CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 2-2024: A 57-Year-Old Woman with Melanoma and Fever

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PRESENTATION OF CASE

Dr. Matthew L. Meizlish (Medicine): A 57-year-old woman with resected stage IIIC cutaneous melanoma was admitted to this hospital because of fever.

The patient had been in her usual state of health until 4 months before the current admission, when bleeding developed from a lesion on the right side of the scalp. After evaluation by her primary care physician, she was referred to a surgical clinic at another hospital; examination of a skin-biopsy specimen revealed ulcerated melanoma with positive margins. The patient was referred to the oncology clinic of this hospital.

Three months before the current admission, a wide local excision of the scalp lesion and a neck lymph-node dissection were performed; examination of the specimens revealed metastatic melanoma in 2 of 26 lymph nodes. A diagnosis of stage IIIC melanoma was made. Molecular profiling identified the *BRAF* V600E mutation, and treatment with adjuvant therapy was planned to begin after the patient had recovered fully from surgery.

One month before the current admission, the patient was evaluated in the oncology clinic for initiation of treatment with a combination of dabrafenib (a BRAF inhibitor) and trametinib (a MEK inhibitor) as targeted therapy for melanoma. She felt well, and the surgical wound had healed. Laboratory test results are shown in Table 1. Treatment with dabrafenib and trametinib was started.

One day after the initiation of treatment with dabrafenib and trametinib, fever and nausea developed. Dabrafenib and trametinib therapy was temporarily discontinued, and treatment with acetaminophen and ibuprofen was started. Fever and nausea resolved after 1 day, and treatment with acetaminophen and ibuprofen was stopped. Once the patient had 1 day without recurrent fever after the antipyretic medications had been stopped, treatment with dabrafenib and trametinib was resumed.

Two weeks before the current admission, fever recurred. The patient was evaluated at the other hospital. The blood levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and alkaline phosphatase were normal, as were the complete blood count and the results of tests of kidney function. Treatment with dabrafenib and trametinib was again stopped, and treatment with

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N Engl J Med 2024;390:255-65.
DOI: 10.1056/NEJMcpc2300974

CME at NEJM.org

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	1 Mo before This Admission, Oncology Clinic, This Hospital	On Admission, This Hospital	Hospital Day 5, This Hospital
Blood				
White-cell count (per μl)	4500–11,000	3810	5190	3430
Differential count (per μl)				
Neutrophils	1800–7700	1810	4560	2720
Lymphocytes	1000–4800	1490	90	460
Monocytes	200–1200	450	—	150
Eosinophils	0–900	20	—	60
Basophils	0–300	30	—	—
Hemoglobin (g/dl)	13.0–16.0	13.0	12.9	9.4
Hematocrit (%)	37.0–49.0	40.6	38.9	27.2
Platelet count (per μl)	150,000–400,000	207,000	87,000	99,000
Prothrombin time (sec)	11.5–14.5	—	16.7	14.3
Prothrombin-time international normalized ratio	0.9–1.1	—	1.4	1.1
Activated partial-thromboplastin time (sec)	22.0–36.0	—	47.9	27.2
D-dimer (ng/ml)	0–500	—	>10,000	3457
Fibrinogen (mg/dl)	150–400	—	135	153
Sodium (mmol/liter)	135–145	138	131	138
Potassium (mmol/liter)	3.4–5.0	4.2	3.8	3.3
Chloride (mmol/liter)	98–108	109	97	107
Carbon dioxide (mmol/liter)	23–32	22	19	22
Urea nitrogen (mg/dl)	8–25	19	42	13
Creatinine (mg/dl)	0.60–1.50	0.86	2.73	1.07
Glucose (mg/dl)	70–110	99	118	99
Albumin (g/dl)	3.3–5.0	4.3	3.6	2.3
Total protein (g/dl)	6.0–8.3	6.6	6.6	4.9
Aspartate aminotransferase (U/liter)	9–32	30	190	407
Alanine aminotransferase (U/liter)	7–33	19	62	138
Alkaline phosphatase (U/liter)	30–100	76	173	510
Total bilirubin (mg/dl)	0.0–1.0	0.2	1.9	2.6
Lipase (U/liter)	13–60	—	42	—
Lactate dehydrogenase (U/liter)	110–210	—	285	658
Lactic acid (mmol/liter)	0.5–2.0	—	1.0	0.8
Creatine kinase (U/liter)	40–150	—	1679	—
Urine				
Color	Yellow	—	Yellow	—
Clarity	Clear	—	Turbid	—
pH	6.0	—	5.5	—
Specific gravity	1.012	—	1.013	—

Table 1. (Continued.)

