ACG CASE REPORTS JOURNAL

CASE REPORT | COLON

Perforating Colitis Secondary to Immune Checkpoint Inhibitor Use in a Patient With Pericolonic Involvement by Rosai-Dorfman Disease

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ABSTRACT

Recently, the use of immunotherapy has increased substantially for the treatment of several malignancies. It is associated with several gastrointestinal adverse events; however, severe complications such as intestinal perforation are rare. We present a 75-year-old man with metastatic melanoma, presented with profuse diarrhea and abdominal pain, after ipilimumab and nivolumab administration. Shortly after, he developed fulminant colitis and intestinal perforation and was found to have concurrent Rosai-Dorfman disease of pericolonic lymph nodes. With the increasing use of immunotherapy, reporting of serious adverse events and their mimics is essential. In addition, further studies are required to investigate whether an association exists between Rosai-Dorfman disease and immunotherapy.

INTRODUCTION

Lately, immune checkpoint inhibitors (ICIs) have become increasingly prevalent in cancer treatment because of improved progression-free survival in certain patient cohorts. Two such antitumoral agents are nivolumab, a programmed death 1 (PD-1) inhibitor, and ipilimumab, an antibody against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Both PD-1 and CTLA-4 inhibitors upregulate T-cell immune function leading to increased activation, proliferation, and tolerance of T cells, which subsequently results in increased tumor cell death. Both these drugs have shown a survival benefit in patients with metastatic melanoma and have been approved for the treatment of several malignancies.[1]

Nevertheless, the use of ICIs has been linked with several immune-related adverse effects across all organ systems. The most common organ system to be affected is the gastrointestinal tract, and diarrhea is the most common complaint.[2] Both PD-1 and CTLA-4 inhibitors can cause autoimmune colitis.[1] Anti-CTLA-4 agents have also been associated with more severe complications, such as intestinal perforation and death. However, these complications are rare ($<$1% of patients).[3]

Rosai-Dorfman disease (RDD) (also known as sinus histiocytosis with massive lymphadenopathy) is a rare idiopathic lymphohistocytic proliferative disease of uncertain pathogenesis.[4] Although RDD classically involves cervical lymph nodes, it has been reported to involve virtually all anatomic locations including the gastrointestinal tract.[5–7] Several studies have attempted to explain the origin of this disease, including for instance, immune dysfunction secondary to viral infections, among others.[8] To date, there are no reported cases of RDD in patients receiving PD-1 and/or CTLA-4 inhibitors.

In this study, we present a rare but serious complication of ICI use that might be easily mistaken for other colitides. In addition, our case is unique in that it is associated with concurrent pericolonic lymph node involvement by RDD.

ACG Case Rep J 2022;9:e00900. doi:10.14309/crj.0000000000000900. Published online: December 19, 2022

