

Case Series

Severe Inflammatory Colitis Related to Encorafenib and Binimetinib following Immune Checkpoint Inhibitor Therapy

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Keywords

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Abstract

Encorafenib, a BRAF kinase inhibitor, in combination with binimetinib, a selective MEK inhibitor have known gastrointestinal adverse events; however, adverse colitis events have not been well studied. We report a case series of 4 patients with melanoma who developed inflammatory colitis after BRAF and MEK inhibition with encorafenib and binimetinib, respectively. In the setting of immune checkpoint inhibitor use, BRAF and MEK inhibitors can cause significant inflammatory colitis with endoscopic patterns of predominant right colon ulcerations. It can lead to significant morbidity and frequent interruption of cancer treatment. Early recognition and prompt intervention are critical to improving patient outcomes.

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Introduction

Encorafenib, a BRAF kinase inhibitor, in combination with binimetinib, a selective MEK inhibitor, were FDA approved for unresectable or metastatic melanoma that has a BRAF V600K or V600E mutation in June 2018 after the phase 3 COLUMBUS trial [1]. Gastrointestinal

adverse events were relatively common, with 34% of patients receiving a combination of encorafenib plus binimetinib were noted to have grade 1–2 diarrhea and 3% with grade 3–4 diarrhea. Nausea, vomiting, and abdominal pain were also reported [1]. We present a case series of patients with severe inflammatory colitis associated with encorafenib and binimetinib after immune checkpoint inhibitor (ICI) use.

Materials and Methods

The MD Anderson Cancer Center Institutional Review Board granted permission for chart review. The electronic medical record was reviewed for these selected 4 patients with a prior exposure to ICI therapy, then received encorafenib and binimetinib, and then developed colitis.

Case Report

Four patients with melanoma that had been previously treated with ICI therapy then subsequently received encorafenib and binimetinib and developed colitis were identified (Table 1; online suppl. Fig. 1a, b; for all online suppl. material, see www.karger.com/doi/10.1159/000525012). Two patients had received nivolumab, an ICI-programmed cell death-1 (PD-1) inhibitor in the past, and 2 had received nivolumab in combination with ipilimumab, an ICI-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor. Each patient developed colitis at a different time point following initiation of encorafenib and binimetinib.

Patient A with stage III melanoma with multiple retroperitoneal nodes received nivolumab, followed by encorafenib plus binimetinib for lack of response to ICI therapy. She had a partial cancer response on this regimen, and after 14 months, a dose increase was attempted. She was subsequently hospitalized due to fever, acute kidney injury, and common terminology criteria for adverse events (CTCAE) grade 2 diarrhea (18 months after initial ICI therapy). A computed tomography scan demonstrated a thickened ascending colon. Infectious work up was negative, while stool inflammatory markers (lactoferrin and calprotectin) were positive. Oral budesonide achieved resolution of the diarrhea symptom, but 3 weeks later, patient developed melena and hematochezia with symptomatic anemia. Computed tomography scan demonstrated worsening colitis. Colonoscopy showed patchy, friable, and ulcerated mucosa in the ascending colon and cecum with pathology confirmation of mild focal active colitis with increased chronic inflammation (endoscopic images for each patient on initial presentation and after treatment are shown in online suppl. Fig. 1a). With continued intermittent hematochezia, encorafenib and binimetinib were briefly held then resumed at a reduced dose. She had no further melena or diarrhea for 3 months after stopping binimetinib, and her metastatic melanoma remains stable on encorafenib monotherapy. At her last follow-up, her encorafenib dose was increased, and her stage 4 melanoma was stable. Her most recent colonoscopy showed a solitary ulcer in the ascending colon with a tight stricture of the lumen from the healing ulcer that required balloon dilatation.

Patient B with stage IV M1c metastatic melanoma with metastasis of liver, lung, and bone was previously treated with a combination of nivolumab and ipilimumab, followed by vinblastine, cisplatin, and dacarbazine with all resulting in disease progression. She was then started on encorafenib and binimetinib and developed hematochezia 8 weeks later (6 months after initial ICI therapy). Colonoscopy showed extensive ulcerative inflammation with biopsy

