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Colonic Crohn's Disease after Cardiac Transplantation: Case Report and Literature Review

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Abstract

Inflammatory bowel disease (IBD) after solid organ transplantation is rare. We report new-onset Crohn's disease successfully treated with anti-tnfa therapy in a cardiac transplantation recipient. Our case highlights the importance of including IBD in the differential of chronic diarrhea despite significant immunosuppression and suggests that anti-tnf alpha therapy is effective in post-transplant IBD.

Introduction

The etiology of inflammatory bowel disease (IBD) involves an aberrant activation of the mucosal immune system potentially in response to intestinal microbiota. The diagnosis of new-onset IBD after solid organ transplantation (SOT) may be delayed due to concerns for infection or post-transplant malignancy and treatment may be more complicated due to existing immunosuppression. We report a pediatric heart transplant recipient who developed colonic Crohn's disease while on significant immunosuppression and who responded to anti-TNF therapy.

Case Presentation

A 17 year old male presented with chronic diarrhea, malnutrition, dehydration, and acute kidney injury. He was taking tacrolimus, sirolimus, and mycophenolate mofetil to prevent rejection after orthotopic cardiac transplantation six years prior for restrictive cardiomyopathy. Notable laboratory studies were CRP 14 (normal < 1.0); hemoglobin 8 (g/dl), albumin 2.4 (g/dl, normal 3.5–5); fecal calprotectin 1205 mcg/g (15–50). ANCA/ASCA testing was not performed. Stool studies were negative for infectious etiology. Abdominal computed tomography (CT) showed thickening of the entire colon without lymphadenopathy. Esophagogastroduodenoscopy was normal. Ileocolonoscopy identified numerous pan-colonic deep and wide ulcers with edema and fibrinous exudate and normal terminal ileum (Figure 1). Histology demonstrated chronic active colitis. Immunohistochemical staining for CMV revealed multiple foci of positivity but without characteristic viral cytopathic changes. Four serum PCR tests for CMV were negative (< 100cpoies/ml). Symptoms persisted despite IV gancyclovir and a repeat colonoscopy three months later showed extensive fibrinous exudates and patchy serpiginous linear ulceration

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throughout the colon with normal intervening areas and normal ileum (Figures 2, 3). Histology showed moderate to severe chronic active colitis with skip lesions, no granulomas, and negative stains for CMV and adenovirus. MR enterography showed pancolonic wall thickening with normal small bowel. A diagnosis of Crohn's colitis was made. Infliximab, 10 mg/kg produced a rapid response after one dose. Within a few weeks of treatment initiation, parenteral nutrition was discontinued and he achieved continuous remission for greater than one year while continuing infliximab.

Discussion

IBD occurring after SOT is rarely described in pediatric literature. Causes of colitis after SOT include infection, allergy, ischemia, post-transplant malignancy, drug-related, and IBD. Adult literature reports associations with acute CMV infection and use of tacrolimus in the development of IBD after SOT. (1) Our patient tested negative for CMV. Colitis in patients on mycophenolate mofetil (MMF) has a wide-range of histopathological features often with a mixed picture of crypt distortion, cryptitis, increased crypt apoptosis, and lamina propria eosinophils. (2) In this patient MMF was discontinued 5 weeks prior to the repeat colonoscopy without clinical improvement. Six children who developed IBD after transplantation did not respond to treatments including tacrolimus, cyclosporine, corticosteroids, and azulfidine (3). The degree of immunosuppression in these patients highlights that fact that the mechanisms of the pathogenesis of IBD are not completely understood.

The pathophysiology of IBD involves interactions between the immune system, the intestinal microbiome, environmental factors, and genetic factors. The innate immune system plays a significant role in IBD. The inflammatory response in the gut involves T helper cell (Th) 1, Th 2, Th17, and T regulatory (Tr) pathways. Tumor necrosis factor (TNF) promotes chemokine secretion from epithelial cells, disrupts the epithelial barrier, and promotes apoptosis of intestinal epithelial cells. Th 2 cytokines (IL-4, IL-5, and IL-13) mediate intestinal inflammation while Th 1 cytokines induce differentiation of naïve CD 4+ T cells into Th1 cells.(4) The proinflammatory Th 17 pathway is associated with Crohn's disease and specific IL-23 gene polymorphisms increase the risk for developing Crohn's disease. Other cytokines, such as IL-1 and IL-6, may play a role in the pathogenesis of Crohn's disease. The aforementioned supports the role of aberrant humoral and cell-mediated immune responses in IBD.

Prior to diagnosis, our patient was treated with immunomodulators (tacrolimus, sirolimus, and mycophenolate mofetil) meant to not only suppress cell mediated but also humoral inflammatory responses. Tacrolimus, an inhibitor of cell-mediated immunity, is a macrolide that prevents the dephosphorylation of the transcription factor NF-AT by calcineurin. This then inhibits T-lymphocyte signal transduction and IL-2 transcription. Sirolimus is a macrolide that prevents the activation of T cells and B cells by inhibiting their response to IL-2. Sirolimus is not commonly used as a first line agent in IBD but has been used to treat refractory Crohn's disease. Mycophenolate mofetil is an immunosuppressant that works to reversibly inhibit inosine monophosphate dehydrogenase in purine biosynthesis which is necessary for the growth of T cells and B cells. Thus, our patient was on an

immunosuppressive regimen that should have theoretically treated IBD by downregulating cell-mediated and humoral response. Recently, sirolimus has been shown to promote expression of IL-12, IL-23 and TNF alpha (5) and to not suppress lipopolysaccharide induced tnf-alpha production (6). Therefore, there are theoretical reasons that anti-tnf blockade might be helpful in addition to the tacrolimus/sirolimus regimen he was on.

The incidence and preferred treatment course of de novo IBD after solid organ transplantation is difficult to ascertain. Before anti-TNF availability, 6 children developed IBD after transplantation and did not respond to azulfidine, corticosteroids, tacrolimus, or cyclosporine (7). A more recent review of 30 cases of IBD after heart or kidney transplant reports remission in 47% though conventional medical and nutritional therapies, 10% with anti-TNF α therapy; 20 % underwent colectomy and 20% had persistent symptoms. One patient died due to colon cancer (8).

Conclusion

Our case demonstrates that therapy with anti-TNF α therapy is effective in posttransplant IBD. The development of IBD following SOT and while on significant immunosuppression highlights the complexity of immune dysregulation in IBD and the challenges of diagnosis and treatment. Further studies are warranted to not only explore the role of certain immunosuppressive regimens but also the mechanisms of interaction of these regimens, and their potential role in the development of IBD.

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Figure 1.
Initial colonoscopy showing deep, wide colonic ulcers

Figure 2.
Follow-up colonoscopy with edema, friability deep and wide, serpiginous ulcers, and
fibrinous exudate.

Figure 3.
Follow-up colonoscopy with edema, friability deep and wide, serpiginous ulcers, and fibrinous exudate.