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Case Report

# BRAF and MEK Inhibitor-induced Acute Necrotizing Pancreatitis: A Case Report and Literature Review

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## Abstract

Colorectal cancer (CRC) with the BRAF V600E mutation is an aggressive subtype often resistant to conventional chemotherapy. While B-Raf proto-oncogene (BRAF) / Epidermal growth factor receptor (EGFR) inhibitor combinations are now standard for metastatic BRAF V600E CRC, these BRAF inhibitors can cause various adverse effects. Among these adverse effects, pancreatitis is a rare but serious complication that is often under-recognized due to current trials having limited durations and populations. We report the case of a 50-year-old female with metastatic BRAF V600E-mutant colon cancer who achieved an exceptional and durable complete response over 3 years with off-label dabrafenib and trametinib plus cetuximab. Notably, she developed acute necrotizing pancreatitis after more than 3 years of treatment, a significantly longer latency than previously reported, and experienced recurrence upon rechallenge. A literature review confirmed that pancreatitis is a rare complication across all Food and Drug Administration-approved BRAF inhibitors, with varying onset times. This case highlights the potential for late-onset, severe pancreatitis with prolonged BRAF inhibitor use. Given the increasing use of BRAF inhibitors, particularly in CRC, routine monitoring and further mechanistic research are required.

**Keywords:** BRAF inhibitor, case report, colorectal cancer, drug-induced pancreatitis, MEK inhibitor

## Introduction

Colorectal cancer (CRC) is the third most common cancer in both men and women and the second leading cause of cancer-related mortality.[1] It is a highly heterogeneous disease with several different genetic alterations, each of which is associated with a distinct prognosis and varying responses to targeted therapies. BRAF mutations occur in up to 10%–15% of cases,[2] with the V600E mutation accounting for more than 90% of all BRAF mutations.[3,4] The BRAF V600E mutation causes constitutive mitogen-activated protein kinase (MAPK) pathway activation and confers resistance to single-agent anti-EGFR therapies, and it is associated with a poor prognosis.[4,5]

Traditionally, the BRAF V600E mutation is considered to be a negative prognostic factor, with a median progression-free

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survival of around 6 months and an overall survival of around 1 year with first-line conventional treatments.[5] Because of its relative chemotherapy insensitivity, triplet chemotherapy with FOLFOXIRI plus bevacizumab was previously the mainstay treatment.[6,7] However, the phase III BEACON clinical trial confirmed the combination of encorafenib and cetuximab, a BRAF/EGFR inhibitor combination, as the new standard of care for BRAF V600E metastatic CRC after at least one prior line of systemic therapy.[8] Recently, the phase 3 Breakwater study showed a significant improvement in overall survival and shifted the paradigm in the treatment of BRAF-mutant CRC.[9]

Dabrafenib in combination with trametinib received accelerated Food and Drug Administration (FDA) approval on June 22, 2022, for the treatment of unresectable or metastatic solid tumors that harbor BRAF V600E mutations and have progressed following prior treatment, with no satisfactory alternative options. The approval was tumor-agnostic, but it specifically excluded patients with CRC due to the poor response rate in trials.[10] The duration of response in other cancer types is variable, but durable responses are uncommon.[11,12]

Because of the relatively short treatment duration and small population size in previous trials, some adverse effects are under-reported or under-recognized. NCI-MATCH Trial Subprotocol H, the study that led to the FDA accelerated approval of dabrafenib and trametinib, did not report pancreatitis as an adverse event.[10] The phase 2 Rare Oncology Agnostic Research (ROAR) trial enrolled BRAF V600E-mutated rare cancers, and only 4 (1.4%) patients developed pancreatitis. Several case reports have documented instances of BRAF inhibitor-induced pancreatitis in patients with melanoma[13-15] and other cancer types;[16] however, the pathophysiology remains unknown. Here, we report the case of a patient with metastatic BRAF V600E-mutated colon cancer who achieved an exceptional durable response with off-label BRAF inhibitor treatment and developed acute necrotizing pancreatitis after several years of treatment.

## Case Report

A 50-year-old female presented to our surgeon's clinic in November 2020 due to bloody stool and was diagnosed with sigmoid colon cancer through colonoscopy. Following complete staging, the disease was staged as cT3N2aM0. She underwent laparoscopic low anterior resection, but a liver lesion was found intraoperatively. The liver lesion was resected completely, and the final pathology report confirmed colon cancer metastasis. Postoperative chemotherapy with a modified FOLFOX regimen was given, but after completing the planned 12 cycles, a follow-up computed tomography (CT) scan revealed several new tumors in the left lung, suggesting metastatic spread.

