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CASE REPORT

Mirroring UC care pathways in refractory immune checkpoint inhibitor (ICI)-mediated colitis: distinct features and common pathways

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Abstract
Immune checkpoint inhibitors (ICI) have transformed the management of cancer, producing durable responses in a subset of treated patients across multiple malignancies. Immune-mediated diarrhea and colitis (imDC) occurs in up to 20% of ICI-treated patients. The risk of ICI imDC is dependent upon the agent and is commoner with anti-CTLA-4 compared to anti-PD-1 ICIs. Generally, imDC is treated with steroids and agents targeting TNFα or α4β7 integrin. However, the management of steroids and/or biologic refractory imDC is unclear. We present a case of imDC in a 68-year-old female who failed to respond clinically, biochemically and immunohistochemically to corticosteroids, infliximab and vedolizumab. A trial of tofacitinib, a pan-JAK inhibitor, led to rapid clinical, biochemical and immunohistochemical control of imDC. ICIs result in a striking accumulation of cytotoxic and proliferative CD8 + T cells within tumor. However, the cellular and molecular mechanisms underlying imDC remain unclear. Herein, we observed significant T cell enrichment; and the successful treatment with tofacitinib highlights the potential of multiple convergent inflammatory pathways in imDC and inflammatory colitis.

Keywords Immune-mediated colitis and diarrhea · Immunotherapy · Tofacitinib · Immune checkpoint inhibitor · Colitis

Introduction

The impact of immune checkpoint inhibitors (ICI) targeting PD-1 or CTLA-4 inhibitory immune checkpoints upon outcomes of patients with metastatic cancers has been revolutionary. ICIs can produce off-target effects in an excessively activated immune system, producing a spectrum of autoimmune pathologies across several organs, collectively termed immune-related adverse events (irAEs). Immune-mediated diarrhea and colitis (imDC) occur at rates of 6–20%, occurring more likely with anti-CTLA-4 or combination anti-PD-1/anti-CTLA-4 therapy [1]. Diarrhea and colitis are currently graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), and this guides treatment with corticosteroids (CS), biologics and, in some instances, fecal microbial transplant [1–3]. However, a significant number of patients are refractory to corticosteroids and biologics, and the management of these patients is unclear. In this study, we detail a case of recurrent imDC in a mismatch repair-deficient (dMMR) colorectal cancer (CRC) patient treated with combination anti-PD-1/anti-CTLA-4 who developed steroid and biologic refractory imDC. A trial of tofacitinib resulted in rapid amelioration of colonic inflammation documented on colonoscopy. Tofacitinib maintenance mitigated imDC with no loss of anti-tumor response.

Case

A 68-year-old female with a history of stage IIC dMMR/microsatellite instability-high (MSI-H) colon adenocarcinoma (CRC) in the transverse colon developed metastatic recurrence in the liver and thoracic spine following definitive

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surgery (ileal resection with extended right hemicolectomy) and adjuvant capecitabine and oxaliplatin. Given MSI-H status, nivolumab and ipilimumab was initiated based on the CheckMate-142 study results [4]. Following 2 cycles, she developed grade 2 imDC. Colonoscopy performed prior to initiation of immunosuppression showed inflammation and erythema in the distal neo-terminal ileum and entire colon consistent with endoscopic Mayo score 1, with histopathological confirmation of acute enteritis and colitis (Fig. 1, histological Geboes score in Supplemental Table 1). High-dose corticosteroids (1.7 mg prednisone/kg/day) were initially successful, yet symptoms recurred one month later when prednisone taper reached a dose of 0.8 mg/kg/day. A trial of infliximab over a 6-week period was initiated with symptom resolution, and steroids were tapered over a 12-week period with no further symptom recurrence.