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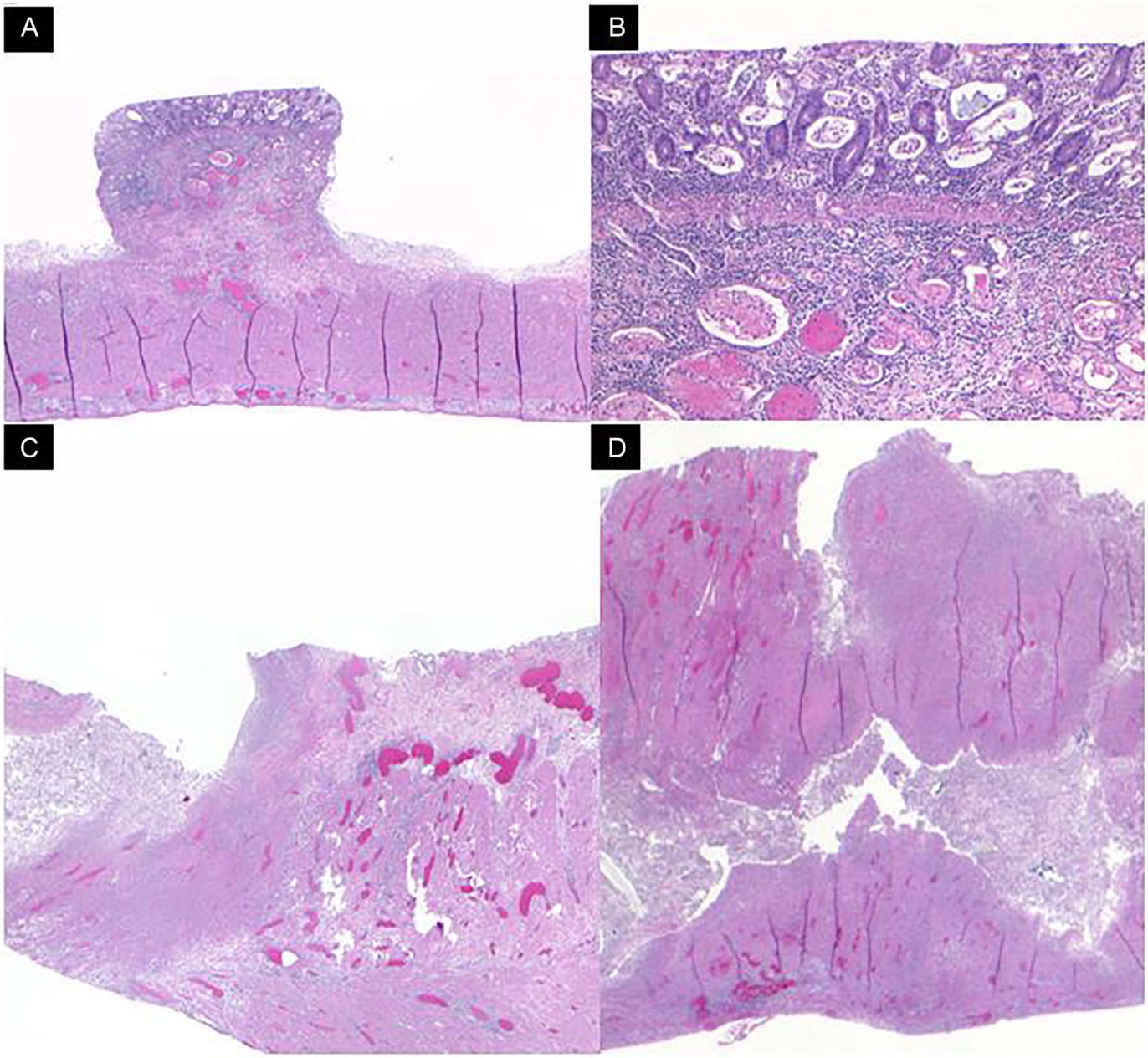

Figure 1. (A) Colon with deep ulceration and inflamed polypoid mucosa (pseudopolyp) (20×, hematoxylin and eosin). (B) Nonulcerated mucosa shows dilated crypts with crypt abscesses, submucosal vascular congestion, and fibrin thrombi (100×, hematoxylin and eosin). (C and D) Fissuring ulcers at areas of perforation (20×, hematoxylin and eosin).

CASE REPORT

A 75-year-old man with a history of metastatic melanoma presented to the emergency department with 2 days of profuse, watery diarrhea and associated abdominal pain. Five days before presentation, the patient had completed his third cycle of ipilimumab and nivolumab. He did not have any personal or family history of inflammatory bowel disease. An abdominal computed tomography scan revealed rectosigmoid wall thickening, enhancement, and mild distension. In addition, there was a small volume of ascites and mild mesenteric fat stranding. The stool polymerase chain reaction was negative for pertinent pathologic organisms and toxins, including *Clostridioides difficile*. Fecal lactoferrin (which indicates the presence of white blood cells) was positive. There was no leukocytosis. Nevertheless, C-reactive protein and erythrocyte sedimentation rate (ESR) were both elevated 4 days before presentation with a value of 8 (reference range: <0.9 mg/dL) and 75 (0–20 mm/hr), respectively. The patient's symptoms corresponded to grade 2 (of 5) based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) grading system.[9] He was initially managed with fluids and broad-spectrum antibiotics. Despite that, the patient's diarrhea continued to worsen, and 2 days later, he experienced