As routine practice, the RAS/BRAF profile was checked, and a BRAF V600E mutation was detected. Due to progression on chemotherapy, she started combination therapy including Erbitux and the compassionate use of dabrafenib and trametinib (cetuximab 500 mg/m$^2$, dabrafenib 150 mg BID, and trametinib 2 mg QD) in late July 2021, as encorafenib was not available at the time (it was not approved by the Taiwan FDA until October 2022). Unfortunately, within weeks, she experienced severe skin toxicities [Figure 1], including extensive scalp lesions, which necessitated several reductions in the dose of Erbitux to 125 mg/m$^2$ every 2–3 weeks, and adjustments to the targeted-therapy regimen (administered every other day). Under this treatment, her cancer was well-controlled, with a complete response on imaging. Although encorafenib was approved and on the market during the treatment course, we decided to continue compassionate dabrafenib and trametinib due to the excellent clinical response.

In October 2024, 3 years after starting the combination therapy. She presented to the emergency room with complaints of epigastric pain and cold sweating. Laboratory tests revealed an elevated lipase level (>6000 U/L) [Figure 2], and a CT scan confirmed the diagnosis of acute necrotizing pancreatitis with no gallstones present [Figure 3]. She did not have a history of any alcohol consumption, and there was no known family history of pancreatitis (including conditions such as autoimmune disease). Apart from colon cancer, she had no other systemic comorbidities. The colon cancer had remained stable on cetuximab plus dabrafenib and trametinib, without any treatment switches or dose modifications. Laboratory investigations showed a triglyceride level of 180 mg/dL (reference range: <150 mg/dL). BRAF and MEK inhibitor-induced pancreatitis was highly suspected after excluding all other potential causes. Dabrafenib and trametinib were withheld, and she was admitted to the hospital and started on antibiotics and supportive care.

After the symptoms had resolved, we attempted to rechallenge with BRAF and MEK inhibitors on November 26, 2024. However, 10 days later, she presented to the emergency department again with epigastric pain and vomiting. Blood tests showed an elevated lipase level (1074 U/L) [Figure 4], and a repeat CT scan showed diffuse walled-off necrosis of the

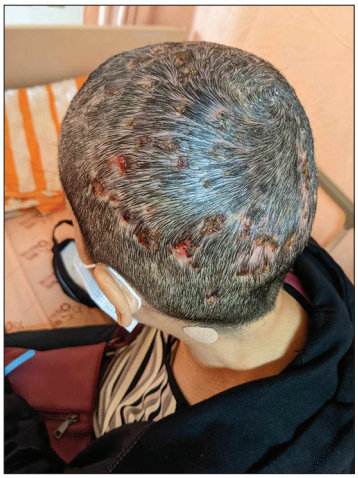

**Figure 1:** Skin toxicities. The patients experienced severe skin toxicities including extensive scalp lesions that led to several dose reductions

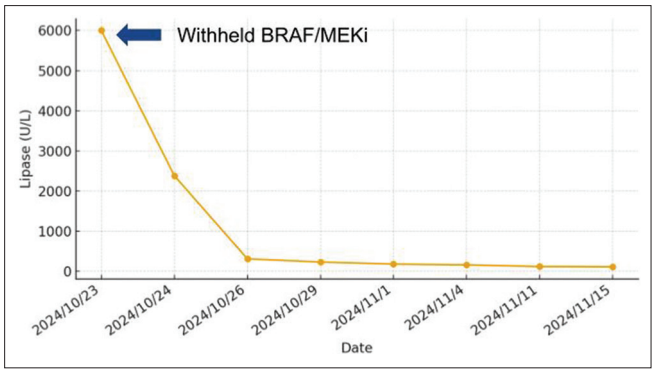


**Figure 2:** Lipase level during the first pancreatitis episode in October 2024. Rapid resolution of acute pancreatitis after withholding dabrafenib and trametinib

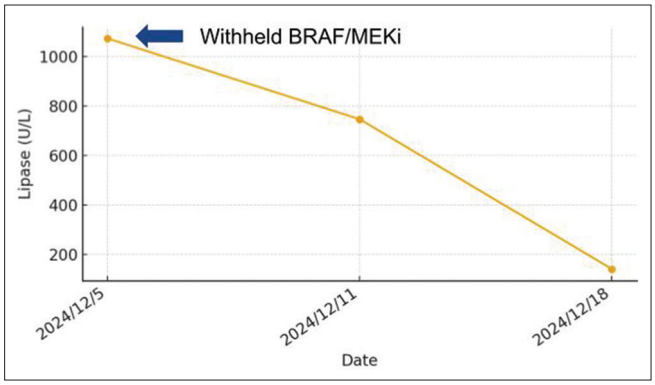


**Figure 4:** Lipase level during the second pancreatitis episode in October 2024. Similar to the prior episode, acute pancreatitis resolved quickly following the cessation of dabrafenib and trametinib

pancreas and pseudocyst formation [Figure 5]. She underwent pigtail drainage and several revisions for the pseudocyst. Due to a limited amount of drainage, the pigtail was removed in April 2025 despite the presence of residual fluid collection. Two months after pigtail removal, follow-up CT showed ongoing improvement, and she remained cancer-free throughout the course [Figure 6].

