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A Case Report of Acute Cellular Rejection Following Intestinal Transplantation Managed With Adalimumab

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A Case Report of Acute Cellular Rejection Following Intestinal Transplantation Managed With Adalimumab

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ABSTRACT

There is a higher incidence of acute cellular rejection (ACR) in small bowel transplantation (SBT) compared with transplantation of other solid organs. Although there are reports on the use of infliximab to successfully treat ACR refractory to other treatments, there are no reports, to our knowledge, regarding the use of adalimumab. We present a case of a female patient with a history of Crohn's disease who underwent an isolated SBT and developed an episode of severe ACR. She was initially treated with methylprednisolone, thymoglobulin, basiliximab, and a dosage adjustment of tacrolimus. Results of repeat endoscopies and biopsies revealed no significant improvement. The patient initiated treatment with adalimumab every 2 weeks for a total of 6 months, in addition to maintenance treatment with prednisone and tacrolimus. Subsequent evaluations showed gradual improvement to normal mucosa and villi without ulceration. A regimen that incorporates adalimumab can thus be used to treat ACR after intestinal transplantation. Larger multicenter studies are needed to show the full efficacy of this therapeutic regimen.

PREVIOUS trials have established the efficacy of adalimumab, a human monoclonal antibody directed against tumor necrosis factor (TNF), in achieving and maintaining remission as well as mucosal healing in moderate to severe Crohn's disease [1–3]. Despite advances in biologic therapies in Crohn's disease, severe complications may arise that lead to multiple resections and intestinal failure. Although small bowel transplantation (SBT) is currently a treatment option for Crohn's disease, it is not without complications. Compared with other solid organ transplantations, SBT is associated with a higher incidence of acute cellular rejection (ACR), leading to graft failure in 6.2% at 30 days, 26.4% at 1 year, and 49.9% at 3 years, respectively [4]. Adjunct immunosuppressive agents are being used to address this concern to prevent and treat rejection episodes. There have been successful cases of incorporating the anti-TNF agent infliximab into the treatment of both early- and late-onset ACR refractory to steroid and thymoglobulin therapy in SBT [5,6]. To the best of our knowledge, there have been no specific reports regarding the use of adalimumab. Adalimumab might be expected to have comparable benefits, given that its use in Crohn's disease is similar to that of infliximab [7]. We present a case of a female patient who underwent an isolated SBT for complicated Crohn's disease in which adalimumab was used for ACR refractory to standard immunosuppression.

CASE REPORT

A 38-year-old white woman was diagnosed with Crohn's disease 21 years ago. Despite trials of multiple agents (mesalamine, 6-mercaptopurine, azathioprine, and infliximab), her course was complicated with small bowel perforation and formation of 3 enterocutaneous fistulas requiring surgical repair. Infliximab was discontinued after a severe allergic response. Two years before presentation, the patient underwent removal of all but a short segment of the small intestine, with resultant short gut syndrome requiring dependence on total parenteral nutrition. She initiated treatment with adalimumab at that time in an attempt to prevent further fistula formation and complications.

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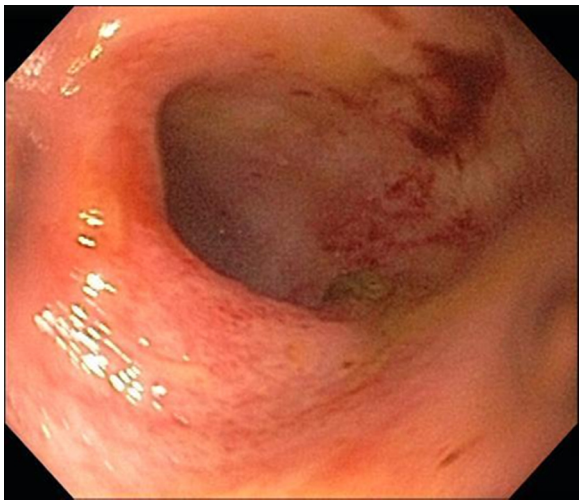

Fig 1. Ileoscopy of the transplanted small intestine. There were macroscopic findings of erythema, ulceration, and bright red blood, which were concerning for acute rejection.

The patient was ultimately referred to the transplant clinic after developing complications of total parenteral nutrition, including progressive cholestasis with fibrosis. She underwent an isolated SBT across a positive crossmatch and initiated treatment with basiliximab, tacrolimus, and prednisone for immunosuppression. Her initial recovery included episodes of increased ileostomy output with renal insufficiency requiring intravenous hydration and the development of steroid-induced diabetes.

