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CASE REPORT | COLON

Graft-vs-Host Disease Colitis After Lung Transplant

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ABSTRACT

Graft-vs-host disease, characteristically a major complication of allogenic hematopoietic stem cell transplantation, is rare after solid organ transplantation. We report a 50-year-old man who presented with abdominal pain, vomiting, and diarrhea shortly after bilateral lung transplantation. Colonoscopy with biopsy revealed diffuse severe active colitis with ulceration and crypt apoptosis consistent with graft-vs-host disease colitis. The diagnosis was confirmed by the presence of donor lymphocytes in the peripheral blood. His symptoms were refractory to corticosteroids but responded to the addition of infliximab and extracorporeal photophoresis. He remained in remission 17 months later.

INTRODUCTION

Graft-vs-host disease (GVHD) occurs when grafted immunocompetent donor T-lymphocytes attack host organs and classically manifests across the skin (rash), liver (cholestatic hepatitis), bone marrow (cytopenias), and gut (diarrhea).[1] Solid organ transplant GVHD most commonly occurs in organs with large amounts of resident lymphoid tissue such as the small bowel and liver.[2,3] Cases in organs with fewer lymphocytes, such as the lung, are especially rare and nearly always fatal. Of the 11 previous cases, 9 patients with lung GVHD died largely because of complications of pancytopenia and sepsis.[4–8] We present a case of GVHD after lung transplantation with initially isolated gastrointestinal (GI) symptoms that was successfully treated.

CASE REPORT

A 50-year-old man, with gastroesophageal reflux disease, a remote history of peptic ulcer disease, and bilateral lung transplantation for pulmonary sarcoidosis 4 weeks before, presented with dull, mid-epigastric abdominal pain, 2 episodes of nonbilious, nonbloody emesis, and a 4-day history of diarrhea of 8–10 loose, maroon-colored stools per day. His active immunosuppression regimen consisted of prednisone 10 mg, mycophenolate 1,000 mg BID, and tacrolimus 1.5 mg BID. Other medications included voriconazole, valganciclovir, and trimethoprim/sulfamethoxazole for infection prophylaxis and a proton pump inhibitor 40 mg BID. He denied sick contacts, recent travel, and alcohol or tobacco use. The donor was cytomegalovirus (CMV) (+) and host was CMV (−). His vital signs were notable for a heart rate of 110 but were otherwise normal. On physical examination, he appeared fatigued and had diffuse epigastric tenderness to palpation without rebound or guarding hyperactive bowel sounds and no heptomegaly. The physical examination was otherwise normal. Liver function tests were notable for an aspartate aminotransferase of 101 U/L, alanine aminotransferase of 269 U/L, and albumin of 3.1 g/dL. Infectious workup including serum CMV immunoglobulin M/polymerase chain reaction (PCR), histoplasmosis, *Coccidioides*, *Cryptosporidium*, and *Strongyloides* antigen was negative. Stool *Clostridium difficile* PCR, stool culture, stool norovirus, enterovirus; adenovirus PCR, ova, and parasite examination; and fungal stains were negative. Colonoscopy revealed diffuse edematous, erythematous mucosa with overlying pseudomembranes from the cecum to the proximal transverse colon. The terminal ileum was denuded and erythematous with ulcerations and loss of villi (Figure 1).

Biopsy of the ascending colon showed marked crypt epithelial apoptosis consistent with GVHD colitis (Figure 2). No granulomas, viral inclusions (CMV, Herpes simplex viruses), fungi, or parasites were seen. The diagnosis of GVHD was confirmed with the presence of donor lymphocyte chimerism in the patient's peripheral blood. Intravenous methylprednisolone was started, and mycophenolate was discontinued, but the patient's diarrhea persisted after 10 days. He then developed a maculopapular rash with

