Case Reports in Oncology

Case Rep Oncol 2024;17:191–201
DOI: 10.1159/000535741
Received: November 7, 2023
Accepted: December 6, 2023
Published online: February 2, 2024

Case Report

Severe Colitis in 2 Patients with Melanoma Treated with BRAF/MEK Inhibitors: Case Report and Literature Review

Chloe Wautier[a] Jolanta Gourmaud[b] Catherine Dong[c] Gregoire Berthod[d]

[a]Department of Internal Medicine, Sion Hospital, Sion, Switzerland; [b]Department of Pathology, Sion Hospital, Sion, Switzerland; [c]Department of Gastroenterology, Sion Hospital, Sion, Switzerland; [d]Department of Oncology, Sion Hospital, Sion, Switzerland

Keywords
Colitis · Gastrointestinal toxicity · Melanoma · Encorafenib · Binimetinib

Abstract
Introduction: Encorafenib and binimetinib, a combination of BRAF and MEK inhibitors, is a standard of care for patients with advanced BRAFV600-mutant melanoma. This combination is known to have gastrointestinal side effects, most of which are mild and managed symptomatically. However, very few studies have reported severe colitis. ***Case Presentation:*** We report here 2 patients with advanced melanoma who developed severe ulcerated right colitis manifested by diarrhea and hematochezia while being treated with encorafenib and binimetinib after immune checkpoint therapy. ***Conclusion:*** This rare but serious adverse event was not described in early phase 3 trials but has emerged in recent years, particularly with the sequential use of immune checkpoint inhibitors followed by BRAF/MEK inhibitors. In a comprehensive review of the existing literature, we identified 20 cases of severe colitis due to BRAF/MEK inhibitors. Clinical, endoscopic, and histological features are described to provide insight into the current understanding of this poorly understood clinical entity.

Catherine Dong and Gregoire Berthod contributed equally to this work.

Correspondence to:
Chloe Wautier, chloe.wautier@hopitalvs.ch

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DOI: 10.1159/000535741

Introduction

Treatment of metastatic melanoma has improved significantly over the past 10 years. Immune checkpoint inhibitors (ICIs), anti-PD1 +/− anti-CTLA4, can provide durable response in a proportion of patients, including those with brain metastasis [1]. The extent of the benefit between gender [2] and general condition of the patient, particularly in frail patients (ECOG >1), remains to be established [3]. Around 50% of patients with metastatic cutaneous melanoma harbor a BRAFV600 mutation. These patients can be treated with either ICIs or a combination of BRAF and MEK inhibitors (BRAF/MEKi). Several phase III trials have shown a significant overall survival benefit with these regimens. Three targeted therapies doublets have been approved: vemurafenib/cobimetinib, dabrafenib/trametinib, and more recently encorafenib/binimetinib [4–6]. In the absence of contra-indications, starting with ICIs and reserving targeted therapies for a later line is usually the preferred option [7].

ICIs are known to cause gastrointestinal immune-related adverse events, particularly colitis. The presentation, pathophysiology, and management of these gastrointestinal adverse effects have been extensively studied and guidelines for their management are available. The BRAF/MEKi combination is also known to have gastrointestinal side effects, which are generally mild and can be managed symptomatically by drug interruption and dose reduction. Very few studies have reported severe colitis due to BRAF/MEKi and the mechanism remains unclear. We report here on 2 patients with melanoma who developed severe right colitis during treatment with encorafenib and binimetinib after ICI therapy. We also reviewed the existing literature on severe colitis induced by BRAF/MEKi to provide insight into this poorly understood clinical entity. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000535741).

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Patient A was a frail, 80-year-old man with a history of B-cell chronic lymphocytic leukemia on ibrutinib at the time of diagnosis of a stage IIIC ulcerated BRAFV600K-mutant melanoma, located on the back. On hematological advice, ibrutinib was stopped and adjuvant treatment with pembrolizumab was started.

