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Ipilimumab-induced Perforating Colitis

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Abstract

Recently, a monoclonal antibody to cytotoxic T-lymphocyte-associated antigen 4, ipilimumab, was approved for the treatment of metastatic melanoma. One of the most common side effects associated with this therapy is diarrhea and colitis. We report 3 cases of perforating colitis induced by ipilimumab requiring colectomy. The histologic findings of mucosal biopsies have been previously described. Herein, we describe novel associated histologic findings (pseudopolyp formation, fissuring ulcers, dilated crypts, and lack of intraepithelial lymphocytosis and epithelial apoptosis) of segmental resections in patients who required subtotal colectomy after perforation due to the severity of their ipilimumab-induced colitis. Although steroid therapy is the standard treatment for ipilimumab-induced colitis, surgery may be necessary. In the setting of progressive or worsening diarrhea after steroid therapy in patients with colitis, bowel perforation should be considered.

In 2011, the Food and Drug Administration (FDA) approved ipilimumab, a monoclonal antibody to anticytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), for the treatment of unresectable melanoma, the first agent approved for this disease in more than a decade.^{1–3} Several other malignancies are also being investigated for response to this drug.

Gastrointestinal side effects are the most common adverse reaction on ipilimumab.^{2,4} The mechanism for the colitis is related to the immune activation that results from CTLA-4 receptor binding blockade. CTLA-4 has an important role in immune surveillance, mainly through T-cell regulation.^{5,6} The antitumor effect of ipilimumab is presumably based on disrupted immune tolerance, which is not only specific to the antitumor activity, but also results in immune-mediated side effects such as enterocolitis, uveitis, dermatitis, hypophysitis, hepatitis, and others. Reportedly, the immune events correlate with tumor regression.⁵

Several reports have been published on autoimmune colitis after ipilimumab.^{4,7,8} Algorithms have been developed for management of the colitis, largely based on the grade of diarrhea. Treatment options range from symptomatic treatment, with or without steroids,

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to adding the antitumor necrosis factor antibody, infliximab, if patients are nonresponsive to steroids within 7 days,⁷ or, in some cases, in lieu of steroids.⁹ Infliximab suppresses the proinflammatory cytokines interleukin 1 and 6, resulting in T-cell suppression.

Histologic features seen on colonic biopsy have been described by Oble and colleagues.¹⁰ These features include variably dense lamina propria lymphoplasmacytic expansion, commonly associated with variable intraepithelial lymphocytosis, frequent apoptosis, plasma cells, and eosinophils with rare neutrophils. They describe a lack of well-formed basal lymphoplasmacytosis, significant architectural distortion, and granulomas, with retention of goblet and endocrine cells. They also reported small numbers of gastric (1), duodenal (1), and ileal (2) biopsies.¹⁰ To the best of our knowledge, no publication has described the histologic changes observed in surgical resections of ipilimumab-induced colitis.

Here, we report the histologic features in three cases with perforating colitis requiring resection, after administration of ipilimumab (at 10 mg/kg) for metastatic melanoma.

CASES

Patient 1

Six weeks before surgery, a 61-year-old man with metastatic melanoma developed 6 watery bowel movements per day after an initial dose of ipilimumab and was admitted to the hospital for administration of high-dose steroids (methylprednisolone 60 mg intravenously every 8 h). Colonic biopsies showed severe active colitis with a mildly increased chronic inflammatory infiltrate (Fig. 1A). Cytomegalovirus immunostains, stool studies, and infectious workup were negative. The frequency of bowel movements decreased on high-dose steroids and he was discharged home on oral prednisone and loperamide as needed. Within a week, the frequency of bowel movements increased to 6 to 8 per day, and he was readmitted to the hospital. Repeat infectious workup was negative. A computed tomography (CT) demonstrated peritonitis and free intra-abdominal air. Intraoperative findings included several right, transverse, and left colon perforations. The transverse colon was frankly necrotic with associated fecal peritonitis. No thrombi were evident. The colon was dusky gray with serosal hemorrhages and yellow-green exudates and omental adipose tissue exudates. The colonic mucosa was diffusely edematous with alternating ulcers and polypoid change (Fig. 1B). Gross inflammatory changes were moderate to severe and pancolonic. Histologically, the colon was extensively ulcerated with occasional pseudopolyps (Fig. 1C). The nonulcerated mucosa had diffuse active cryptitis with neutrophilic infiltration of dilated crypts, vascular congestion, patchy, limited intraepithelial lymphocytosis, and increased lamina propria lymphoplasmacytic inflammatory infiltrate (Fig. 1D). His clinical course improved initially after surgery, and he was able to be extubated; however, 1 day after extubation, he developed respiratory failure and required reintubation, with progressive organ dysfunction eventually dying 1 month after surgery.