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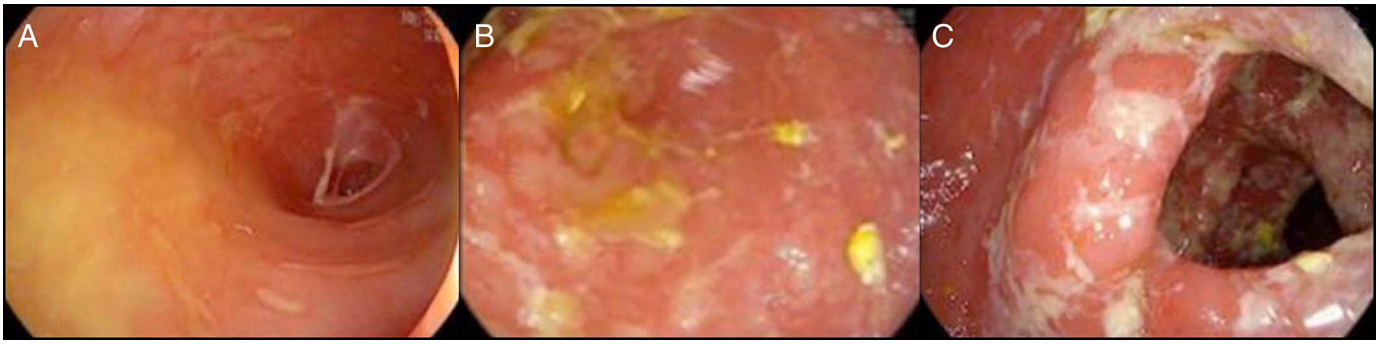

Figure 1. Colonoscopy images of the (A) terminal ileum, (B) cecum, and (C) transverse colon.

skin biopsy being consistent with GVHD. One dose of infliximab 5 mg/kg was given, and he was started on extracorporeal photophoresis (ECP) for steroid-resistant GVHD. His diarrhea ceased, rash resolved, and follow-up colonoscopy showed complete healing of colonic mucosa 3 months later (Figure 3). The initial transaminitis was attributed to hepatic GVHD and resolved after the dose of infliximab. He remained in remission 17 months later.

DISCUSSION

The pathogenesis of gut GVHD is thought to begin when preconditioning chemoradiation, underlying disease, or surgery inflicts a preliminary insult to host tissue. The resulting release of host proinflammatory cytokines (tumor necrosis factor-α, interleukin-1, interleukin-6) upregulates host antigen-presenting cells and subsequently donor T cells to mediate mucosal damage.[1,4]

GVHD most commonly involves the distal small bowel and colon.[9] Secretory diarrhea is the predominant GI manifestation of acute GVHD, the volume of which may be used to grade disease severity and predict outcomes.[9–11] Additional symptoms include anorexia, nausea/vomiting, abdominal pain, hematochezia, and protein malabsorption. Within the first 20 days of transplant, GVHD cannot be reliably distinguished from the effects of preconditioning chemoradiation and is considered between 20 and 100 days post-transplant. The clinical presentation of gut GVHD is nonspecific and requires histopathologic correlation on biopsy. Most of the studies support rectosigmoid biopsies, given their high sensitivity (82%–95%) regardless of the symptom profile.[11,12] In hemopoeitc stem cell transplant patients with diarrhea, colonoscopy and sigmoidoscopy are equivalent in diagnosing GVHD, so the latter may benefit patients with a high procedural risk.[12] Endoscopically, GVHD displays erythema, edema, erosions, and denudation of mucosa; however, approximately half of patients with normal colonoscopies and 60% with normal EGDs had histologic evidence of GVHD—strongly supporting obtaining biopsies irrespective of normal-appearing mucosa.[13] Chimerism or the presence of donor lymphocytes in the patient's peripheral blood can confirm clinical suspicion of GVHD. Greater than 10%–20% chimersim has been shown to be highly specific for GVHD in liver transplantation.[13]