After 3 months of anti-PD1 treatment, the CT scan showed rapidly progressive disease with lung, liver, and subcutaneous metastases. Due to the presence of BRAFV600K mutation, treatment was changed to BRAF/MEKi (encorafenib and binimetinib). One month later, he was admitted to the hospital due to deterioration of his general condition and fever. He presented with liquid diarrhea 2–3 times a day and episodes of hematochezia without abdominal pain. Laboratory tests revealed anemia (hemoglobin 77 g/L) with inflammatory syndrome (CRP level 82 mg/L) and low albumin level of 18.9 g/L. Fecal analyses were negative for bacteria and viruses. Fecal calprotectin concentration was 265 mg/kg. CMV PCR was negative. Blood cultures were positive for *Enterococcus faecium* and *Escherichia coli*, suggesting bacteremia of digestive origin. CT scan showed circumferential thickening of the ascending colon. Liver metastases were stable. Colonoscopy revealed inflammation of the right colon with a deep ulceration estimated to be 5 cm long and 2 cm wide (Fig. 1a, b). Mucosa of the left colon appeared endoscopically normal. Histologically, the mucosa of the right colon showed discrete and nonspecific changes, with architectural irregularities and edema of the lamina propria. There was eosinophilic infiltration but no neutrophilic activity, plasmacytosis, or intraepithelial lymphocytosis (Fig. 2a, b).

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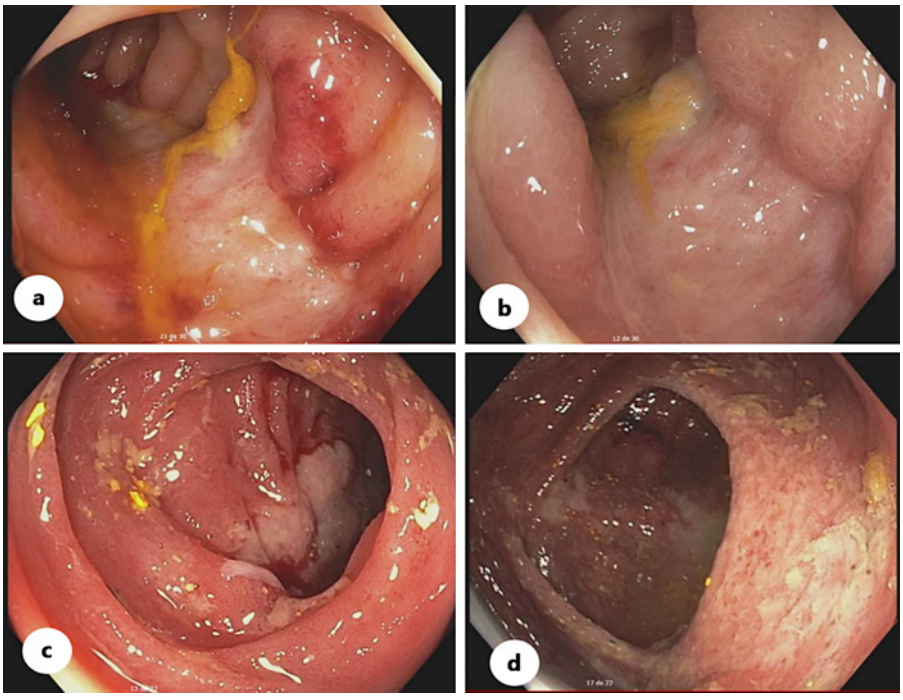

Fig. 1. Endoscopic images showing a deep ulcer in the right colon of patient 1 (**a**, **b**). Extensive superficial ulcers in the ileum (**c**), cecum, and right colon of patient 2 (**d**).

Antibiotherapy was started for the bacteremia. Discontinuation of encorafenib and binimetinib resulted in a marked improvement of diarrhea and hematochezia. Unfortunately, the patient died of an opportunistic respiratory infection during the hospital stay.