Given hepatic progression while off ICI therapy, nivolumab monotherapy was started 2 months after the third

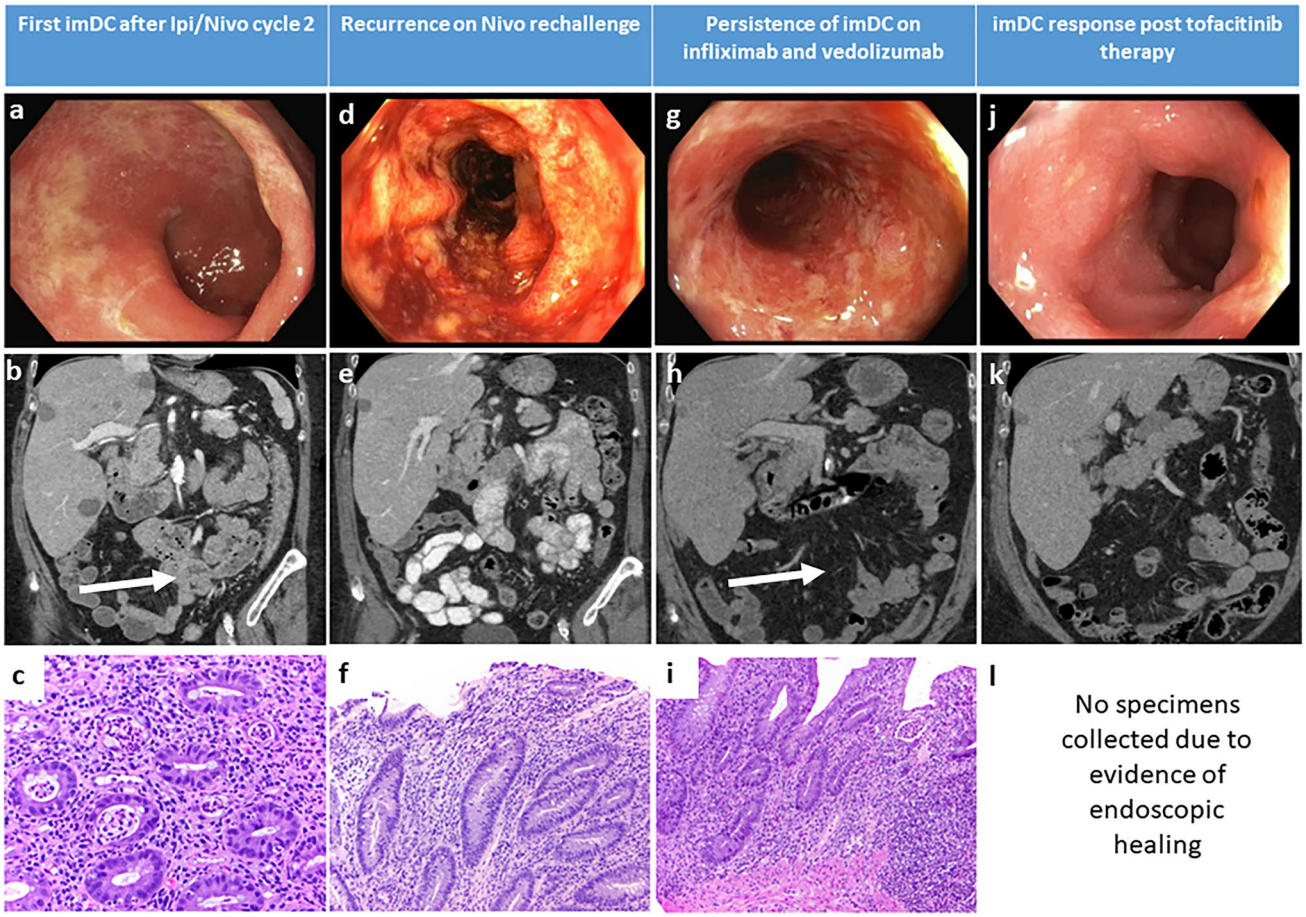

Fig. 1 Timeline of endoscopic, radiological, and histological features of the imDC case. Workup of first imDC event with bloody diarrhea included (**a**) endoscopy with moderate inflammation in the neo-terminal ileum (patchy ulceration, and altered vascularity), Mayo 1 pancolitis, characterized by mild congestion, erythema, and decreased vascular patterns (imaged) (**b**) CT scan with intravenous contrast revealed mildly thickened and hyperemic rectosigmoid and descending colon (arrow), suggesting colitis, as well as multiple liver lesions consistent with metastasis (**c**) pathology with acute ileitis and colitis characterized by cryptitis, crypt abscesses and mild crypt distortion along with prominent crypt apoptotic figures. Workup upon recurrence of imDC with chronic diarrhea after Nivo challenge (**d**) healthy neoterminal ileum and anastomosis, but diffuse area of moderately hemorrhagic, ulcerated decreased vascular pattern in the entire colon (Mayo 3 colitis) (**e**) CT scan with oral contrast shows minimal bowel thickening, and no new liver lesions, some decreased in size (**f**) histopathology revealed mildly active colitis with no evidence of dysplasia or immunostaining for cytomegalovirus. Workup after non-response to infliximab and vedolizumab, presenting as intractable diarrhea and abdominal pain (**g**) sigmoidoscopy with diffuse, severely erythematous mucosa with exudates and friability along the rectum extending to the sigmoid colon where an area of luminal narrowing was appreciated (image) (**h**) CT with intravenous contrast shows left colon and rectum are mildly thickened with surrounding fat stranding (arrow) compatible with proctocolitis (**i**) histopathological features of acute and chronic colitis (cryptitis, crypt abscess, lymphoplasmacytic expansion of lamina propria and mild crypt distortion) along with prominent crypt apoptotic figures. imDC response to tofacitinib (**j**) diffuse mildly erythematous and edematous mucosa with residual shallow ulcerations in the entire examined colon, much improved in comparison to previous exam (**k**) radiology with improvement in previously noted colitis findings (**l**) no histopathology samples obtained. *imDC* immune-mediated diarrhea and colitis, *Ipi/Nivo* ipilimumab/Nivolumab

