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CASE REPORT | COLON

Double Whammy: A Case Report of Immune Checkpoint Inhibitor Colitis and Concomitant *Cytomegalovirus* Colitis in a Patient on Nivolumab

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ABSTRACT

Immune checkpoint inhibitors commonly cause gastrointestinal immune-related adverse effects. These patients also carry an increased risk of concomitant infections. This 66-year-old man with immune checkpoint inhibitor colitis was discovered to have concurrent *Yersinia* and *Cytomegalovirus* colitis. Such infections may mimic or complicate disease course. Hence, clinicians must monitor patient symptoms, have a low threshold for infectious testing and colonoscopy, and consider treatment strategies to mitigate their risk.

KEYWORDS: immune checkpoint inhibitors; immune checkpoint inhibitor colitis; immune-related adverse effects; CMV colitis; *Yersinia* infection

INTRODUCTION

Immune checkpoint inhibitors (ICI) such as nivolumab and ipilimumab are standard of care for numerous malignancies. However, gastrointestinal (GI) immune-related adverse effects (irAEs) are common. Such patients often develop concurrent microbial infections. We hereby describe a case wherein a patient with metastatic melanoma on ICI therapy developed steroid-refractory immune checkpoint inhibitor colitis (ICIC) along with viral and bacterial colitis.

CASE REPORT

A 66-year-old man with metastatic melanoma after Mohs surgery presented with grade 2 diarrhea (4-–6 stools/d). He had received 2 cycles of ICI therapy with ipilimumab/nivolumab and radiotherapy after resection of brain metastases. Diphenoxylate/atropine and loperamide had provided limited symptomatic relief. Stool GI pathogen panel by polymerase chain reaction (PCR) and *Clostridioides difficile* testing at the time were negative. ICI therapy was held, and prednisone 80 mg PO daily was initiated for concern of ICIC.

After initial response to steroids, diarrhea recurred, with ≥7 stools/d (grade 3). Steroid-refractory ICIC was suspected, and prednisone was increased to 100 mg with plans to initiate infliximab infusion. However, colonoscopy showed indeterminate colitis and biopsies revealed a neutrophilic infiltrate, suggestive of acute infectious colitis. *Cytomegalovirus* (CMV) was not detected by immunohistochemistry (IHC), but repeat stool GI pathogen panel by PCR was positive for *Yersinia*. The diarrhea improved significantly with ciprofloxacin plus steroids, and he was discharged with a steroid taper. Four days after nivolumab was resumed, he presented again with diarrhea that rapidly progressed to ~20 stools/d (grade 4). Stool GI pathogen panel by PCR and *C. difficile* testing were negative. IV methylprednisolone (1 mg/kg/d) was started, and a repeat colonoscopy showed pancolonic diffuse

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congestion, erosions, erythema, and friability (Figure 1). Repeat colonic biopsies revealed active colitis with mononuclear infiltrate, attenuation of the colonic epithelium, and crypt dropout, which could be attributed to ICIC or infectious colitis (Figure 1). This time, however, concomitant CMV colitis was detected by IHC and presence of CMV-positive cells in the biopsy (Figure 1). With a 3-week course of IV ganciclovir and PO steroid taper, the patient improved and was discharged. A sigmoidoscopy 1 month later revealed moderate chronic colitis with no ulceration or granulomas and IHC showed a single CMV-positive cell in the lamina propria. The patient has since had no recurrence of diarrhea and remained off ICI therapy with continued surveillance for cancer.

DISCUSSION

ICIC is a frequently reported irAE associated with ICI therapy.[1] Intestinal infections often masquerade as ICIC because their symptoms are indistinguishable. In these situations, missing the diagnosis can lead to serious clinical consequences. Our case highlights the importance of ruling out infectious causes in a patient on ICI presenting with diarrhea and also demonstrates the complexity of managing ICIC with concomitant infection. Opportunistic infections may develop along the clinical course of ICIC in the setting of an immunosuppressed state and hinder recovery or cause deterioration. A high level of clinical suspicion can lead to prompt identification of the pathogen and appropriate intervention. For example, antimicrobial treatment in our patient addressed the underlying infectious etiology, preventing the inappropriate use of immunosuppressive therapy. The diagnosis of *Yersinia* infection and the patient's subsequent improvement with targeted antibiotics led to the decision to withhold infliximab, an immunosuppressant that may have worsened the infection. Furthermore, when the patient developed a second infection with CMV, this finding influenced the management plan by shortening the duration of intravenous steroid therapy. Antimicrobial treatment does not circumvent the need for immunosuppressive therapy but can prevent the prolonged use of immunosuppressive agents and unnecessary treatment escalation, which can exacerbate infections and lead to further complications.