Patient B was a 68-year-old man, diagnosed in 2018 with BRAFV600E-mutant cutaneous melanoma, stage IIIB, of the left ear. He underwent surgery and adjuvant pembrolizumab for 6 months, which was discontinued due to arthralgia. One year later, he progressed with liver and bone metastases. Due to the high tumor burden in the liver, he started dabrafenib and trametinib. After 6 weeks, the CT scan showed a good response. Treatment was switched to nivolumab and ipilimumab. After one cycle, the patient developed immune-mediated pneumonitis, leading to discontinuation of ICIs and the initiation of corticosteroid therapy. Given the stability of his melanoma, the patient underwent therapeutic abstention for 1 year. In May 2021, encorafenib/binimetinib was given for a new disease progression. Fourteen months later, he developed diarrhea twice a day with hematochezia. Laboratory tests revealed anemia with a hemoglobin level of 108 g/L (143 g/L 2 months before), a CRP level of 83.3 mg/L, and a serum albumin level of 28.8 g/L. Stool analysis revealed no infectious etiology. Colonoscopy showed right ulcerative ileocolitis with extensive superficial ulcers in the ileum, cecum, and right colon (Fig. 1c, d). Histology revealed acute ulcerative ileitis and multifocal erosive and ulcerated colitis in the cecum with focal eosinophilic infiltration (Fig. 2c, d). As the patient was already receiving prednisone 20 mg/day for rheumatoid arthritis, the prednisone was increased to 60 mg/day, and encorafenib/binimetinib was discontinued.

The patient's symptoms resolved within 1 week, with improvement in anemia and biological parameters. A follow-up colonoscopy 4 months later showed complete resolution of the right ileocolitis.

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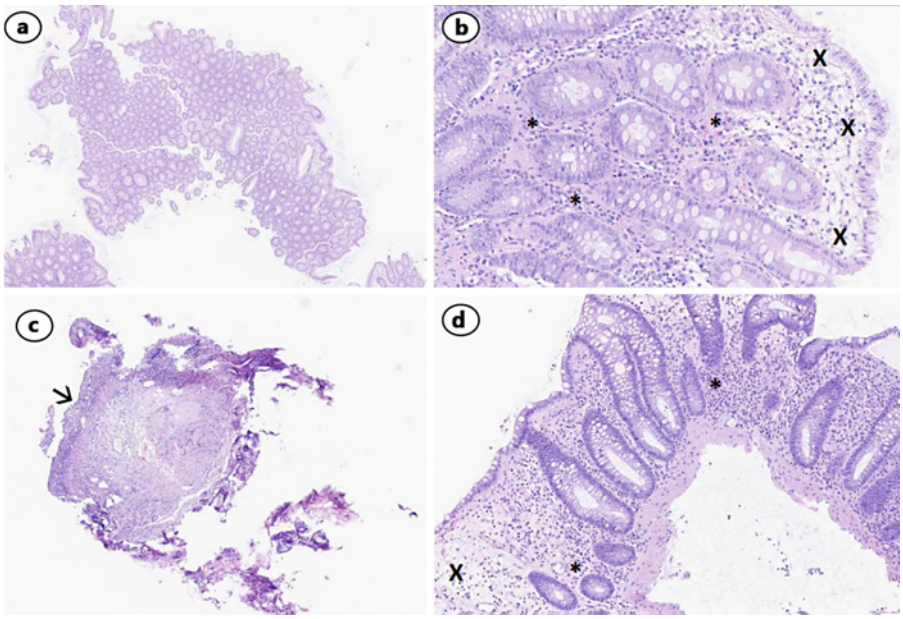

Fig. 2. Histological examination of the right colon, close to the ulcer in patient 1, reveals mild architectural irregularities (**a**, ×50) and edema of the lamina propria (X), along with eosinophilic infiltration (*) without neutrophils (**b**, ×200). Cecal biopsies from patient 2 are similar, with ulcerated areas (→) (**c**, ×50), and other areas show edematous lamina propria (X) with mild lymphocytic and plasmacytic infiltrates, accompanied by neutrophils and eosinophils (*) (**d**, ×100). Notably, in all cases, there is no basal plasmacytosis, intraepithelial lymphocytosis, or increased apoptotic bodies.