infliximab dose. However, she developed recurrent diarrhea requiring admission and severe imDC was confirmed on endoscopy (endoscopic Mayo score 3) and on biopsy (see Fig. 1, Supplemental Table 1). Despite high-dose corticosteroids, infliximab (2 doses) and α4β7 integrin inhibitor vedolizumab (1 dose) over the subsequent 2 weeks of hospitalization, the patient remained symptomatic, with daily fecal calprotectin remaining above 2000 µg/g (normal < 50 µg/g). A trial of tofacitinib 10 mg twice daily was initiated. Following this, her symptoms subsided with a rapid downtrend in laboratory and imaging biomarkers, and a colonoscopy one week after initiation of tofacitinib revealed improved mucosal inflammation (see Fig. 1, Supplemental Table 1). Prednisone was slowly tapered, and tofacitinib continued for 4 months until complete clinical remission was achieved. ICI was not restarted and restaging imaging and tumor markers showed stable-appearing disease. The patient did not develop other irAEs.

Discussion

imDC is conventionally treated with steroids, and biologics are reserved for steroid-refractory imDC. However, approximately 3% of imDC are refractory to both, and the management of these patients is unclear [5]. Dysregulated Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling is implicated in multiple inflammatory pathologies and cancers [6]. Tofacitinib is an orally bioavailable small molecule that competitively and reversibly inhibits JAK1/JAK3 with a lesser degree of interaction with JAK2 [7, 8]. Tofacitinib is FDA-approved for the treatment of rheumatoid arthritis, psoriatic arthritis and ulcerative colitis (UC). Prior studies have established overlap in the clinical manifestations, as well as inflammatory pathways between UC and imDC, going as deep as changes in microbiome profiles [9], and even metabolomic pathways associated with favorable clinical response [10].

The use of tofacitinib has been described in refractory imDC in recent case studies [7, 8, 11, 12]. However, while these reports underscored the safety and success of tofacitinib in ameliorating imDC manifestations, there exists little information regarding the effects of tofacitinib exposure upon tumor response. Given the critical roles of JAK/STAT signaling in mediating ICI efficacy, there exists the potential for loss of effective antitumor control. This case illustrates the successful use of tofacitinib to induce clinical, endoscopic and histologic remission of imDC within a short interval of time while providing compelling evidence regarding the maintenance of continued anti-tumor control. Taken together with the earlier reports of tofacitinib efficacy in mediating steroid and biologic refractory imDC, these data argue in favor of considering JAK/STAT inhibitors in instances of treatment-refractory imDC.