Table 1. Characteristics of patients

Patient	A	B	C	D
Age at onset	70s	50s	60s	70s
Gender	Female	Female	Female	Female
Cancer type	Melanoma	Melanoma	Melanoma	Melanoma
Previous ICIs	Nivolumab	Ipilimumab Nivolumab	Ipilimumab Nivolumab	Nivolumab
Time between first dose of ICIs and colitis presentation, months	18	6	8	15
Time between previous ICIs and encorafenib/binimetinib initiation, weeks	9	16 (nivolumab later restarted after encorafenib/binimetinib initiation)	9	31
Time since initiation of encorafenib/binimetinib, months	30	17	15	8
Initial GIAEs presentation	Diarrhea, melena	Hematochezia and symptomatic anemia	Diarrhea and hematochezia	Hematochezia
Initial CTCAE	Grade 2 diarrhea and colitis	Grade 3 colitis	Grade 2 diarrhea and colitis	Grade 2 colitis
Colitis treatments	Oral budesonide, binimetinib cessation	Prednisone, methylprednisolone, budesonide, infliximab, vedolizumab, ustekinumab, followed by FMT	Prednisone, methylprednisolone, budesonide, infliximab, ustekinumab, vedolizumab, FMT, and a brief hold of binimetinib and encorafenib	Budesonide and binimetinib cessation
Time from presentation to initial endoscopic evaluation, days	26	3	2	5
Upper endoscopy	Negative	Nonbleeding clean-based gastric and duodenal ulcers	Nonbleeding erosive gastropathy, erythematous duodenopathy	Negative
Colonoscopy (online suppl. Fig. 1)	Multiple ulcers	Extensive ulcers	Extensive ulcers	Large ulcer
Location of colitis/ulcers	Ascending colon	Ileum, cecum, ascending colon	Sporadic through the entire colon including the left colon	Ascending colon
Clinical remission	Yes	Yes	Yes	Yes
Endoscopic remission	Yes	No	No	Yes
Colonic stricture due to healing ulcer	Yes	No	Yes	Yes
Follow up duration after colitis onset, months	13	11	14	4
Current cancer treatment	Encorafenib	N/A	Encorafenib and binimetinib	Encorafenib and binimetinib
Vital status at the end of study period	Alive	Deceased due to cancer progression	Alive	Alive
Cancer status at last follow-up	Stable	Progression	Progression	Progression

showing moderate active colitis. Prednisone was started for possible ICI/targeted therapy induced colitis. However, she soon developed recurrent hematochezia with severe anemia requiring transfusion 2 weeks later. She responded to 3 doses of infliximab but steroid tapering triggered recurrent diarrhea and hematochezia 7 weeks later. Another repeat colonoscopy showed slightly improved patchy inflammation and new luminal stenosis in the ascending colon from the healing ulcer. Encorafenib and binimetinib were briefly held then resumed at half-dose. She was then treated with 3 doses of vedolizumab with improvement in her symptoms. Colonoscopy performed 6 weeks after initiation of vedolizumab showed improving colonic inflammation. Then, encorafenib and binimetinib were increased to full dose and 2 doses of nivolumab were also given for cancer progression. Despite vedolizumab maintenance, her hematochezia recurred with severe anemia requiring hospitalization and transfusion again. Another colonoscopy was performed which showed a large area of ulceration in the terminal ileum and cecum. Encorafenib and binimetinib were stopped. Ustekinumab was initiated and achieved initial symptom improvement for 5 weeks; then, she returned to the hospital again for recurrent hematochezia and severe anemia. After multidisciplinary evaluation, she ultimately received fecal microbiota transplantation (FMT) as compassionate treatment. She had no recurrent gastrointestinal bleeding for 4 months after FMT, but eventually died due to cancer progression.

Patient C had stage IV M1d metastatic melanoma with metastasis in the lung and liver was treated initially with nivolumab followed by dabrafenib and trametinib, which were discontinued for disease progression, and then ipilimumab and nivolumab complicated by colitis. She was initially hospitalized with worsening bloody diarrhea refractory to budesonide (8 months after ICI therapy was initiated). Colonoscopy showed diffuse colitis with superficial ulcers and biopsies showing moderate active chronic colitis. After resolution of colitis 5 weeks following prednisone and 2 doses of infliximab, encorafenib, and binimetinib were initiated. A week later, she was hospitalized with nonbloody diarrhea and treated again with corticosteroids and infliximab, then subsequently switched to vedolizumab with improvement. A repeat colonoscopy after 3 doses of vedolizumab showed persistent superficial ulcers with a deep ulcer over the ileocecal valve and biopsies showed focal cryptitis and lamina propria neutrophilia, for which vedolizumab was switched to ustekinumab. Three months later, she was hospitalized again with nonbloody diarrhea in the setting of colitis. Binimetinib was held, and she received compassionate FMT via colonoscopy 2 weeks later. She achieved clinical remission of colitis after FMT and discontinuation of encorafenib and binimetinib. A follow-up colonoscopy 2 months after FMT showed one residual ulcer in the ascending colon similar in appearance to the prior colonoscopy. Paclitaxel was failed afterward, and the patient was resumed on encorafenib and binimetinib for the cancer progression.