Variable	Reference Range, Adults†	1 Mo before This Admission, Oncology Clinic, This Hospital	On Admission, This Hospital	Hospital Day 5, This Hospital
Glucose	Negative	—	Negative	—
Ketones	Negative	—	Negative	—
Leukocyte esterase	Negative	—	Negative	—
Nitrite	Negative	—	Negative	—
Blood	Negative	—	2+	—
Protein	Negative	—	1+	—
Red cells (per high-power field)	—	—	0–2	—
White cells (per high-power field)	—	—	0–10	—

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for lactic acid to milligrams per deciliter, divide by 0.1110.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

acetaminophen and ibuprofen was started. Fever and nausea resolved after 1 day, and treatment with acetaminophen and ibuprofen was stopped. Once the patient had 1 day without recurrent fever after the antipyretic medications had been stopped, treatment with dabrafenib and trametinib was again resumed.

Four days before the current admission, fever recurred. The patient was again evaluated at the other hospital. Results of liver tests and kidney-function tests were again normal, as was the complete blood count. Treatment with dabrafenib and trametinib was again stopped, and treatment with acetaminophen and ibuprofen was initiated. Daily fevers persisted for 4 days, and the patient was advised to present to the emergency department of this hospital for evaluation.

On evaluation, the patient reported fatigue that had started 1 month earlier and had gradually increased in severity, as well as light-headedness when standing from a seated position. She also reported intermittent vomiting, loose stools, and pain in the right upper quadrant that increased after eating but no diarrhea or dysuria. She had a dry cough without shortness of breath.

Other medical history included carpal tunnel syndrome that had been treated with carpal tunnel release surgery. The patient had no known drug allergies. She worked as a nurse and lived with her husband and two adult children in a coastal region of New England. She did not drink alcohol, smoke cigarettes, or use illicit drugs. Her father had hyperthyroidism; her mother had hypertension, diabetes mellitus, and cerebrovascular disease.

The temporal temperature was 40.2°C, the blood pressure 85/53 mm Hg, the pulse 108 beats per minute, and the oxygen saturation 94% while the patient was breathing ambient air. She was diaphoretic and appeared ill. The mucous membranes were moist, and no lesions were present in the oropharynx. The heart sounds were regular, with no murmurs, and the lungs were clear on auscultation. There was mild tenderness in the right upper quadrant. No rash was present.

The white-cell count was 5190 per microliter (reference range, 4500 to 11,000); 20% of the cells were bands (reference range, 0 to 10), and 10% were metamyelocytes (reference value, 0). The platelet count was 87,000 per microliter (reference range, 150,000 to 400,000). The blood level of creatinine was 2.73 mg per deciliter (241 μmol per liter; reference range, 0.60 to 1.50 mg per deciliter [53 to 133 μmol per liter]), AST 190 U per liter (reference range, 9 to 32), ALT 62 U per liter (reference range, 7 to 33), and alkaline phosphatase 173 U per liter (reference range, 30 to 100). Tests of a nasopharyngeal swab for adenovirus, human rhinovirus and enterovirus, influenza virus types A and B, parainfluenza virus types 1 through 4, respiratory syncytial virus, and

severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were negative. A blood specimen was obtained for culture. Other laboratory test results are shown in Table 1. Imaging studies were obtained.