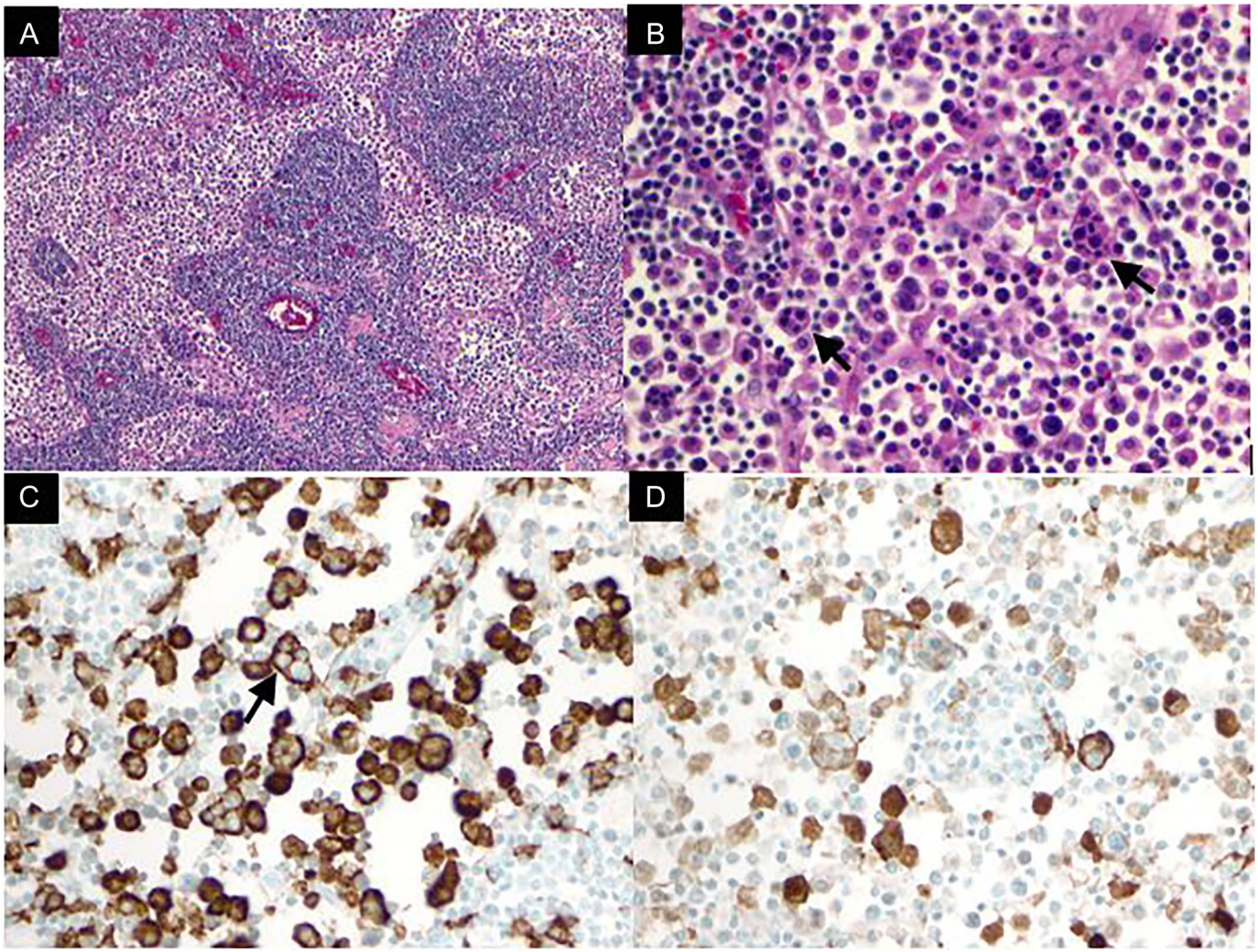

Figure 2. (A) Pericolonic lymph node with Rosai-Dorfman disease (RDD) (100×, hematoxylin and eosin). (B) Lymph node sinuses are expanded with histiocytes, some of which show emperipolesis (arrows) (400×, hematoxylin and eosin). (C and D) CD163 and S100 stains highlight the cytoplasm of RDD histiocytes (400×).

acute abdominal distension, tachycardia, and confusion (CTCAE grade 4). An abdominal x-ray revealed significant pneumoperitoneum. Subsequent exploratory laparotomy revealed feculent peritonitis with multiple perforations of the left colon. The entire colon appeared inflamed, necessitating total colectomy. The patient was stable after the surgery. He reported no residual symptoms and was last seen 3 years after the surgery.

Gross examination showed diffuse mucosal cobblestoning. There was a focus of dusky mucosal changes associated with a transmural defect and purulent debris. Microscopic examination demonstrated diffuse active colitis with ulceration, pseudopolyps, and evidence of perforation. Scattered areas showed ischemic-like injury as well (Figure 1). Immunohistochemistry for *Cytomegalovirus* was negative.

In addition, some of the pericolonic lymph nodes demonstrated distended sinuses that were filled with atypical cells. Immunohistochemical stains for Melan-A, SOX-10, and HMB-45 were negative, excluding the possibility of involvement by the patient's melanoma. Further workup revealed sinus histiocytosis with emperipolesis of small lymphocytes by CD163 and S100-positive histiocytes, consistent with nodal RDD (Figure 2).

DISCUSSION

Immunotherapy-induced diarrhea and colitis have become increasingly common as the use of ICIs grows. Occasionally, these drugs lead to severe complications, including intestinal perforation.

Watery diarrhea is the most common presenting symptom. Its severity can be graded using the CTCAE grading system.[9] Briefly, it stratifies based on the frequency and severity of symptoms, with grade 1 being the mildest and grade 5 the most severe. The recommended treatment of mild diarrhea is supportive care. Patients with ongoing mild diarrhea require colonoscopy and corticosteroid therapy. Conversely, patients presenting with severe diarrhea require discontinuation of ICI therapy and initiation of a systemic

corticosteroid. If no improvement is seen after 48–72 hours, infliximab may be initiated.