Patient D with stage IV M1d metastatic melanoma with metastasis in the lung, liver, and soft tissue failed to respond to dabrafenib and trametinib and subsequent nivolumab, then started encorafenib and binimetinib therapy. Two months later, she was hospitalized for rectal bleeding and severe anemia requiring transfusion (15 months after ICI therapy was initiated). Colonoscopy showed severe ulceration at the ileocecal valve and the ascending colon with biopsies showing acute inflammation and apoptotic bodies. Budesonide was started, and binimetinib was held leaving encorafenib as monotherapy for her cancer. A follow-up colonoscopy 4 weeks later showed healing of the previous large ulcer with significant luminal stricture that required balloon dilatation. All the clinical symptoms of colitis resolved.

The colitis of patients A and D proved responsive to binimetinib cessation and budesonide, while patients B and C had more aggressive and refractory disease courses which consisted of minimal improvement with potent immunosuppressants, cessation of both encorafenib

and binimetinib, and ultimately responsive to FMT. Patient A remains stable on encorafenib therapy alone, while the other 3 patients experienced cancer progression.

Discussion

Encorafenib and binimetinib are important targeted therapies for unresectable or metastatic melanoma. Diarrhea is a well-documented adverse event that is related to these agents and other BRAF/MEK inhibitor combinations [1, 2]. However, severe GI bleeding with ulceration of the colon is rarely reported in the literature. The mechanism of inflammation has not been well characterized but may be related to alteration of the MAPK signaling pathway which has previously been shown to affect endothelial and epithelial stress and inflammatory responses [3, 4]. It is notable that all the presented cases in this study had received ICI prior to receiving BRAF/MEK inhibitor therapy, and ICI-induced GI toxicity is frequently encountered and studied [5]. A prior case series reported on a combined regimen of BRAF/MEK inhibition and ipilimumab leading to colitis and perforation in 2 patients [6]. Another case series reported three cases of colitis or enteritis associated with MEK inhibition, two of whom had received prior ICI therapy. The inflammation resolved after MEK inhibitor cessation in all the cases [7]. Similarly, a small pilot prospective single-arm trial identified 1 patient who received binimetinib monotherapy for melanoma and developed fibrinous colitis [8]. In accordance with these cases from the literature, the clinical course in the presented cases would suggest that MEK inhibition with binimetinib was the primary driver of bleeding and mucosal ulceration in the GI tract given the response to dose reduction and cessation; therefore, recognition of severe colitis related to targeted therapy and the role of endoscopy evaluation with additional treatment including steroid, biologics, and even FMT for selected cases is very critical to achieve the resolution of colitis. In addition, there is a potential contributing factor from prior ICI exposure. The luminal stricture secondary to healing colonic ulceration predominantly in ascending colon in our cases has a unique pattern that is different from ICI colitis and could pose a significant risk of delayed colonic obstruction and potential requirement for surgical intervention. The wide variation in the timeline between ICI exposure, and colitis onset may argue against their strong correlation in certain cases. Future studies with larger sample size can better characterize the gastrointestinal adverse event related to ICI and BRAF/MEK inhibitors and assess the treatment options and long term outcomes.

Statement of Ethics

The MD Anderson Cancer Center Institutional Review Board granted permission for chart review and informed written consent to publish this case including pathology images was waived (protocol PA18-0472).

Conflict of Interests Statement

Yinghong Wang serves as a consultant for Tillotts Pharma and AzurRx Pharma. The other authors declare no conflict of interest related to the study findings.

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Author Contributions

Yinghong Wang: study concept and design and review and revision of the manuscript. David Szafron and Aaron G. Issac: acquisition of data, analysis and interpretation of data, and drafting of the manuscript. Dongguang Wei: provided pathology images. Jennifer L. McQuade: provided critical review and revision of the manuscript. All the authors reviewed and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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