Dr. Jiyoon Kang: Ultrasonography of the right upper quadrant (Fig. 1A and 1B) revealed cholelithiasis without evidence of cholecystitis or biliary ductal dilatation. Computed tomography (CT) of the chest, abdomen, and pelvis (Fig. 1C through 1F), performed without the administration of intravenous contrast material, revealed findings suggestive of hepatic steatosis, pulmonary edema, small bilateral pleural effusions, subsegmental linear atelectasis, and bilateral lung nodules that were similar in appearance to those seen on staging CT performed 1 month earlier.

Dr. Meizlish: Intravenous fluids were administered, and the blood pressure improved; empirical treatment with vancomycin, cefepime, metronidazole, and azithromycin was initiated. The patient was admitted to the hospital.

On hospital day 2, fever and nausea resolved. There was no vomiting or loose stools. However, pain in the right upper quadrant had worsened. On hospital day 3, blood cultures were without growth, and treatment with vancomycin, cefepime, metronidazole, and azithromycin was discontinued. The patient remained afebrile. On hospital day 5, the blood level of AST was 407 U per liter, ALT 138 U per liter, and alkaline phosphatase 510 U per liter. Other laboratory test results are shown in Table 1.

A diagnostic test was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Amir M. Mohareb: I was involved in the care of this patient, and I am aware of the final diagnosis. The patient had recently begun adjuvant therapy with combination BRAF–MEK inhibitors for resected stage IIIC melanoma. Her early treatment course was complicated by two episodes of fever that rapidly resolved after brief discontinuation of treatment with BRAF–MEK inhibitors. The current admission is characterized by an acute illness with high fevers that persisted for 4 days after discontinuation of treatment with BRAF–MEK inhibitors. She also had hypotension, acute kidney injury, and acute liver injury.

In this case, defining a clinical syndrome and developing a differential diagnosis is challenging because the patient presented with numerous abnormalities involving multiple organ systems. The challenge is in selecting the clinical problems that are most pertinent to the cause of the underlying disease, rather than abnormalities that are consequences of the underlying disease or are incidental findings. If the clinical problem that is selected is too nonspecific (e.g., fatigue), the differential diagnosis becomes unmanageable. On the other hand, if the syndrome selected is too specific, there is a risk of focusing too narrowly and missing the underlying disease. For this patient, I will focus on the clinical syndrome of fever.

In many patients who present with fever, an infectious cause can be rapidly identified on the basis of a set of localizing symptoms and findings on diagnostic testing (e.g., the presence of cough and lung opacities). In addition, an organism may be quickly identified by means of microbiologic testing, completing the diagnostic evaluation. However, in this patient, no diagnostic imaging findings or microbiologic studies pointed to a specific infectious cause of fever. Therefore, I will approach her case systematically by considering the time course of the fevers, the host immune system, the environment and exposures, and key diagnostic findings.

TIME COURSE OF FEVERS

When evaluating the time course of fevers, I consider the severity (i.e., maximum temperature), duration, and pace of illness. In this patient, fever developed 4 weeks before the current admission and 1 day after starting BRAF–MEK inhibitors for the treatment of melanoma.[1] These therapies are known to cause treatment-related pyrexia.[2,3] This patient had three discrete febrile episodes after beginning treatment with BRAF–MEK inhibitors, the last of which persisted and progressed despite the discontinuation of these therapies. A key question was whether the third febrile episode leading to hospitalization was part of a syndrome that had lasted for 4 weeks and was consistent with treatment-related pyrexia from BRAF–MEK inhibitor therapy or whether it was an acute illness that was separate from the previous episodes. When the patient initially presented to the emergency department, she was