Discussion

Three combinations of BRAF/MEKi have shown a survival benefit in metastatic melanoma harboring a BRAFV600 mutation. The latest, encorafenib and binimetinib, was approved by the FDA in April 2020. This combination is known to have gastrointestinal side effects, most of which are mild and can be managed symptomatically [4, 8, 9]. In particular, the pivotal COLOMBUS trial reported 34% grade 1–2 diarrhea, 3% grade 3–4 diarrhea, and no cases of colitis. Since then, ICIs have become part of the therapeutic arsenal and are often prescribed as the first-line treatment, leaving targeted therapies for later lines. In the last few years, several cases of severe colitis with BRAF/MEKi have been published.

Carbonnel et al. [10] reported the largest series of 10 patients with advanced melanoma who had severe BRAF/MEKi-related colitis requiring hospitalization. Nine patients were treated with encorafenib and binimetinib and 1 patient with dabrafenib and trametinib. Most patients experienced diarrhea and hematochezia, but only two had abdominal pain. Blood tests showed anemia, elevated CRP, and low serum albumin levels in most patients. All patients had ulcerations of the right colon. One patient had ileal involvement and 4 patients had ulcerations distal to the right colon. Interestingly, 6/10 patients had received ICIs prior to targeted therapy. Their clinical presentation was indistinguishable from that of patients who had not been exposed to ICIs. The median time from the last dose of ICIs to colitis was 17 months. Six patients recovered after drug withdrawal, four of them required corticosteroid with or without infliximab. Two patients required bowel resection, one became corticosteroid-dependent and one died.

Issac et al. [11] reported 4 patients with metastatic melanoma who all developed hematochezia and three of them had diarrhea after encorafenib and binimetinib. Colonoscopy showed extensive ulceration, predominantly in the right colon. All 4 patients were previously

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treated with ICIs between 6 and 18 months prior to the start of the BRAF/MEKi combination. All were in clinical remission after stopping treatment, two of them had prednisone and infliximab followed by vedolizumab.

Mourad et al. [12] performed a retrospective analysis of gastrointestinal toxicities in 119 melanoma patients treated with MEKi alone or in combination with BRAFi or anti-PD1. They described 6 (5%) patients with severe grade 3–4 gastrointestinal toxicity: 2 cases of perforation, 3 cases of severe colitis, and 1 case of severe diarrhea. Among the 3 patients with colitis, all had ulceration of the ileum, colon, or rectum. These adverse events were reversible after discontinuation of treatment.

Gelsomino et al. [13] reported a man with BRAF-mutant non-small cell lung cancer who was treated with encorafenib and binimetinib. Initial radiological assessment showed thickening of the right colon. Colonoscopy showed diffuse mucosal erythema of the right upper colon and deep and extensive ulcerations of the cecum. Encorafenib and binimetinib were discontinued. No specific treatment was given as the patient had mild symptoms.

Our 2 patients are in line with those described in these case series, with similar clinical and endoscopic features. Their characteristics are summarized in Table 1. Colitis associated with BRAF/MEKi seems to have mild initial clinical presentation, mainly with diarrhea and hematochezia, but less frequently with abdominal pain. Stool frequency may be lower than that usually observed in ICI-induced colitis. However, if treatment is not discontinued, severe complications such as stenosis or perforation have been described. Laboratory tests may show anemia, elevated CRP, and hypoalbuminemia. Colonoscopy usually shows inflammation and large ulcers in the ileum and the right colon. Pathology examination reveals an unspecific mixed inflammatory infiltration with predominant neutrophils and eosinophils but low lymphoplasmacytic infiltration, more suggestive of drug-induced colitis than ICI-induced colitis. Specifically, there are marked histological differences between the two processes, with BRAF/MEKi-related inflammation lacking intraepithelial lymphocytes or epithelial apoptotic bodies commonly seen in ICI-related inflammation.

The mechanisms by which BRAF/MEKi can lead to colitis and ulceration are not yet understood. The Ras-MEK-ERK signaling pathway plays a critical role in the proliferation, differentiation, migration, and survival of the gastrointestinal epithelium. MEK inhibitors block this pathway, which may explain the mucosal damage leading to gastrointestinal toxicity [13, 14].

