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]