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

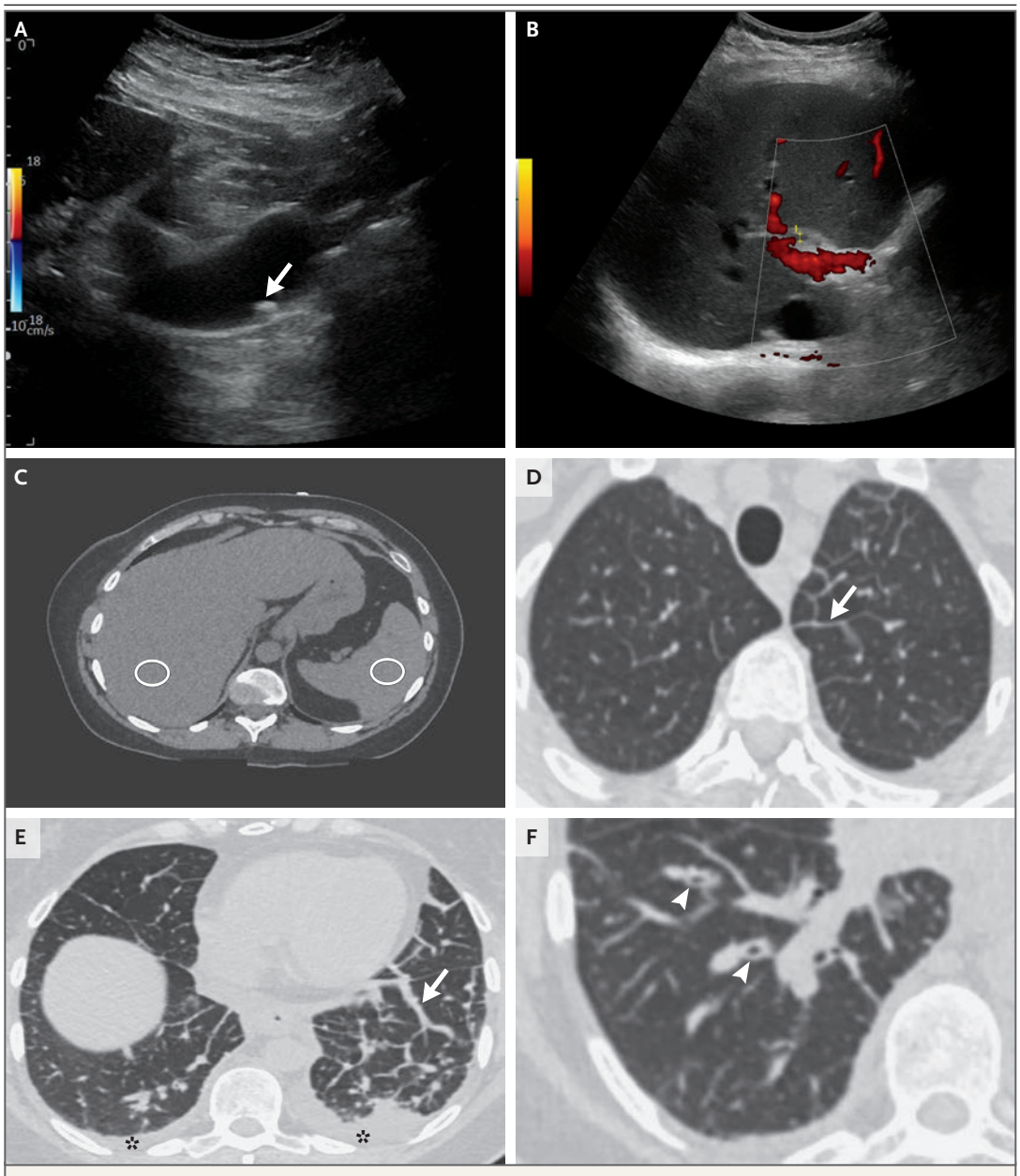

Figure 1. Imaging Studies of the Abdomen, Pelvis, and Chest.

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]

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