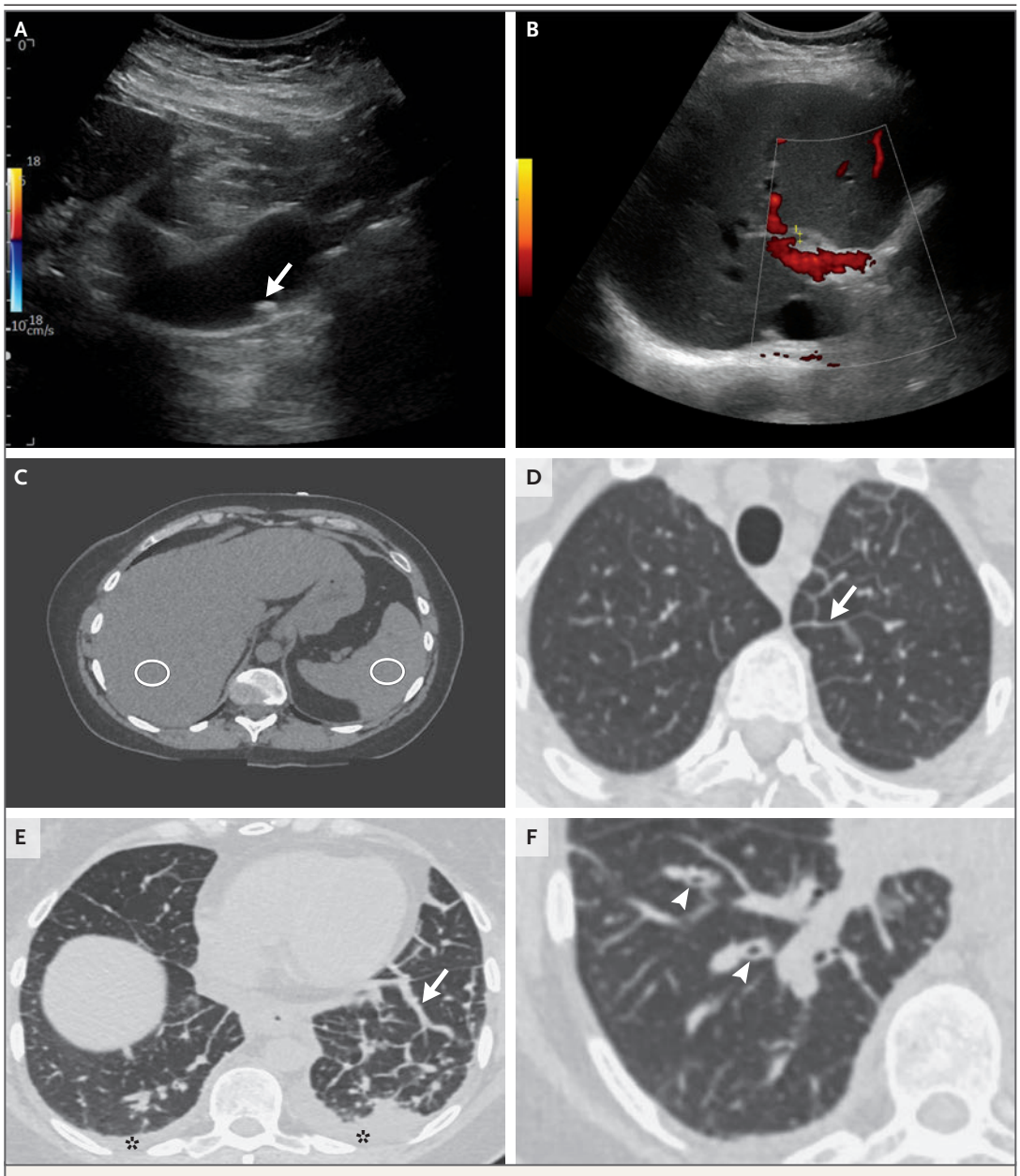

Figure 1. Imaging Studies of the Abdomen, Pelvis, and Chest.

Ultrasound images of the right upper quadrant (Panels A and B) show a mobile echogenic focus indicating cholelithiasis (arrow) without gallbladder-wall thickening or pericholecystic fluid. The common bile duct is normal in caliber, measuring 3 mm. A CT image of the abdomen and pelvis (Panel C), obtained without the administration of intravenous contrast material, shows diffuse hypoattenuation of the liver, with a mean attenuation level of 36 Hounsfield units (HU) (as compared with the spleen, which has an attenuation level of 46 HU), a finding that suggests hepatic steatosis (white circle on left side). CT images of the chest (Panels D, E, and F), obtained without the administration of intravenous contrast material, show smooth interlobular septal thickening both at the apex and at the lung bases (arrows), small bilateral pleural effusions (asterisks), and bronchial wall thickening (arrowheads), findings that suggest pulmonary edema.

febrile, hypotensive, and generally appeared ill; she was treated for a presumed severe bacterial infection (for which fluid resuscitation and broad-spectrum antibiotic therapy were administered), since that was the most life-threatening possibility.