Ten months posttransplantation, the patient was admitted with a 7-day history of right lower quadrant abdominal pain, increasing ileostomy output, and generalized malaise. Vital signs on admission were remarkable for fever (39.4°C) and tachycardia (122 beats/min). On examination, the patient had lower abdominal tenderness with no peritoneal signs along with watery stool from her ostomy. Results of laboratory testing were notable for leukocytosis (22.6 K/μL), acute kidney injury (2.2 mg/dL [from a baseline measurement of 1.7 mg/dL]), and a tacrolimus trough level of 7.4 ng/mL. Results of a complete infectious evaluation were unremarkable. She underwent ileoscopy, with macroscopic findings of small intestine erythema, ulceration, and bright red blood (Fig 1). Biopsy results showed features of severe grade three ACR (Fig 2). Donor-specific antigen was negative. She received intravenous methylprednisolone 500 mg/d for 3 doses, 1 dose of basiliximab, 2 doses of thymoglobulin, and dosage adjustment of tacrolimus. A repeat endoscopy was performed and revealed only mild improvement in findings. She was given an additional 2 days of methylprednisolone 250 mg/d along with 2 additional doses of thymoglobulin, and her daily prednisone was increased. A repeat scope was performed, which revealed persistent erythematous mucosa with some villi formation. The transplantation team discussed the case, and treatment with adalimumab was initiated. The patient initially received 2 consecutive daily doses of adalimumab 80 mg. An ileoscopy 10 days later demonstrated initial improvement with less erythematous mucosa and the development of moderate villi that were flat but confluent. The patient exhibited a clinical response with decreased abdominal pain, improved stool consistency, and toleration of an advanced diet. Her discharge immunosuppressive regimen consisted of adalimumab 40 mg every 2 weeks along with titrated adjustments of tacrolimus (trough target level, 8–10 ng/mL) and prednisone (discharged on 20 mg, which was eventually tapered down to 2.5 mg daily). Her repeat scopes continued to show improvement, with those at 3 months and 7 months after admission revealing normal mucosa and villi.

DISCUSSION

Initial attempts to treat this patient's episode of severe ACR with standard therapy failed, and she had persistent mucosal injury. It was only after the incorporation of adalimumab that the patient began to exhibit a more significant response in mucosal healing and villi formation. This response was maintained several months after the episode of ACR by continuing adalimumab as a part of her maintenance regimen.

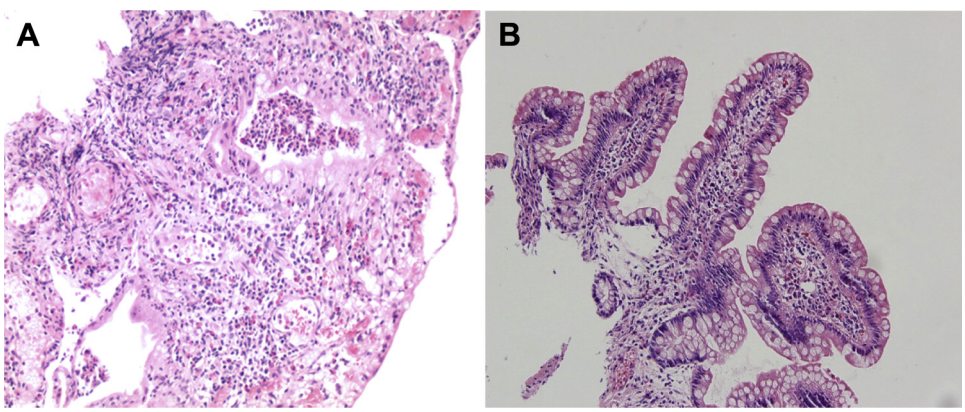

Fig 2. (**A**) Biopsy of transplanted small intestine (shown at 10× magnification; hematoxylin and eosin staining). Fragments are almost completely ulcerated with a dense, mixed inflammatory infiltrate with many eosinophils. Normal villous architecture is not appreciated. Lamina propria blood vessels disclose marked congestion and neutrophilic margination. (**B**) Biopsy specimen taken 7 months after initiation of adalimumab showing superficial fragments of small intestinal mucosa (shown at 20× magnification; hematoxylin and eosin staining) with normal villous architecture.

Our results are consistent with previous studies demonstrating the promising utility of anti-TNF agents in small bowel immunosuppression. It is important to emphasize that this efficacy was demonstrated in concert with the use of tacrolimus. At a molecular level, an early study in SBT animal models showed that one of the most significant cytokines expressed was TNF-alpha, with expression early on in ACR along with increasing levels in higher grades of rejection [8]. Later reports in humans have shown promising results in utilizing the TNF pathway in managing ACR in small intestine transplantations. A case series in SBT patients found significant clinical and histologic response after the administration of rescue therapy with infliximab in patients not responding to escalated doses of immunosuppression, including thymoglobulin, steroid bolus, and titration of maintenance immunosuppressive agents. Serum TNF-alpha levels measured during their rejection episodes remained significantly elevated despite administration of thymoglobulin. In addition, some of the patients in the series were able to maintain lower trough levels of tacrolimus with adjunctive infliximab therapy, thus preventing potential complications of calcineurin-related nephrotoxicity [5,6]. The results of our case expanded on these findings by using an alternative anti-TNF agent. The severe ACR in this case resolved only after utilizing adalimumab in combination with standard immunosuppressive agents. Larger multicenter trials are needed to further delineate the full efficacy of regimens incorporating anti-TNF agents in SBT immunosuppression.

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