kg. Subsequent laboratory tests showed consecutively normal complete blood counts, increased serum albumin, and normal C-reactive protein. During this period, the patient did not have any infectious complications. As such, anti-tumor necrosis factor (anti-TNF) therapy will be maintained indefinitely under close surveillance for the appearance of complications, especially infectious complications.
DISCUSSION

CGD is a rare, genetically heterogeneous disease occurring in 1:250,000 births and caused by mutations in any one of the five components of the NADPH oxidase in phagocytes. It is characterized by recurrent life-threatening bacterial and fungal infections and granuloma formation, and, contrary to our case, most patients are diagnosed before age 5 years.

Although female carriers of X-linked CGD have been previously considered to be unaffected, it is increasingly recognized that they may suffer from problems similar to those experienced by CGD patients. It is known that female carriers generally do not have an increased rate of infections. Nonetheless, as with our patient, they may be more predisposed to have inflammatory manifestations associated with CGD. GI manifestations of CGD include abdominal pain, diarrhea, colitis, proctitis, strictures, fistulae, and obstruction. In a series of 140 CGD patients, 43% of X-linked and 11% of autosomal recessive CGD patients had GI manifestations. Because Crohn’s disease is much more frequent than CGD, it is important to identify distinctive histopathological patterns. However, knowledge is still scarce.

Pigmented histiocytes within the lamina propria present in colonic biopsies from patients with CGD have been suggested as the major distinctive feature.

Corticosteroids are the most commonly used therapy for inflammatory manifestations of CGD. However, immunosuppressors are usually required for long-term maintenance. Several options are described in the literature, including mesalazine, thalidomide, gamma-interferon, azathioprine, and anti-TNF agents, but none are formally recommended. In extreme cases, surgery and hematopoietic cell transplantation can also be considered, with the latter being potentially curative, although associated with a significant mortality.

In addition to effective maintenance of clinical remission induced by corticosteroids, anti-TNF alpha agents can be effective in inducing clinical remission. However, an increased risk of serious infectious complications has been described compared with other conditions. So, if their use is to be considered, the intensification of antimicrobial prophylaxis is critical, as well as an aggressive treatment of infectious complications.

There are several reports of invasive aspergillosis in adults with Crohn’s disease treated with infliximab. Because Crohn’s-like colitis can be the initial or sole manifestation of CGD in some cases, it is possible that these cases may actually represent undiagnosed CGD. In a cases series including 5 patients, infliximab was highly effective in the treatment of refractory CGD-associated colitis but was associated with serious bacterial and fungal infections, including 2 deaths. However, these were patients with the full spectrum of the disease, so in these cases careful attention should be given before starting these therapies because of the high risk of serious infections. There is not enough evidence of the use in symptomatic carriers to draw a conclusion on the risks and benefits. However, due to the unwillingness of our patient to start corticosteroids, and the need for rapid and effective induction of clinical response, we chose to start infliximab therapy under close surveillance for infectious complications.

DISCLOSURES

Author contributions: A. Peixoto, R. Coelho, and F. Magro wrote and critically revised the manuscript. T. Maia, A. Sarmento, and G. Macedo revised the manuscript for important intellectual content. F. Magro is the article guarantor.

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REFERENCES

1. Battersby AC, Cale AM, Goldblatt D, Gennery AR. Clinical manifestations of disease in X-linked carriers of chronic granulomatous disease. J Clin Immunol. 2013;33(8):1276–84.
2. Wolach B, Scharf Y, Gavriel R, de Boer M, Roos D. Unusual late presentation of X-linked chronic granulomatous disease in an adult female with a somatic mosaic for a novel mutation in CYBB. Blood. 2005;105(1):64–6.
3. Roos D, de Boer M. Molecular diagnosis of chronic granulomatous disease. Clin Exp Immunol 2014;175:139–49.
4. Liu S, Russo PA, Baldassano RN, Sullivan KE. CD-68 expression is markedly different in Crohn’s disease and the colitis associated with chronic granulomatous disease. Inflamm Bowel Dis. 2009;15(12):1213–7.
5. Mitomi H, Mikami T, Takahashi H, et al. Colitis in chronic granulomatous disease resembling Crohn’s disease: Comparative analysis of CD-68 positive cells between two disease entities. Dig Dis Sci. 1999;44:452–6.
6. Quie PG, Belani KK. Corticosteroids for chronic granulomatous disease. J Pediatr. 1987;111:393–4.
7. Noel N, Mahlaoui N, Blanche S, et al. Efficacy and safety of thalidomide in patients with inflammatory manifestations of chronic granulomatous disease: A retrospective case series. J Allergy Clin Immunol. 2013;132:997–1000.
8. Uzel G, Orange JS, Polnik N, Marciano BE, Heller T, Hallan SM. Complications of tumor necrosis factor-α blockade in chronic granulomatous disease-related colitis. Clin Infect Dis. 2010;51(12):1429–34.
9. Seger RA. Hematopoietic stem cell transplantation for chronic granulomatous disease. Immunol Allergy Clin North Am. 2010;30:195–208.