In vitro analysis of patients with imDC suggest that the inflammatory pathology is mediated by a distinct population of $CD8^+$ tissue-resident memory cells that express high levels of CXCR6 and CXCR3, the ligands for which (CXCL16 and CXCL9/CXCL10 respective) are known to be regulated by both IFNγ and TNFα-providing rationale for targeting this pathway by JAK inhibitors in imDC [11, 13]. In UC patients, however, where many patients receive tofacitinib after non-response to tumor necrosis factor (TNF) inhibitors, distinct molecular signatures are suggested to be regulated by JAK inhibition and TNF blockade [14]. Further studies are underway to underscore the immune-related gene expression in imDC and understand the commonalities with UC. Comprehensive single-cell analysis of immune cell populations of imDC patients compared to healthy controls and/or patients with inflammatory bowel disease has implicated an IL-1β transcriptional program and tissue-resident $CD8^+$ central memory, $CD8^+$ effector memory, $CD8^+$ T effector cells and myeloid cells in the etiopathogenesis of imDC [13]. Separately, others have linked the composition of host gut flora to the development of IL-1β-mediated inflammatory program, and imDC [15].

Nevertheless, given that JAK signaling is involved in multiple pro-inflammatory and anti-tumor pathways, there are significant concerns that the use of JAK inhibitors may compromise anti-tumor efficacy of ICIs. Indeed, loss of function mutations in JAK1/2 is associated with both primary and acquired resistance to ICI therapy [16, 17]. In addition, evidence from prospective trials of tofacitinib in autoimmune diseases including rheumatoid arthritis and UC suggest an increased risk of non-melanoma skin cancer and other cancers with tofacitinib compared to tumor necrosis factor inhibitors, especially after 18 months of therapy [18, 19]. However, other risk factors may contribute to this risk, namely duration of inflammatory disease, age > 65 years, and prior exposure to carcinogens including ultraviolet light [20]. In addition, studies on baricitinib and fedratinib (other JAK inhibitors) demonstrated downregulation of PD-L1 expression, which could offer an anti-tumor augmented effect for patients with cancer on both JAK inhibitors plus immune-checkpoint blockers [21, 22]. As tofacitinib has selective JAK1/3 inhibition, further studies are warranted to understand the impact of its use on malignant tumor response to ICI therapy.

The management of steroid- and biologic-refractory colitis is uncertain. The use of tertiary adjuncts such as tofacitinib may be considered in carefully selected patients. The above case illustrates **both** the rapid time to onset of tofacitinib and the durable response elicited with clear evidence of ongoing anti-tumor immune responses despite cessation of ICI therapy. The management of steroid and biological

refractory colitis is a pressing problem and should be a focus of rational drug development. Future studies should emphasize the use of rationally selected agents (fecal microbiome transplant, selective JAK1 inhibitor upadacitinib) targeting pathways implicated in imDC etiopathogenesis (gut dysbiosis, JAK/STAT signaling) and require histopathologic efficacy assessment and concurrent consideration of the degree of anti-cancer control.

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Declarations

Conflict of interest J.S., R.M. B, R.E.B, J.R and M.S. have no conflict of interest to disclose. R. P. has the following disclosures: Consultant for Alimentiv. D.D. has the following disclosures: Grants/Research Support (institutional): Arcus, CellSight Technologies, Immunocore, Merck, Regeneron Pharmaceuticals Inc., Tesaro/GSK. Consultant: Clinical Care Options (CCO), Finch Therapeutics, Gerson Lehrman Group (GLG), Medical Learning Group (MLG), Xilio Therapeutics. CE Speakers' Bureau: Castle Biosciences. Stockholder: None. Intellectual Property: US Patent 63/124,231, "Compositions and Methods for Treating Cancer", Dec 11, 2020 US Patent 63/208,719, "Compositions and Methods For Determining Responsiveness to Immune Checkpoint Inhibitors (ICI), Increasing Effectiveness of ICI and Treating Cancer", June 9, 2021.

Ethical approval The patient has consented through the University of Pittsburgh IRB protocol CR20010266-005.

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