A 19-year-old woman presented to a community hospital with a 4-day history of abdominal pain, located in the right upper quadrant and epigastrium, with occasional radiation to her back. She described the pain as intermittent and variable in intensity, associated with nausea, and occurring independently of oral intake or body position. A review of systems was notable for profound fatigue and a 13.6-kg (30-lb) weight loss during the preceding months, which she attributed to stress in the wake of her parents’ recent divorce. She reported no fever, sweats, jaundice, dyspnea, vomiting, diarrhea, constipation, urinary abnormalities, joint aches, or rash.

An anatomical approach is helpful in formulating the differential diagnosis of abdominal pain. Diseases of the liver and pancreaticobiliary tree are the most common causes of right-upper-quadrant abdominal pain, and in a young person, acute viral hepatitis, autoimmune hepatitis, and hepatic injury due to ingestion of alcohol or another toxic substance should be considered. Cholelithiasis or choledocholithiasis may occur in young adults with predisposing risk factors such as obesity, a family history of gallstones, or an underlying chronic hemolytic disorder. The FitzHugh–Curtis syndrome, or pelvic inflammatory disease with perihepatitis, is manifested in young women as right-upper-quadrant pain and may mimic hepatobiliary disease. Pancreatitis, gastritis, and peptic ulcer disease are common causes of epigastric and midabdominal pain that may also involve the right upper abdomen. The patient’s recent weight loss, although apparently circumstantial, is of sufficient magnitude to prompt serious consideration of chronic infection, rheumatologic disease, or cancer.

The patient had a history of hereditary spherocytosis. Ten years earlier, she had undergone laparoscopic splenectomy and cholecystectomy for chronic hemolytic anemia with symptomatic gallstones, with complete resolution of the hemolytic crises. She had received all requisite vaccinations. Her medications included folic acid and an oral contraceptive. She had smoked one pack of cigarettes per day for 4 years, drank alcohol sparingly, and reported no illicit drug use. She was sexually active with one male partner and reported that she did not have unprotected intercourse. Her most recent menstrual period was 2 weeks earlier. She worked as a waitress, lived in a small town in New England, and had not recently traveled outside the northeastern United States. Her family history was notable for hereditary spherocytosis in her mother and siblings.

The patient’s history raises the question of whether hereditary spherocytosis or a complication of splenectomy might explain her abdominal pain. Gallstones, anemia,
symptomatic splenomegaly, and aplastic crises are common sequelae of hereditary spherocytosis; their occurrence is rare after splenectomy, although the presence of retained or accessory splenic tissue can lead to recurrent anemia. It is uncertain whether rates of failure differ between laparoscopic and open splenectomy, although laparoscopic splenectomy is the preferred procedure for children with hereditary spherocytosis. Complications of splenectomy include infections with encapsulated bacteria, which are preventable with the appropriate vaccinations; postsurgical adhesions, which may become symptomatic years after surgery; and postsplenectomy thrombosis, which appears to be a risk primarily in patients with underlying chronic hemolytic disorders who have persistent thrombocytosis after splenectomy.

On physical examination, the patient was afebrile, with focal right-upper-quadrant abdominal tenderness and no evidence of Murphy’s sign. Laboratory studies showed an alanine aminotransferase level of 275 U per liter (normal range, 7 to 35) and an aspartate aminotransferase level of 275 U per liter (normal range, 8 to 30). Levels of alkaline phosphatase, total bilirubin, albumin, amylase, and iron were normal. Serologic tests for hepatitis A, B, and C were negative. Ultrasonography and computed tomography (CT) showed a well-defined, noncystic lesion, measuring 4.5 cm in diameter, originating from the inferomedial aspect of the right side of the liver. On gadoxetate disodium–enhanced magnetic resonance imaging (MRI), the lesion appeared as an exophytic mass that did not contain fat, did not enhance on arterial phase, and did not show delayed uptake of gadoxetate (Fig. 1). Serum alpha-fetoprotein and human chorionic gonadotropin levels were normal. Endoscopic retrograde cholangiopancreatography revealed normal biliary anatomy without stones or other obstruction.