## Discussion

We searched PubMed and Embase using the keywords (((BRAF inhibitor) OR (MEK inhibitor(s)) OR (dabrafenib) OR (encorafenib) OR (vemurafenib)) AND (pancreatitis) up to October 12, 2025. The search identified 734 publications in PubMed and 261 in Embase. After detailed review and manual screening, nine articles were related to our investigation.[13-20,21] Seven case reports and one case series overlapped between PubMed and Embase, and Embase yielded one additional relevant case report. These seven case reports, one case series,[13-15,17-21] and one database study[16] are summarized in Table 1.

Case reports of pancreatitis were noted with all three FDA-approved BRAF inhibitors, and the indications for these drugs were distributed across several different cancer types,

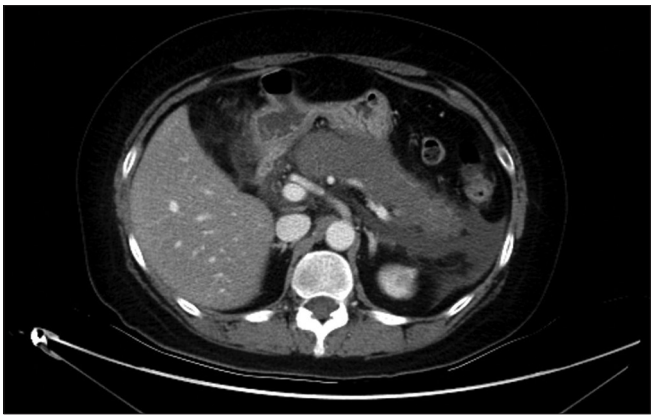

**Figure 3:** Image of acute pancreatitis. Three years after starting the combination therapy, the patient presented to our emergency room with complaints of epigastric pain and cold sweating. Laboratory tests revealed an elevated lipase level (>6000 U/L), and computed tomography showed acute necrotizing pancreatitis

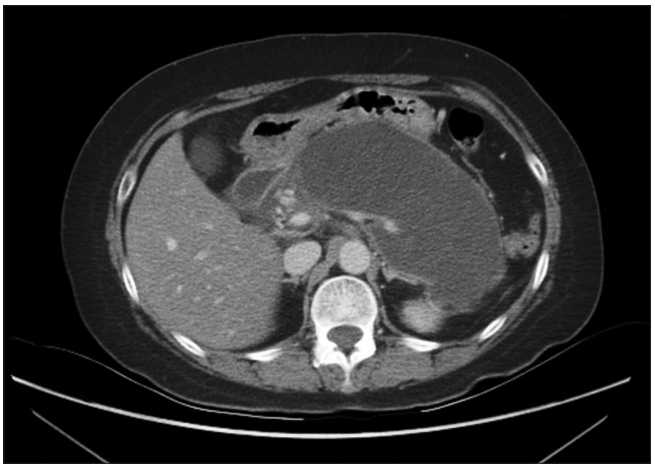

**Figure 5:** Walled off pancreatic necrosis. Two months after the first event of acute pancreatitis, a repeat computed tomography scan showed diffuse walled-off necrosis of the pancreas and pseudocyst formation

as well as a nonmalignant disease (Erdheim–Chester disease). Some of the reports described single-agent monotherapy, while others involved combination therapy with MEK inhibitors and an EGFR monoclonal antibody. The time to onset of pancreatitis ranged from 1 day to 4 months, but no case occurred after more than 1 year. The peak lipase level ranged from 224 U/L to more than 10,000 U/L. Most cases were self-limited after supportive care, but one patient died of pancreatitis-related complications, including abdominal abscess and acute respiratory distress syndrome. Some cases were rechallenged with a BRAF inhibitor at a lower dose and had a response; however, recurrence of pancreatitis developed in some cases, leading to permanent discontinuation.

