Noninfectious causes of liver injury that may occasionally also cause fever include drug-induced liver injury, sarcoidosis, the Budd–Chiari syndrome, and some autoimmune diseases. Among all possible diagnoses, drug-induced liver injury was the most important consideration in this patient, given the mixed cholestatic and hepatocellular pattern of liver injury. The patient did not report recreational drug or herbal medicine use, so the most likely culprits were the BRAF–MEK inhibitors dabrafenib and trametinib.

Further investigative testing that was recommended at this point included examination of a peripheral-blood smear and serologic and nucleic acid testing for acute viral infections, vector-borne infections, and atypical infections, such as those noted above. Although drug-induced liver injury was considered to be the most likely diagnosis in this patient, a liver biopsy was performed on hospital day 5, given continued diagnostic uncertainty and the presence of increasing levels of ALT and AST.

DR. AMIR M. MOHAREB'S DIAGNOSIS

BRAF–MEK inhibitor–related toxic effects.

PATHOLOGICAL DISCUSSION

Dr. Stuti G. Shroff: Examination of a core-biopsy specimen of the liver (Fig. 2) revealed regenerative hepatic parenchyma with numerous well-formed, nonnecrotizing epithelioid granulomas involving the portal tracts and lobules. Associated patchy mixed inflammation that was predominantly mononuclear, with plasma cells, occasional neutrophils, and rare eosinophils, was also present. No histologically significant biliary epithelial injury was seen. The lobular parenchyma was punctuated by numerous apoptotic hepatocytes. Staining of the biopsy specimen for acid-fast bacilli was negative, and Grocott–Gomori methenamine silver staining and periodic acid–Schiff staining showed no fungal organisms. Immunohistochemical staining was negative for cytomegalovirus inclusion bodies and herpes simplex virus. In situ hybridization for Epstein–Barr virus–encoded RNA was also negative. A spirochete immunostain was negative, and no bacteria were identified on Gram's staining of the liver tissue.

The differential diagnosis for well-formed epithelioid granulomas involving the liver parenchyma is broad and encompasses infectious and noninfectious processes. In this patient, several infections were ruled out on histologic examination. Given the absence of evidence supporting an alternative diagnosis such as infection or sarcoidosis, the most likely cause of this patient's syndrome is drug-induced liver injury resulting from BRAF–MEK inhibitor therapy (dabrafenib and trametinib).

PATHOLOGICAL DIAGNOSIS

BRAF–MEK inhibitor–related toxic effects.

DISCUSSION OF MANAGEMENT

Dr. Mohareb: After the patient's liver biopsy, fever resolved and the elevated ALT and AST levels rapidly decreased. Sarcoidosis was thought to be an unlikely diagnosis on the basis of the clinical response to the discontinuation of dabrafenib and trametinib therapy. A peripheral-blood smear showed immature granulocytes and no parasites. Infectious-disease studies, including evaluations for anaplasma and ehrlichia DNA and for hepatitis A, B, and C viruses, were negative. The findings from the liver biopsy, together with resolution of fevers and liver injury after the discontinuation of dabrafenib and trametinib, confirmed the diagnosis of BRAF–MEK inhibitor–related toxic effects.

Dr. Kamaneh Montazeri: BRAF is a protein kinase that plays a role in the activation of the mitogen-activated protein kinase (MAPK) signaling pathway, which regulates cell proliferation and survival.[5] *BRAF* V600 activating mutations are acquired mutations that occur in approximately 50% of patients with cutaneous melanomas[6] and result in downstream MEK and ERK activation and oncogenesis.[7] The combination of BRAF inhibitors and MEK inhibitors has substantially improved outcomes in patients with *BRAF*-mutated melanoma, and this treatment has been shown to be effective both in advanced disease and in the adjuvant setting.[8-11] The combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib has been approved by the Food and Drug Administration for the adjuvant treatment of melanoma that harbors the *BRAF* V600 mutation in patients with lymph-node involvement.[12]

COMMON TOXIC EFFECTS ASSOCIATED WITH BRAF–MEK INHIBITORS

As with other selective kinase inhibitors, BRAF–MEK inhibitors are associated with distinct and predictable adverse effects that may lead to treatment interruption or discontinuation or decreased effectiveness. Almost all the patients who were treated with BRAF–MEK inhibitors in early trials had some degree of drug-related toxic effects, with 45 to 55% of patients having adverse events that led to dose interruptions or modifications[13] and 13 to 15% of patients permanently discon-