HOST IMMUNE SYSTEM

When assessing the host immune system, I evaluate for acquired and inherited causes of immunosuppression, including immunosuppressive medications, viral infections, and liver and kidney disease, all of which have systemic effects that may alter the immune system. I also consider local immunologic changes related to anatomical alterations, previous surgeries, previous radiotherapy, and the presence of implanted hardware or prostheses. This patient had not been treated with immunosuppressive chemotherapy; however, she was receiving immunomodulating therapy for melanoma, and these agents can alter the host–pathogen immune response and cause aberrant tissue inflammation.

ENVIRONMENT AND EXPOSURES

When considering the patient's environment and epidemiologic risk factors, I rely heavily on history taking. I inquire about habitation, occupation, travel, food and diet, medication use, sexual exposures, and proximity to animal and environmental vectors. I also consider possible community-acquired exposures and remain vigilant for current outbreaks and epidemics in the community, for which public health authorities provide an excellent resource.[4] This patient is a nurse, which puts her at risk for health care exposures, including needlestick injuries and respiratory infections such as tuberculosis. She lives in a coastal region of New England, which puts her at risk for tickborne and mosquito-borne diseases in the appropriate season.

KEY DIAGNOSTIC FINDINGS

What other key examination and diagnostic findings can help refine the clinical syndrome of fever in this patient? She initially presented with abdominal tenderness, liver injury, thrombocytopenia, abnormal coagulation test results, acute kidney injury, and an elevated creatine kinase level. Several of these abnormalities did not abate after the administration of fluid resuscitation and broad-spectrum antibiotic therapy. She had worsening tenderness in the right upper quadrant, leukopenia, and progressive elevation in the levels of ALT, AST, and bilirubin. Therefore, the differential diagnosis must include conditions that would explain the patient's acute liver injury in the context of 4 weeks of intermittent fever, with prioritization of diseases that may also cause leukopenia.

ACUTE LIVER INJURY, FEVERS, AND LEUKOPENIA

Life-threatening causes of acute liver injury and fevers — such as cholecystitis, cholangitis, appendicitis, liver abscess, and perihepatitis (the Fitz-Hugh–Curtis syndrome) — were ruled out at the time of admission, given the relatively normal findings on ultrasonography and CT. Liver injury, fever, and leukopenia can accompany acute viral infections, including those caused by SARS-CoV-2, human immunodeficiency virus, herpes simplex virus, varicella–zoster virus, Epstein–Barr virus, and cytomegalovirus, as well as viral hepatitis, among others. Many of these infections can be ruled out by serologic or nucleic acid testing. Vectorborne infections can also produce a syndrome of fever, leukopenia, and elevated levels of ALT and AST, including Lyme disease, anaplasmosis, ehrlichiosis, rickettsial disease, West Nile virus infection, and Powassan virus infection, all of which are caused by organisms that are present in New England. This patient lacked the requisite travel or exposure history for other types of arboviral infections, such as those caused by Zika virus, dengue virus, and chikungunya virus.

It is important to consider the duration of fever. Fevers that persist for several weeks suggest the possibility of subacute infective endocarditis, which can be associated with embolic disease and immune activation and should be evaluated with several sets of blood cultures before the administration of antibiotic agents, as was done in this case. Chronic fever with liver injury can also be associated with infections such as *Mycobacterium tuberculosis* infection, nontuberculous mycobacterial infection, brucellosis, and endemic mycoses. Most of these infections can also cause leukopenia, either through bone marrow suppression or through direct bone marrow infiltration. This patient's occupation as a health care worker puts her at risk for tuberculosis, although she reported that previous latent tuberculosis testing was negative.