Mechanism of ICIC: Neoplastic cells often use CTLA-4 and PD-1 pathways to inhibit T-cell function and develop immune tolerance. ICI therapy targets these pathways. However, this mechanism of action is nonspecific, and the heightened immune activation can lead to autoimmunity. ICIC is caused by the knockout of CTLA-4 and PD-1 axis in GI mucosa resulting in infiltration by activated cytotoxic and helper T cells. GI microbiota can influence the development of ICIC.[2,3] Several other factors such as nonsteroidal anti-inflammatory drug use, vitamin D level, pre-existing autoimmune conditions, type of cancer, and specific ICI agents used also play a role.[4]

Clinical presentation: A robust response to ICI therapy and improved survival in patients is associated with increased

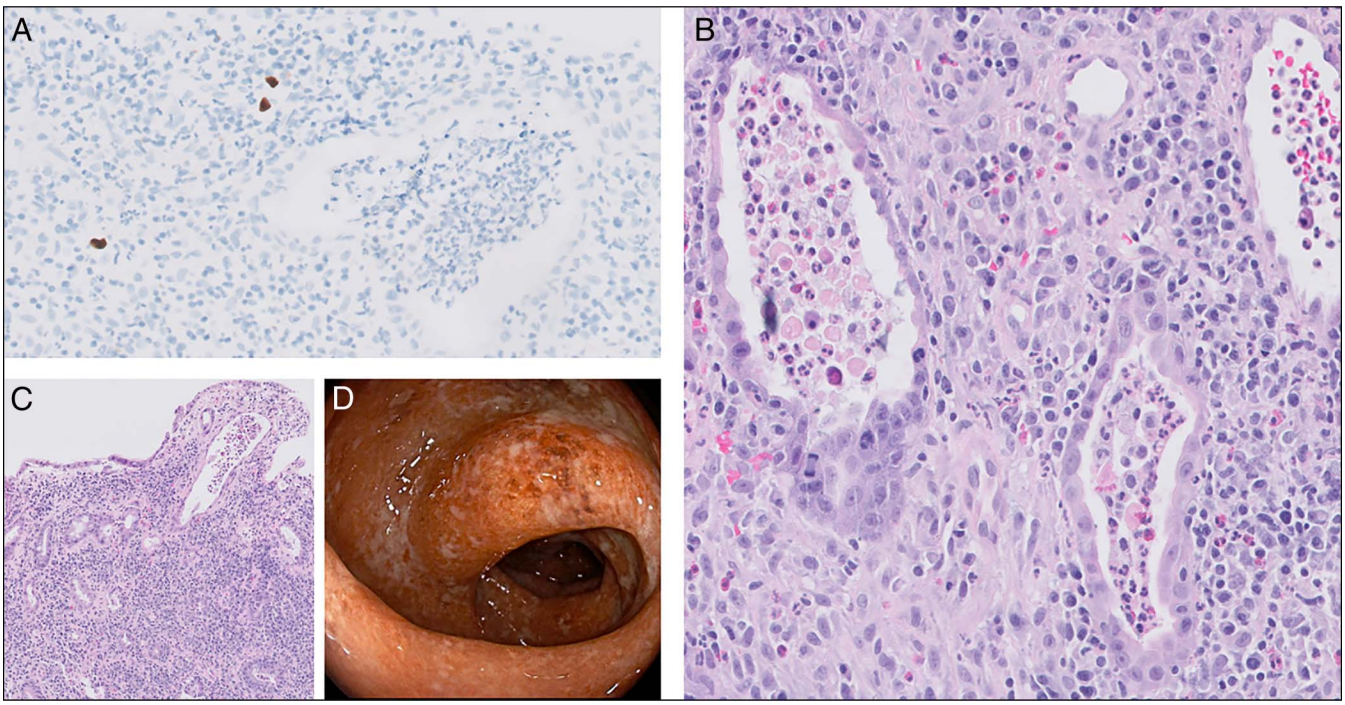

Figure 1. (A) Immunohistochemical stain for *Cytomegalovirus*, demonstrating the presence of several *Cytomegalovirus*-positive cells within an inflammatory polyp, (B) high power (40×) of crypt abscesses with marked attenuation of colonic epithelium, (C) low power (4×) of active chronic colitis with withering crypts, a crypt abscess, and crypt dropout, and (D) colonoscopy showing diffuse continuous congestion, erosions, erythema, and friability noted in whole colon.