In phase III trials, a minority of patients had prior exposure to immunotherapy (30% in the COLOMBUS trial [1], 10% in Larkin et al. [5], and 22% in Robert et al. [6]). However, in current clinical practice, most patients receiving BRAF/MEKi therapy have received prior immunotherapy. Some studies [11, 15] suggest that prior ICI exposure may be a contributing factor to BRAF/MEKi-induced colitis. The study by Kuang et al. [15] shows that the sequence of anticancer treatments may influence the severity of gastrointestinal toxicity. Specifically, they found that patients who received ICIs followed by BRAF/MEKi combination experienced more severe gastrointestinal toxicity (50.0% grade 3–4 diarrhea and 38.9% grade 3–4 colitis) than patients treated with BRAF/MEKi followed by ICIs (14.3% and 0%, respectively). The introduction of BRAF/MEKi may potentiate a subclinical, ongoing colonic inflammation initiated by prior ICI therapy, ultimately leading to the development of severe symptoms. This may explain the recent emergence of severe colitis as a significant adverse effect that was not well identified in initial phase III trials. If treatment with BRAF/MEKi is planned after treatment with ICIs, it might be interesting to measure fecal biomarkers of inflammation (e.g., fecal calprotectin) and undergo gastroenterological evaluation if elevated.

The optimal treatment approach remains uncertain. BRAF/MEKi should be discontinued, leading to a rapid improvement of symptoms in a proportion of patients. Although most patients have received corticosteroids and second-line immunosuppressive

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Table 1. Characteristics of the patients with colitis due to BRAF/MEKi

	Drugs	Age, years /sex	Treatment prior BRAF/MEKi	Time between initiation of BRAF/MEKi and colitis	Symptoms	Colonoscopy	Histology	Medical therapy of colitis	Outcome
Patient A (*melanoma*)	Enco + Bini	80/ man	Pembro (melanoma) Ibrutinib (CLL)	2–5 weeks	Diarrhea, hematochezia	Deep ulceration of the right colon	Discrete architectural irregularities and edema of the lamina propria. Eosinophilic infiltration without neutrophils	Enco + Bini withdrawal No steroid	Improvement of diarrhea and hematochezia within 1 week. Death (lung infection)
Patient B (*melanoma*)	Enco + Bini	68/ man	Pembro Dabra/Trame Nivo + Ipi (pneumonitis)	14 months	Diarrhea, hematochezia	Ulcerated right ileocolitis with large superficial ulcerations	Ulcerated ileitis with edema of the lamina propria with some neutrophils and eosinophils. Ulcerated multifocal colitis in the cecum with mild lymphocytic and plasmacytic infiltrates, accompanied by neutrophils and eosinophils	Enco + Bini withdrawal Increase in prednisone (20 mg/d to 60 mg/d)	Symptoms resolved within 1 week Colonoscopy 4 months later: complete healing
Carbonnel et al. [10] (2023) (*melanoma*)	Enco + Bini	65/ woman	Enco + Bini Nivo + Ipi (hepatitis)	2 months	Abdominal pain, fever	Large, deep ulceration of the right colon	Histological details not provided	Enco + Bini withdrawal Steroids + infliximab refractory	Subtotal colectomy Recovery
Carbonnel et al. [10] (2023) (*melanoma*)	Enco + Bini	63/ woman	Nivo + Ipi (ileitis/ hepatitis)	9 months	Diarrhea, fever	Ulcerations of the colon, very large in the right colon	Ulceration with moderate inflammatory infiltrate of the lamina propria (plasma cells, lymphocytes, and neutrophils). Spotty hemorrhage, Intracapillary thrombi, vascular congestion	Enco + Bini withdrawal + steroids Infliximab	Recovery Enco + Bini resumed, led to relapse of diarrhea
Carbonnel et al. [10] (2023) (*melanoma*)	Enco + Bini	90/ woman	Pembro	14 months	Diarrhea, enterococcus fecalis septicemia	Ulcerations of the right colon	Histological details not provided	Enco + Bini withdrawal	Recovery Stenosis of the ileocecal valve

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Table 1 (continued)