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-

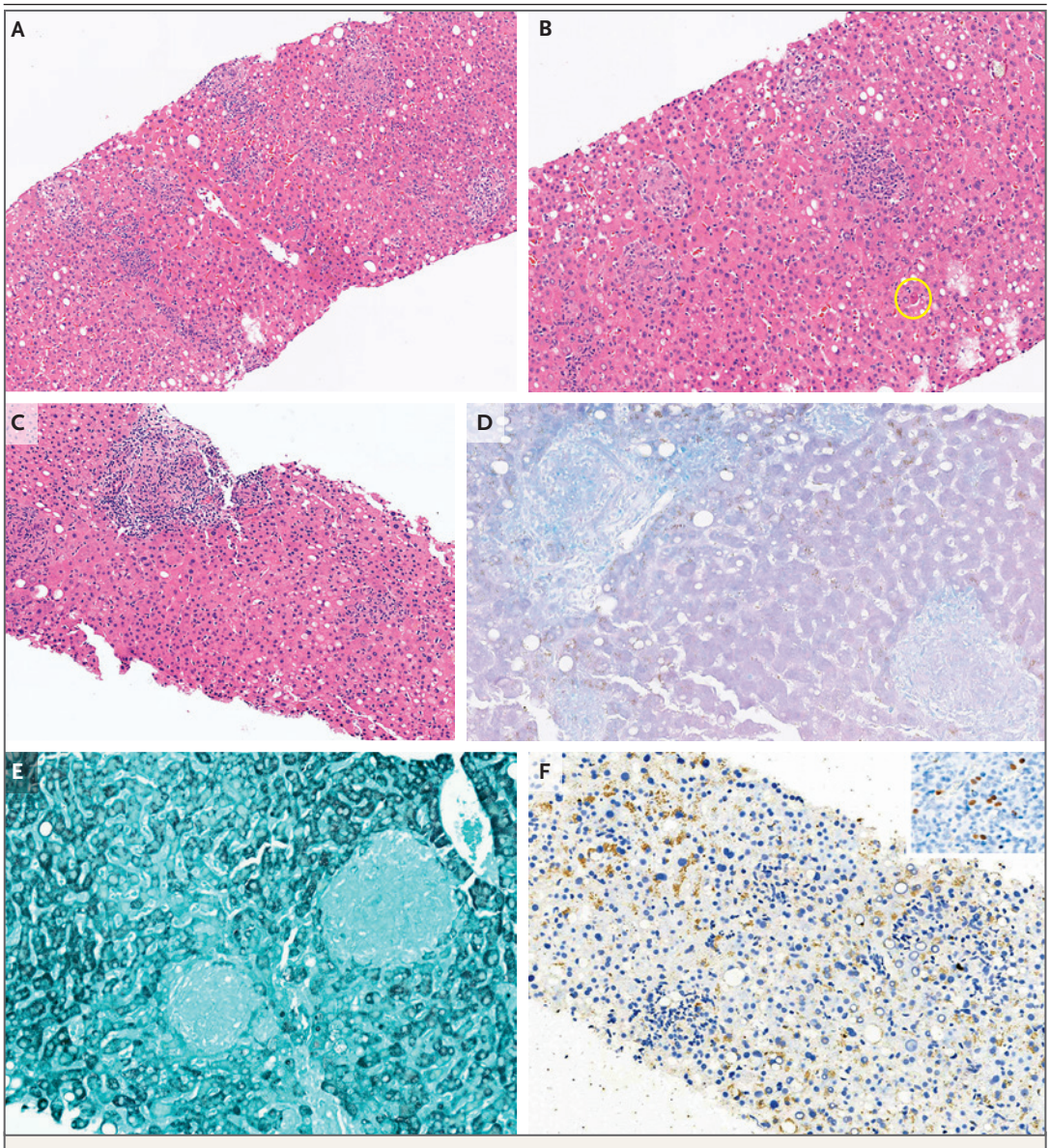

Figure 2. Biopsy Specimens of the Liver.

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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