GI symptoms and history of ICI use:
1. Assess for other irAE
2. Exclude other causes of GI symptoms including infection, IBD, other drug-related, ischemic, radiation induced*
3. Endoscopy and Biopsy
4. CT abdomen for suspected complications

*Laboratory studies:
- GI pathogen PCR, Ova and parasite, C. difficile testing
- CBC, Serum CRP, LRG, IL-17, Antigen antibodies
- Stool calprotectin, lactoferrin

Figure 2. Considerations during ICIC diagnosis. CT, computed tomography; CBC, complete blood count; GI, gastrointestinal; ICIC, immune checkpoint inhibitor colitis; IL, interleukin; irAE, immune-related adverse event; LRG, leucine-rich A2-glycoprotein; PCR, polymerase chain reaction.

incidence of ICIC.[5] Presentations depend on the extent/pattern of disease ranging from aphthous ulcers, gastritis, enteritis, and pancolitis. The most common symptom is diarrhea, but hematochezia, pain, nausea/vomiting, and severe complications such as toxic megacolon, intestinal ischemia, and perforation can occur. These typically present within 4–6 weeks of ICI initiation, although onset several months later has been reported.[6] The severity of diarrhea is graded per the Common Terminology Criteria for Adverse Effects v5.0 (CTCAE v5.0).

Diagnosis: Before diagnosing ICIC, it is crucial to rule out diarrhea due to infection or other causes such as inflammatory bowel disease or celiac disease. Infectious colitis may superimpose in patients with ICIC (Figure 2). ICI therapy augments immunity against tumor cells but suppresses immunity against *Cytomegalovirus*, *Salmonella, C. difficile*, parasites, and less frequently encountered infectious culprits such as *Yersinia*.[7] Notably, steroids and hematological malignancies are independent risk factors for CMV infection.[8] Although not broadly available, a biomarker, serum leucine-rich a2-