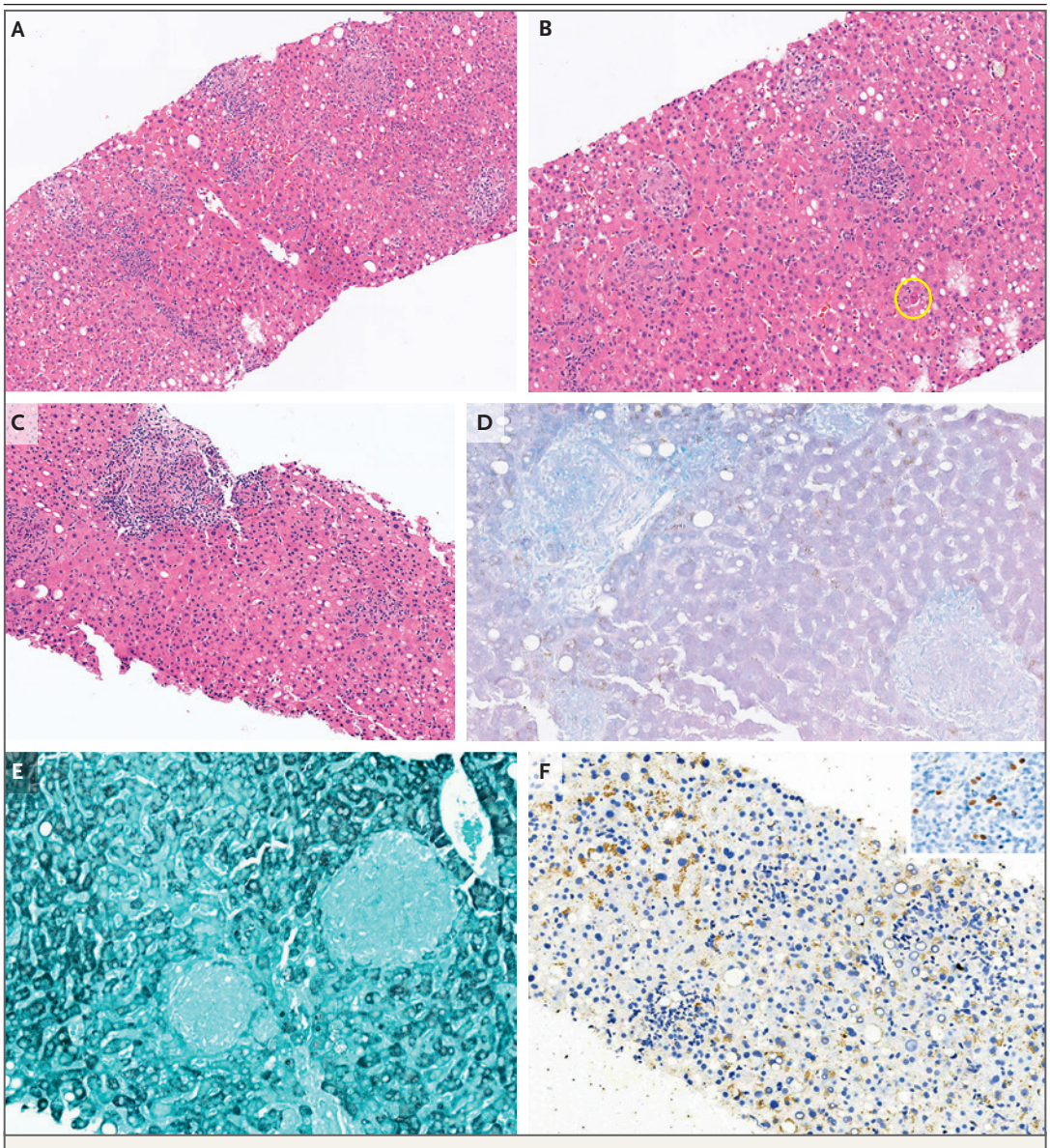

Figure 2. Biopsy Specimens of the Liver.

Hematoxylin and eosin staining of a core-biopsy specimen (Panel A) shows well-formed nonnecrotizing epithelioid granulomas involving the lobular parenchyma (Panel B) and portal tracts, without histologically significant accompanying biliary injury (Panel C). The lobular parenchyma shows numerous apoptotic hepatocytes (Panel B, circle). Staining for acid-fast organisms (Panel D) is negative, as is Grocott–Gomori methenamine silver staining for fungal organisms (Panel E). In situ hybridization for Epstein–Barr virus–encoded RNA (Panel F) is also negative; the inset shows a positive control.

tinuing treatment because of adverse events.[14-16] The most common adverse events that were reported with dabrafenib and trametinib combination therapy were fever, chills, elevations in ALT and AST levels, fatigue, diarrhea, hypertension, and vomiting. Fever led to dose interruption in approximately 30% of patients, dose reduction in approximately 14% of patients, and treatment discontinuation in 2 to 3% of patients. The median time to the onset of the first episode of pyrexia was 4 weeks,[14] and half the patients had recurrent pyrexia episodes.[17-19]

MANAGEMENT OF PYREXIA SYNDROME DURING BRAF–MEK INHIBITOR THERAPY

For patients receiving targeted therapy with BRAF–MEK inhibitors, prompt management of treatment-related pyrexia is important to enable patients to continue receipt of targeted therapy and improve their outcomes. There is no standardized guideline for the definition and management of treatment-related pyrexia in patients treated with dabrafenib and trametinib combination therapy.