	Drugs	Age, years /sex	Treatment prior BRAF/MEKi	Time between initiation of BRAF/MEKi and colitis	Symptoms	Colonoscopy	Histology	Medical therapy of colitis	Outcome
Carbonnel et al. [10] (2023) (*melanoma*)	Enco + Bini	51/ woman	Adjuvant Nivo + Ipi, followed by Dabra + Trame and Nivo + Ipi	3 months	Intestinal obstruction, anemia	Ulcerations of the right colon, stenosis of the ileocecal valve	Lymphocytic phlebitis	Dose reduction of Enco + Bini, steroids, endoscopic dilatation	Resection of terminal ileum and right colon. Recovery
Carbonnel et al. [10] (2023) (*melanoma*)	Enco + Bini	82/ woman	None	1.5 months	Diarrhea, hematochezia shock	Ulcerations of the right colon	Histological details not provided	Enco + Bini withdrawal steroids	Death
Carbonnel et al. [10] (2023) (*melanoma*)	Enco + Bini	50/ woman	Adjuvant Pembro followed by Nivo + Ipi (colitis)	3 months	Diarrhea, hematochezia	Colitis of the transverse and right colon	Histological details not provided	Enco + Bini withdrawal steroids Infliximab	Enco + Bini resumed at low dose after clinical remission of colitis. No relapse of colitis. Progression of melanoma, death
Carbonnel et al. [10] (2023) (*melanoma*)	Enco + Bini	78/ woman	None	5 months	Abdominal pain, anemia, mild diarrhea, hematochezia	Colitis of the transverse and right colon	Histological details not provided	Enco + Bini withdrawal	Recovery
Carbonnel et al. [10] (2023) (*melanoma*)	Enco + Bini	71/ man	Nivo + Ipi (jejunitis and colitis)	0.5 month	Diarrhea, hematochezia	Large and deep ulcerations over the colon, very large in the sigmoid	Histological details not provided	Enco + Bini withdrawal Enco + Bini resumed at half dose Enco + Bini withdrawal + steroids	Improvement Relapse of diarrhea Recovery
Carbonnel et al. [10] (2023) (*melanoma*)	Enco + Bini	56/ woman	Dabra + Trame	2 months	Intestinal obstruction	Ulceration and stenosis of the ileocecal valve	Histological details not provided	Enco + Bini withdrawal steroids	Recovery

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Table 1 (continued)

	Drugs	Age, years /sex	Treatment prior BRAF/MEKi	Time between initiation of BRAF/MEKi and colitis	Symptoms	Colonoscopy	Histology	Medical therapy of colitis	Outcome
Carbonnel et al. [10] (2023) (*melanoma*)	Dabra + Trame	79/ woman	None	1 month	Diarrhea	Large and deep ulcerations over the colon, deep ulcerations in the sigmoid and the rectum	Histological details not provided	Dabra + Trame withdrawal Dabra + Trame resumed at half dose, relapse of diarrhea Steroids	Remission Steroid dependency
Issac et al. [11] (2022) (*melanoma*)	Enco +Bini	70/ woman	Nivo	Not described	Diarrhea, hematochezia anemia, fever	Colitis and ulceration of the right colon and cecum	Mild focal active colitis with increased chronic inflammation	Oral budesonide Enco + Bini withdrawal Enco alone resumed at a reduced dose	No effect Recovery Balloon dilatation of colonic stricture
Issac et al. [11] (2022) (*melanoma*)	Enco + Bini	50/ woman	Nivo + Ipi	8 weeks (6 months after ICI)	Grade 3 colitis Hematochezia anemia	Extensive ulcers of the ileum, cecum, and right colon	Moderate active colitis	Steroids, infliximab, vedolizumab, ustekinumab Enco + Bini withdrawal + FMT	Improvement followed by relapse Colitis recovery Cancer progression
Issac et al. [11] (2022) (*melanoma*)	Enco + Bini	60/ woman	Dabra + Trame Nivo + Ipi (colitis)	1 week	Non-bloody diarrhea	Superficial ulcers with a deep ulcer over the ileocecal valve	Focal cryptitis and lamina propria neutrophilia	Steroids, infliximab, ustekinumab, vedolizumab FMT, hold of Enco + Bini	Improvement followed by relapse Colitis recovery
Issac et al. [11] (2022) (*melanoma*)	Enco + Bini	70/ woman	Dabra + Trame Nivo	2 months (15 months after ICI)	Grade 2 colitis Hematochezia anemia	Severe ulceration at the ileocecal valve and the right colon	Acute inflammation and apoptotic bodies	Bini withdrawal Continuation of Enco + steroid	Balloon dilatation Colitis recovery