Less common presentations include bloody diarrhea, anal pain, constipation, and perforation. If the latter is suspected, treatment with corticosteroids and infliximab should be avoided. Partial or complete colectomy is the treatment of choice in such cases.[1,3] In our case, the patient had an acute mild-to-moderate diarrhea. The severity did not justify the initiation of a corticosteroid. However, the patient's condition rapidly progressed to perforation and peritonitis, and a colectomy was performed.

Early recognition of these side effects is crucial because timely intervention might prevent progression to dreaded complications. The American Gastroenterological Association released a clinical practice update in which they advised early testing for a complete blood count (looking for leukocytosis), ESR, and C-reactive protein. They further recommended early stool testing for the inflammatory markers (lactoferrin and/or calprotectin) in selected patients to stratify them for endoscopic evaluation. Regardless, patients with grade 2 or higher CTCAE need to be evaluated endoscopically, before steroid initiation, because endoscopy and tissue biopsies are considered gold standards for diagnosing, assessing severity, and risk-stratifying patients with immune-mediated colitis.[10]

The interval between treatment with ICIs and the development of complications varies.[1,3] The onset of symptoms after ipilimumab therapy tends to occur within days to weeks after the last dose or 7–13 weeks after initiating therapy. However, rare cases of late-onset inflammatory bowel disease-like syndrome have been reported up to 3 years after ipilimumab use. In anti-PD-1 therapy, symptoms tend to occur approximately 1–19 weeks after the initiation of treatment.[1]

The histologic patterns associated with immunotherapy-induced colitis are variable and overlap with other colidities. Infectious etiologies should always be excluded. The histologic features are most often described on biopsies, with few studies describing changes in surgical resections. Mitchell et al described 3 cases of ipilimumab-induced perforating colitis in resection specimens. Their findings included fissuring inflammation, variably dilated crypts with crypt abscesses, and multifocal crateriform ulceration with pseudopolyps.[11] All these features were seen in our case.

Both CTLA-4 inhibitors and PD-1 inhibitors show considerable histologic overlap, with lamina propria expansion by mixed inflammation, cryptitis, crypt abscess, and increased epithelial cell apoptosis.[1] A granulomatous response has been reported in rare cases treated with PD-1 inhibitors, and prolonged therapy with PD-1 inhibitors is known to cause chronic mucosal injury.[12,13] No granulomas or chronic mucosal injuries were seen in our case.

Overall, the findings in our case are more compatible with CTLA-4-induced colitis. However, given the overlap in histologic presentation, we cannot be certain whether ipilimumab alone or the combination of both drugs led to this patient's complications. It is well known that combination therapy causes more severe complications than single-agent treatment.[14]

In addition to our patient's colitis, several pericolonic lymph nodes were involved by RDD. As mentioned earlier, RDD is a rare non-Langerhans cell histiocytosis that often presents with fever and markedly enlarged cervical adenopathy.[4] However, other nodal and extranodal sites also may be involved.[5–7] Laboratory evaluations often demonstrate leukocytosis, polyclonal hypergammaglobulinemia, anemia, and elevated ESR. Although spontaneous resolution may be observed in some cases, other treatment modalities have been effective including surgery, corticosteroids, and chemotherapy, among others.[4] No uniform approach has been outlined for RDD. That being said, the international consensus guidelines for the diagnosis and management of RDD provide excellent guidelines for evaluation and treatment.[4]

To the best of our knowledge, this is the first time such association has been reported. Interestingly, Muenst et al studied the distribution of programmed death-ligand 1 (PD-L1) expression in different reactive lymph node conditions and found that PD-L1 is highly expressed in the germinal center of RDD.[15] However, Gatalica et al studied multiple histiocytoses, including RDD, and found that none of their 4 cases showed high expression of PD-L1.[16] All these cases were extranodal; however, it remains unclear whether RDD is a potential complication of ICI therapy or just an incidental finding. Further investigation is warranted to determine the relationship between RDD and ICIs.

DISCLOSURES

Author contributions: A. Bakhshwin put most of the article together with the exception of the case presentation. J. Robertson did the case presentation and references. M. Sarwate took all the pictures and managed the figure legends. D. Roberts is the senior author who modified the article based on his expertise, updated the references, and is the article guarantor.

Acknowledgments: The first author thanks King Abdulaziz University in Jeddah, Saudi Arabia, for their support.

Financial disclosure: None to report. Informed consent was obtained for this case report.

Received November 8, 2021; Accepted September 16, 2022

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