Patient 2

A 69-year-old woman with metastatic melanoma developed conjunctival injection and pruritus after an initial dose of ipilimumab, which resolved with steroid eye drops. Twenty-

four hours after the second dose, she developed watery, small volume diarrhea. The frequency gradually increased to 3 to 4 episodes per day and was unresponsive to diphenoxylate/atropine. She was given budesonide, and the frequency increased to every 2 to 3 hours. The bowel movements were associated with intermittent left upper quadrant pain, relieved by passing gas. She was admitted to hospital and treated with methylprednisolone 2 mg/kg intravenously. On flexible sigmoidoscopy, the bowel had diffuse erythema, edema, and pus from rectum to the sigmoid junction. Histologically, the rectal biopsy had active colitis with prominent surface epithelial damage and denudation, active cryptitis, occasional crypt abscesses, and reactive crypts. The biopsy lacked significant intraepithelial lymphocytes, architectural distortion, or basal lymphoplasmacytosis. Although undergoing slow tapering of steroid therapy, the frequency of her bowel movements decreased and she was discharged home on prednisone. After discharge, she had intermittent stool incontinence on passing gas, with persistent soft stool. Approximately 1 month after initial onset of diarrhea, she was admitted to the hospital with abdominal pain. A chest x-ray revealed free abdominal air, a finding confirmed on CT scan. Intraoperative findings included distended small bowel and colon, colonic friability, and left colonic adhesions to the abdominal wall. She was found to have distal transverse and sigmoid colonic perforations and underwent transverse and left colon resection and appendectomy. The perforated bowel had adjacent wall attenuation and mucosal and serosal yellow hemorrhagic exudates (Fig. 2A). The bowel was diffusely edematous and residual polypoid mucosa near ulcerations (Fig. 2B). Histologically, the residual surface epithelium was attenuated with mucin loss and denudation. The lamina propria was expanded by lymphoplasmacytic inflammation and edema, without increased eosinophils, granulomas, crypt architectural distortion, basal lymphoplasmacytosis, or Paneth cell metaplasia (Fig. 2C). Multifocal fissuring inflammation was seen, with nearby lymphocytic inflammation, most prominent in areas of perforation (Fig. 2D). Her postoperative course was complicated by intra-abdominal sepsis and respiratory failure necessitating subsequent total colectomy with end ileostomy. She initially required an open abdomen and multiple lavages and gastrostomy tube placement for nutritional concerns, but ultimately recovered from her intra-abdominal sepsis and had abdominal closure. She was discharged 1 month after admission to a rehabilitation facility.

Patient 3

A 51-year-old man with metastatic melanoma developed nausea, vomiting, and abdominal cramps and discomfort, 1 week after ipilimumab infusion. His discomfort and cramps resolved after therapy with prochlorperazine. Four days later, he developed loose stools that did not resolve with loperamide. He then developed a fever, fatigue, ongoing cramps, decreased appetite, and malaise. He was prescribed rapid prednisone taper, starting at 60 mg once daily. He took 10 to 20 mg and was admitted 15 days after his initial presentation for management of his worsening symptoms. On admission, he was started on 1 mg/kg of methylprednisolone q 12 hours. A CT scan indicated pancolitis without obstruction or free air. The transverse colon was markedly distended. Clostridium difficile toxin assay was positive. His abdominal pain worsened; he developed a rigid abdomen and an abdominal x-ray showed free air, after which he had subtotal colectomy. Postoperatively, he did well and was discharged home.

At surgery, the colon was markedly dilated with multifocal frank perforation. Grossly, the dilated colon was dusky and fecal material oozed from cecal and sigmoid perforations (Fig. 3A). There were multiple crateriform ulcers, with erythematous granular mucosa, lacking discrete, raised plaque like exudate (Fig. 3B). Histology confirmed crater-like ulcers and foci of fissuring inflammation (Fig. 3C), and occasional pseudopolyp-like regeneration. The mucosa had a background of reactive epithelium, intact mucosal architecture, increased lymphoplasmacytic inflammation, myeloid precursors, and only scattered neutrophils in the lamina propria (Fig. 3D). Occasional dilated crypts and crypt abscesses were seen. Luminal fibrinous exudate was prominent only in the appendix.

DISCUSSION

Although previous studies have reported colonic perforation complicating ipilimumab-induced colitis, no detailed and sequential histologic descriptions exist. Prior reports of ipilimumab colitis histology were limited to mucosal biopsy findings. Given the antitumor effectiveness and recent FDA approval, physicians will likely see an increase in frequency of ipilimumab-induced colitis cases, most commonly on biopsy and, rarely, on colectomy. In our series, it is likely that *C. difficile* colitis played a role in the development of perforating colitis in patient 3; however, not only did this resection lack the typical mushroom-like neutrophilic exudates and other features of *C. difficile* colitis, there were morphologic similarities among all 3 cases.