Mycophenolate mofetil (MMF), a common immunosuppressive drug used to lower the risk of graft rejection, causes colitis that clinically and pathologically resembles acute GVHD. Both share histologic features of crypt apoptosis; however, MMF enterocolitis can be differentiated by the presence of increased eosinophils (>15 per 10 high-power field), the absence of endocrine cell aggregates within the lamina propria, and the lack of apoptotic microabscesses that are characteristic of GVHD. Crypt apoptosis combined with the lack of eosinophils and the persistence of symptoms after discontinuation of MMF favored GVHD colitis in the presented patient.[14]

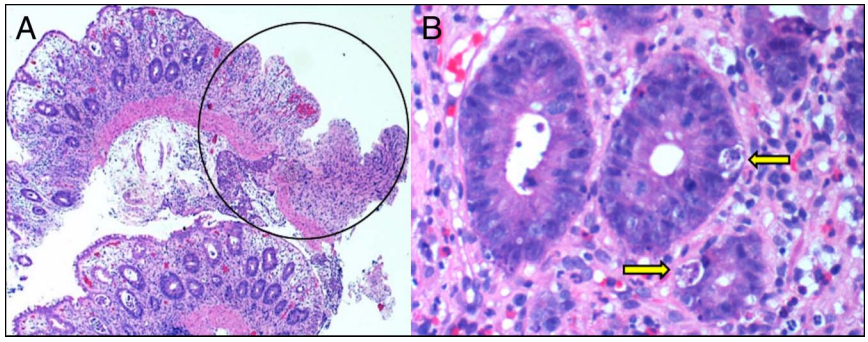

Figure 2. (A) Severe cryptitis with ulceration and crypt dropout (circle), and (B) apoptotic colonic epithelial cells aka "exploding crypt cells" (arrows).

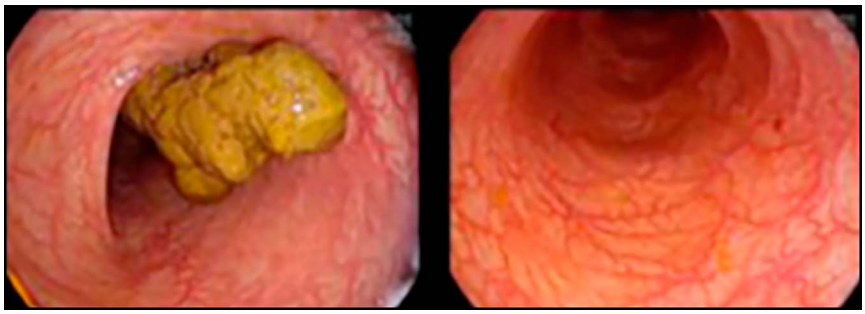

Figure 3. Follow-up colonoscopy 3 months after infliximab therapy showing complete healing of colonic mucosa.

Infectious mimics of GVHD, most notably CMV and *Cryptosporidium*, but also herpes simplex virus, adenovirus, *Clostridium difficile*, *Campylobacter*, and fungi, must be ruled out. There is a 0.2% incidence of de novo post-transplant inflammatory bowel disease, higher than that seen in the general population, and it is most commonly seen after liver transplant.[15,16] There have been no cases of de novo inflammatory bowel disease reported post-lung transplant.

There is no standard treatment for GVHD, and approaches aim to suppress donor T-lymphocyte function initially with systemic corticosteroids. Budesonide increases treatment response for GI GVHD, and octreotide may control diarrheal volume.[17] Infliximab has been shown to be effective in steroid-refractory GVHD, particularly in patients with GI involvement. Calcineruin inhibitors, MMF, monoclonal anti-IL2, and anti-CD3 have also been used. ECP provides a means to treat steroid-refractory GVHD without generalized immunosuppression via the reintroduction chemo-irradiated peripheral lymphocytes obtained through apheresis.[18] The presented case appears to be the only known case of lung transplant GVHD successfully treated with ECP. Solid organ transplant GVHD is notoriously steroid refractory and requires expeditious diagnosis with prompt treatment to combat its poor prognosis.

DISCLOSURES

Author contributions: K. Kanthasamy wrote the manuscript and is the article guarantor. MT Chang and M. Kaur edited the manuscript.

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