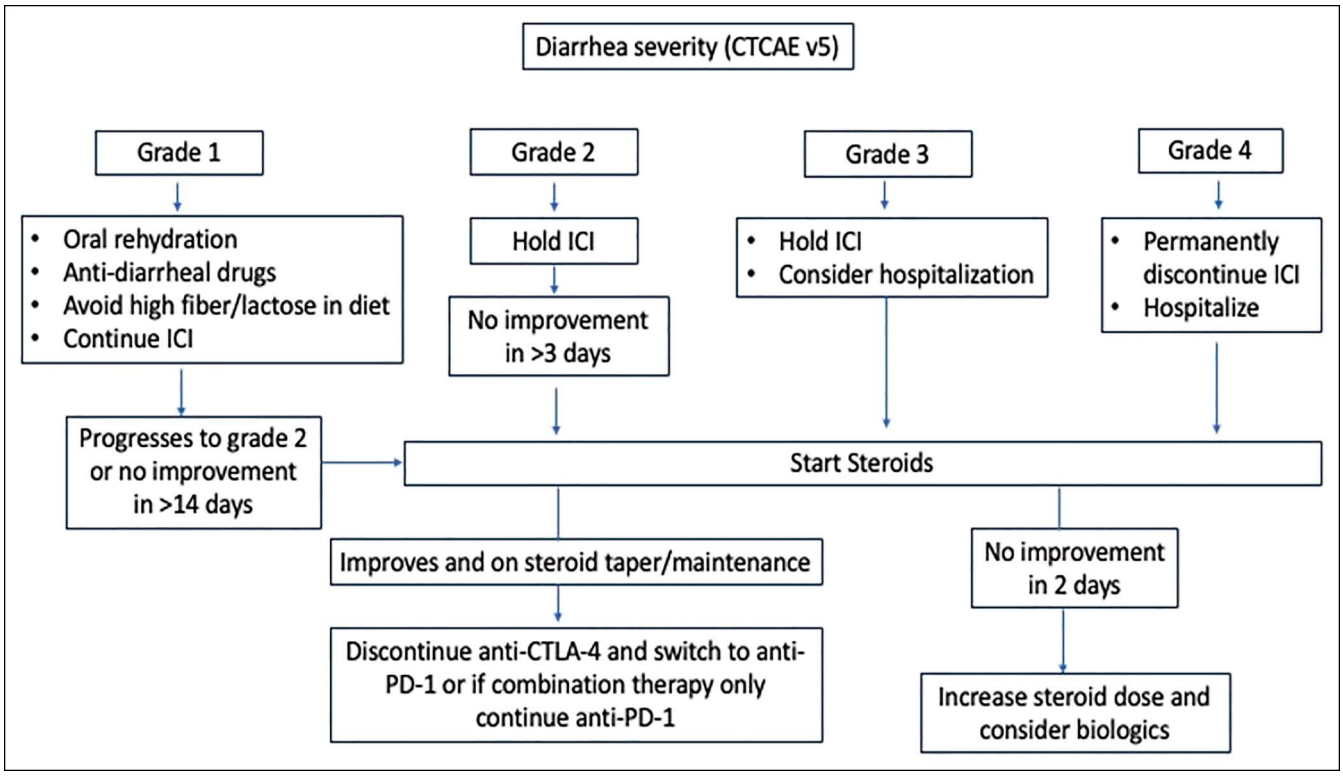

Figure 3. Management of ICIC and diarrhea based on CTCAE grade. Grade 1: increase of <4 stools/d from baseline; grade 2: increase of 4–6 stools/d from baseline; grade 3: increase of ≥7 stools/d; grade 4: life-threatening consequences; and grade 5: death. CTCAE v5.0, Common Terminology Criteria for Adverse Events: version 5.0 for diarrhea and colitis; ICIC, immune checkpoint inhibitor colitis.

glycoprotein may distinguish ICIC from CMV colitis or other drug-related colitis.[9] C-reactive protein, fecal calprotectin, and lactoferrin correlate to clinical remission and can serve as a less invasive modality to monitor disease.[10,11] Abdominal imaging can reveal signs of inflammation; however, colonoscopy with biopsy is preferred early in the disease course to confirm diagnosis and assess prognosis.[12] Still, tissue biopsies may reveal nonspecific histologic findings; hence, physicians must correlate clinical clues, such as concurrent medication use and presence of other irAEs. Endoscopic findings such as ulcers and extensive disease are not associated with symptom severity; however, they may be indicative of steroid-refractoriness and such patients often require biologic medications—vedolizumab or infliximab.[9,13] This emphasizes the role of endoscopy in addition to symptoms severity when choosing treatment.

Treatment: Current guidelines are based on symptom severity (summarized in Figure 3). However, development of algorithms taking endoscopic findings into consideration is required. In addition to significant side effects, the detrimental effects of anti–tumor necrosis factor drugs on ICI efficacy have been described.[14] Vedolizumab is a gut-targeted α4β7 integrin antibody that prevents leukocyte binding to the endothelial surface and its extravasation into affected tissue, enabling selective GI immunosuppression and is now preferred in steroid-refractory ICIC.[15] In severe unremitting ICIC, other biologics (anakinra, ixekizumab, and ustekinumab) can be used, and several others are under investigation for an even more targeted approach (tocilizumab, secukinumab, and tofacitinib).[16–18] Unfortunately, inpatient biologics are difficult to use because of cost prohibitions. Adjunctive treatments such as fecal microbiota transplant may have some benefits but need further investigation.[19] On symptom resolution, ICI therapy is resumed per patient and physician discretion guided by various society recommendations. The risk of recurrent ICIC is overall low, and initial risk is seen more with anti-CTLA-4 than PD-1/PD-L1 therapy.[20]

DISCLOSURES

Author contributions: V. Jahagirdar, H. Mahadevia, K. Sanders, and J. Campbell: conception or design of the work and acquisition; interpretation of data for the work. M. Gautam: drafting the work. P. Sylvestre, R. Chhabra, W. Clarkston, and S. Jonnalagadda: reviewing it critically for important intellectual content and final approval of the version to be published, ensuring that questions related to the accuracy are appropriately investigated. S. Jonnalagadda is the article guarantor.

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