One database study using the Food and Drug Administration Adverse Event Reporting System between July 2011 and June 2024 investigated the association between BRAF inhibitors (vemurafenib, dabrafenib, and encorafenib) and pancreatitis and identified 169 cases of pancreatitis linked

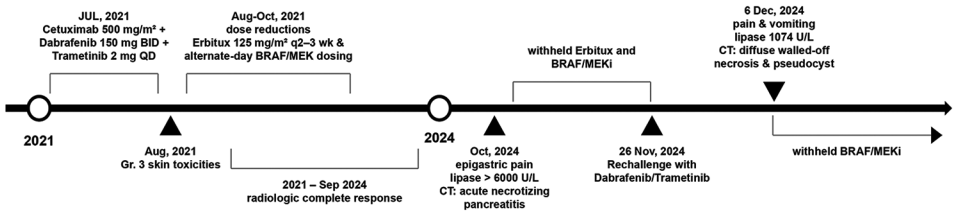


**Figure 6:** Timeline of BRAF and MEK inhibitor-induced acute necrotizing pancreatitis

**Table 1: Case reports or case series describing BRAF inhibitors associated with pancreatitis, listed in order of publication date**

| Article number | Drug | Indication | Peak lipase | Onset | Rechallenge with lower doses | Reference |
|---|---|---|---|---|---|---|
| 1 | Vemurafenib | Melanoma | 1544 U/L | 2 weeks | Yes, with recurrent pancreatitis | [14] |
| 2 | Vemurafenib | Hairy cell leukemia | 1893 U/L | 1 week | Yes, tolerable | [17] |
| 3 | Dabrafenib | Melanoma | 2000 U/L | 4 months | No | [15] |
| 4 | 5 cases, vemurafenib or dabrafenib | Erdheim-chester disease | 224–14.950 U/L | 1–50 days | Yes, 4 rechallenge, 1 recurrent pancreatitis | [20] |
| 5 | Encorafenib | Colon cancer | 300 U/L (amylase)* | 1 month | Yes, tolerable | [19] |
| 6 | Vemurafenib | Melanoma | 1769 U/L | 1 day | No | [13] |
| 7 | Encorafenib | Colon cancer | 577 U/L | 1 month | No | [18] |
| 8 | Dabrafenib | Thyroid cancer | 2266 U/L | 2–3 days | No | [21] |

*Lipase level was not specified in this report

to BRAF inhibitors. All three inhibitors showed a positive signal for pancreatitis, with vemurafenib and encorafenib exhibiting comparable signal intensities, while dabrafenib showed a weaker signal. The median time to the onset of pancreatitis was shortest with vemurafenib (6.5 days), followed by encorafenib (14.0 days) and dabrafenib (129.5 days).[16]

Off-label dabrafenib and trametinib were used to treat BRAF V600E-mutant CRC in our patient because of limited resources and drug accessibility at the time of treatment initiation. She received prolonged treatment with a durable and deep response. Pancreatitis developed after more than 3 years of treatment, which is longer than in all previously reported cases. This side effect occurred despite a lower treatment dose and recurred after rechallenge. There was no other possible explanation for the pancreatitis, and it was considered to have a definite causal relationship according to the Naranjo algorithm.[22]

Acute pancreatitis is a rare but serious complication associated with BRAF inhibitors. The phase 2 ROAR study reported an incidence rate of 1.4%;[12] however, the incidence has never been reported in phase 3 studies. The exact mechanism by which BRAF inhibitors induce pancreatitis is not understood; however, there are several possible explanations. BRAF inhibitors can sometimes lead to a "paradoxical activation" of the MAPK pathway, and this paradoxical activation in pancreatic acinar or ductal cells could lead to an inflammatory response.[23,24] Alternatively, pancreatitis may be related to off-target effects on other kinases or cellular processes in the pancreas, contributing to inflammation or cellular damage.[25]

Although the exact causal mechanism linking BRAF inhibitors to pancreatitis remains under investigation, it is essential to monitor pancreatic function when administering these agents due to the low cost of pancreatic enzyme tests and the serious consequences if pancreatitis is not promptly recognized and managed. As the number of clinical trials involving BRAF and MEK inhibitors continues to increase, the use of these targeted therapies will likely become more widespread, particularly in CRC, which is the third most common cancer worldwide. Consequently, pancreatitis should be included in the differential diagnosis of acute abdominal pain in patients receiving BRAF and MEK inhibitors.

BRAF mutations are now an approved indication for tumor-agnostic therapies, and related clinical trials are advancing rapidly. Pancreatitis is a rare complication of BRAF-inhibitor treatment. Given that severe pancreatitis can be life-threatening, routine monitoring should be considered, and further mechanistic research is needed.

## Declaration of patient consent

This study was performed in accordance with and conforming to the Declaration of Helsinki. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

## Declaration of generative AI use

Generative artificial intelligence tools, including ChatGPT and Gemini, were used to check grammar and improve writing.

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We appreciate the multidisciplinary team at our hospital for their delicate care.

## Author contributions

T.J. Lin: Conceptualization, Investigation, Writing - original draft. H.W. Chen: Investigation, Resources, Writing - review and editing. All authors have read and agreed to the published version of the manuscript.

## Data availability statement

The datasets generated during and/or analyzed during the current study are publicly available.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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