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Table 1 (continued)

	Drugs	Age, years /sex	Treatment prior BRAF/MEKi	Time between initiation of BRAF/MEKi and colitis	Symptoms	Colonoscopy	Histology	Medical therapy of colitis	Outcome
Mourad et al. [12] (2019) (*melanoma*)	Enco + Bini	41/ woman	Ipi	3 weeks	Grade 3 diarrhea + abdominal pain	Ulcerated colitis of the ileum, ileocecal valve, left colon, and sigmoid	Focal mucosal ulcerations with exudates of fibrin and leucocytes. Inflammatory infiltrate of the lamina propria, with neutrophils, lymphocytes, and plasmocytes	Enco + Bini held + corticosteroids Infliximab Enco + Bini withdrawal	Corticodependance Not beneficial Recovery
Mourad et al. [12] (2019) (*melanoma*)	Trame alone	76/ woman	Anti-CTLA4; anti-PD1, TVEC, temozolomide	1 week	Grade 4 diarrhea	Limited supra anal ulceration	Nonspecific vascular and exudative changes of the colic mucosa with dystropic modifications of the cryptes. No granuloma or abscess	Trame discontinuation	Symptom improvement Put on supportive care
Mourad et al. [12] (2019) (*melanoma*)	Trame + dabra + anti-PD1	72/ man	None	3.5 months	Diarrhea, protein-losing enteropathy	Normal colonoscopy VCE: deep, centimetric ulcerations of the ileum	Histological details not provided	Discontinuation of all melanoma treatments	Recovery with healing of almost all ulcerations
Gelsomino et al. [13] (2022) (*non-small cell lung cancer*)	Enco + Bini	70/ man	None	2 months	Asymptomatic	Colitis of the right upper colon. Deep and extensive ulcerations of the cecum	Inflammatory infiltrate in the caecum's lamina propria + severe eosinophilia. No intraepithelial lymphocytes. No epithelial apoptotic bodies	Enco + Bini withheld	Recovery → treatment resumed at the same doses. Still alive and without recurrence of toxicity

Bini, binimetinib; CLL, chronic lymphocytic leukemia; Dabra, dabrafenib; Enco, encorafenib; FMT, fecal microbiota transplantation; ICI, immune checkpoint inhibitor; Ipi, ipilimumab; Nivo, nivolumab; Pembro, pembrolizumab; Trame, trametinib; TVEC, talimogene laherparepvec; VCE, video capsule endoscopy.

drugs, mainly due to the previous use of ICIs and suspected gastrointestinal immune-related adverse events, their role remains unclear. The reintroduction of a reduced dose combination or a BRAF inhibitor alone has occasionally been performed but should be done with caution.

Conclusion

Severe BRAF/MEKi-induced colitis is still rarely described in the literature. We report here 2 patients with melanoma who developed severe ulcerated right colitis during treatment with encorafenib and binimetinib. These 2 patients had previously received immunotherapy. They had relatively mild digestive symptoms compared with laboratory and endoscopic findings. Clinicians should be aware of this potential complication of BRAF/MEKi and investigate symptoms such as persistent or severe diarrhea, hematochezia, or abdominal pain. Further studies are needed to evaluate the mechanism of gastrointestinal toxicity of BRAF/MEKi and its management.

Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the patient (patient B) and patient A's wife (patient A, deceased) for publication of this case report, included identifying details of participants like individual age, gender, illness, and any accompanying images. Ethical approval is not required for this case report in accordance with local guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study did not require any funding.

Author Contributions

Wautier Chloe: conceptualization, obtaining patient consent, collecting literature data, writing – original draft, and writing – review and editing; Dong Catherine and Berthod Grégoire: data curation, conceptualization, investigation, validation, and writing – review and editing; Gourmaud Jolanta: validation and writing – review and editing.

Data Availability Statement

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

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