In our practice, patients and their caregivers receive both oral and written education regarding the potential side effects of BRAF–MEK inhibitors and treatment-related pyrexia. It is important for patients to be aware that they should stop BRAF–MEK inhibitor therapy and communicate with their treatment team if they begin to have fevers, since continuation of BRAF–MEK inhibitor therapy through an episode of treatment-related pyrexia can result in further complications.

In clinical trials, pyrexia syndrome is defined by a fever with a temperature of 38°C or higher. Multiple trials have shown that the temporary discontinuation of both dabrafenib and trametinib is more effective in controlling pyrexia than the discontinuation of dabrafenib alone.[8,20,21] Treatment with antipyretic medications, including acetaminophen and ibuprofen, is recommended. Treatment with both dabrafenib and trametinib can be restarted at the previous doses 24 hours after the resolution of fever without antipyretic medications, as was done in this case.

Recurrent episodes of uncomplicated pyrexia syndrome should be managed in a similar manner, by temporarily discontinuing both dabrafenib and trametinib and initiating treatment with antipyretic medications. It is important to perform a clinical evaluation and laboratory tests, including the complete blood count and tests for liver abnormalities and kidney function, to assess for any associated complications. It is important to note that treatment with dabrafenib and trametinib can be restarted at the previous doses 24 hours after the resolution of fever without antipyretic medications if there are no additional complications. Treatment with glucocorticoids is sometimes recommended if pyrexia syndrome does not abate after 48 hours.[18] Prophylactic treatment with glucocorticoids has been used in patients with frequent recurrent episodes of uncomplicated pyrexia syndrome, although the data are limited.[21]

Severe (complicated) pyrexia syndrome is defined as pyrexia syndrome that results in hospitalization or that is complicated by other conditions that are assessed as grade 2 or higher in severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events. These conditions can include liver or kidney dysfunction, hypotension, dehydration, or vomiting. For patients with severe (complicated) pyrexia syndrome, clinical evaluation for infectious causes of fever is recommended, in addition to temporarily discontinuing both dabrafenib and trametinib. After infectious causes of fever have been ruled out, restarting treatment with both dabrafenib and trametinib at reduced doses at least 24 to 48 hours after resolution of fatigue, weakness, and nausea without antipyretic medications is advised. Intermittent administration of BRAF–MEK inhibitor therapy is not recommended because it has been shown to decrease the effectiveness of the therapy. Permanent discontinuation of BRAF–MEK inhibitor therapy should be considered in patients with recurrent episodes of pyrexia syndrome (either uncomplicated or severe [complicated]) despite dose interruption, dose reduction, or treatment with glucocorticoids.

This patient had severe (complicated) pyrexia syndrome. Options for further management of stage IIIC melanoma were discussed with her, including adjuvant therapy with an immune checkpoint inhibitor (ICI), resuming adjuvant targeted therapy with dose reduction once she had complete resolution of the drug-related toxic effects, or active surveillance. The patient decided to opt out of further targeted therapy.

We planned to proceed with adjuvant ICI therapy with the anti–programmed death 1 (anti–PD-1) immunotherapy drug pembrolizumab once kidney and liver injury had completely resolved. Because of persistent abdominal pain, esophagogastroduodenoscopy was performed, which revealed erythematous mucosa in the antrum, small linear ulcers in the fundus, and nonbleeding ulcers in the duodenum. Treatment with oral omeprazole was started, and the patient was advised not to take ibuprofen and other nonsteroidal antiinflammatory drugs. The patient was discharged home on hospital day 10.

One week after discharge, the results of kidney-function tests had returned to the patient's baseline levels and the results of liver tests had improved. Three weeks after discharge, results on liver tests had returned to near-normal levels and treatment with pembrolizumab was scheduled. Unfortunately, follow-up imaging revealed disease recurrence in the liver; a biopsy confirmed metastatic melanoma. The patient began treatment with ICI therapy in combination with nivolumab (an anti–PD-1 drug) and ipilimumab (an anti–cytotoxic T-lymphocyte antigen 4 antibody drug).

Shortly after starting ICI therapy, the patient had evidence of further visceral disease progression, new osseous and peritoneal metastases, and rapid clinical decline. We had planned to continue ICI therapy and add BRAF–MEK inhibitor therapy, at a reduced dose, with encorafenib and binimetinib to help control symptoms. However, the patient was subsequently admitted with nausea, vomiting, and constipation. She underwent exploratory laparotomy with lysis of an omental band. Her course after surgery was complicated by ileus, followed by tachycardia and dyspnea with evidence of ground-glass opacities on chest imaging that were suggestive of pneumonia or possible pneumonitis related to ICI therapy. The patient expressed her wishes to stop further cancer-directed therapy and any aggressive measures and to instead focus on comfort measures. Two days later, she died peacefully in the hospital.

FINAL DIAGNOSIS

BRAF–MEK inhibitor–related toxic effects.

This case was presented at Cancer Center Grand Rounds.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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