Novel histologic findings that we observe as common to our cases include deep, fissuring inflammation, variably dilated crypts with small crypt abscesses, reactive epithelial changes, and multifocal crateriform ulceration with pseudopolyps. Pertinent negative findings include a lack of granulomas, muscular or neuronal hyperplasia, transmural fibrosis or transmural reactive lymphoid aggregates as typical in Crohn's disease, and lack of basal lymphoplasmacytosis, crypt architectural distortion, or Paneth cell metaplasia as typical in ulcerative colitis and/or Crohn's disease. Determination of the cause of the bowel perforation rests on clinical and pathologic correlation. In these cases, in addition to the progression of clinical symptoms, exclusion of infectious agents clinically and negative *C. difficile* toxin all argue against infectious etiology, *C. difficile* colitis and inflammatory bowel disease. When combined with the pathologic findings that include the lack of significant chronic colitis to suggest inflammatory bowel disease, the absence of the typical pattern of crypt atrophy with mucosal hyalinosis to suggest ischemia and the exudative pattern of *C. difficile* colitis, the overall clinicopathologic features render ischemia, new-onset inflammatory bowel disease, infection, and *C. difficile* colitis as unlikely etiologies of bowel perforation. Although steroid use has been reportedly associated with intestinal perforation, this is most commonly noted in diverticular disease,^{11,12} notably none of the current series of patients had colonic diverticula. The resections and biopsies from the current cases lacked some of the characteristic histologic findings previously described in mucosal biopsy, namely intraepithelial lymphocytes with increased apoptosis (often summarized as an autoimmune colitis like pattern) and frequent eosinophils. In our review experience,¹³ these typically described features represent just 1 pattern in the spectrum of changes in ipilimumab-induced colitis. In our review of 75 biopsies from 11 patients with ipilimumab-induced enterocolitis, 4 patients had an infectious, neutrophil rich, enterocolitis-

like pattern, 4 patients had an autoimmune colitis-like pattern, and 3 patients had overlapping features.¹³ Although all 11 of these patients received steroids, only 1 patient subsequently perforated.

The specific mechanism of the perforation in this immune-mediated enterocolitis is not well characterized, and the histopathologic features do not necessarily aid in characterizing the pathophysiology, although it helps to exclude other etiologies of intestinal perforation.

The histologic features described here are not specific to ipilimumab-induced colitis and overlap with varying phases of inflammatory bowel disease and other severe colitides, such as drug-induced and infectious colitis. From a clinical standpoint, the degree of active inflammation on mucosal biopsies may be helpful, particularly in patients with ongoing diarrhea. Steroid therapy may also blunt the clinical symptoms of bowel perforation, and diminish the severity of the histopathologic inflammatory response seen. Persistent or worsening diarrhea after steroid therapy in the setting of ipilimumab colitis may be a reliable indicator for deteriorating bowel integrity. Notably, prior reports suggest that major complications occur in patients who do not receive prompt treatment or are poorly compliant with steroid therapy.⁴ Although many cases of ipilimumab-induced colitis may resolve after treatment with steroids, severe complications can include colonic perforation and death.⁴

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FIGURE 1.

A, Colon biopsy with reactive epithelium with dilated crypts, surface epithelial damage, and increased lamina propria inflammation ($\times 100$, hematoxylin and eosin). B, Grossly ulcerated colon with multiple pseudopolyps (formalin-fixed resection). C, Colon resection with multifocal deep ulcers and residual polypoid (pseudopolyp) mucosa ($\times 20$, hematoxylin and eosin). D, Dilated crypts within nonulcerated mucosa of resection ($\times 100$, hematoxylin and eosin).

FIGURE 2.

A, Grossly perforated colon with residual boggy, polypoid mucosa (formalin-fixed resection). B, Multifocal deep ulcers with pseudopolyps ($\times 20$, hematoxylin and eosin). C, Mucosa of resection with dilated crypts with crypt abscesses, reactive epithelium, and increased lamina propria lymphoplasmacytic inflammation without chronic colitis (resection— $\times 100$, hematoxylin and eosin). D, Fissuring-type inflammation in area of perforation (resection— $\times 20$, hematoxylin and eosin).

FIGURE 3.

A, Gross perforation of colon oozing fecal material (unfixed resection). B, Ulcerated colon with erythematous residual mucosa lacking plaque-like exudate (unfixed resection specimen). C, Multifocal deep ulcers with pseudopolyps ($\times 20$, hematoxylin and eosin). D, Reactive epithelium, crypt abscesses, and increased lamina propria inflammation ($\times 100$, hematoxylin and eosin).