The differential diagnosis of a parenchymal liver mass in a young patient includes hepatic adenoma, focal nodular hyperplasia, liver cyst, hemangioma, and pyogenic or amebic abscess. This patient uses oral contraception, which has been associated with hepatic adenoma and focal nodular hyperplasia. Cancers involving the liver are uncommon in young patients, although hepatocellular carcinoma may occur in young adults in association with long-term hepatitis B virus infection. Gadoxetate disodium–enhanced MRI can sometimes help to distinguish among these lesions, but the mixed radiographic features seen here preclude further interpretation. Liver biopsy or resection, although useful in the evaluation of persistent, large, or symptomatic masses, is not indicated for focal nodular hyperplasia or small hepatic adenomas, because these lesions may regress spontaneously after oral contraception is discontinued.

Oral contraception was withheld for 1 month, yet the patient's abdominal pain persisted. Ultrasound-guided, percutaneous biopsy of the liver mass was performed with the use of an 18-gauge needle. Preliminary pathological review showed hematopoietic elements and a number of CD45+ B cells, which raised concern about lymphoma. The patient was admitted to a university hospital for expeditious evaluation.

Because cessation of oral contraception may lead to gradual regression of hepatic adenoma or focal nodular hyperplasia over a period of several months, the persistence of abdominal pain at this point is not necessarily worrisome. The initial pathological reading is cause for concern, but final assessment requires careful review by a skilled pathologist, taking into account the patient’s clinical presentation. Among the lymphomas that typically affect young adults — namely, acute lymphoblastic lymphoma–leukemia, Burkitt's lymphoma, diffuse large-B-cell lymphoma, mediastinal large-B-cell...
lymphoma, anaplastic large-cell lymphoma, and Hodgkin's lymphoma — extranodal involvement in the form of a solitary liver mass is uncommon; an exception is Burkitt's lymphoma, in which metastatic liver deposits may occur, but patients with this diagnosis are generally very ill. Excisional rather than percutaneous liver biopsy might have been preferable in this patient, because preservation of tissue architecture is important for establishing a diagnosis of lymphoma, hepatic adenoma, and hepatocellular carcinoma.

Review of systems indicated ongoing abdominal pain, fatigue, and sore throat. On physical examination, the patient appeared tired but was not in acute distress. Her temperature was 38.0°C (100.4°F), blood pressure 112/64 mm Hg, heart rate 74 beats per minute, respiratory rate 12 breaths per minute, and oxygen saturation 98% while she was breathing ambient air. The examination was merely incomplete. Posterior cervical, left supraclavicular, and bilateral inguinal lymphadenopathy developed in the month after the patient's initial presentation or whether the initial lymphadenopathy is frequent in patients with complete asplenia in the context of an infectious or inflammatory stimulus.

Lymphadenopathy can be categorized as either reactive or pathologic. Lymph nodes that appear abruptly and are small, tender, supple, or mobile tend to be reactive, whereas lymph nodes that are large, firm, rubbery, or fixed in position tend to be pathologic. Chronic lymph-node enlargement is frequently benign if unaccompanied by other constitutional symptoms, but it may occur in certain infections, inflammatory diseases, or low-grade lymphoproliferative disorders. In the present case, the chronicity of lymphadenopathy is difficult to gauge, because it is uncertain whether lymphadenopathy developed in the month after the patient's initial presentation or whether the initial examination was merely incomplete. Posterior cervi-

cal lymphadenopathy, as seen in this patient, may occur with eczema of the scalp (which drains into the posterior cervical lymph-node chain), infectious mononucleosis or mononucleosis-like syndromes, human immunodeficiency virus (HIV) infection, tuberculosis, cancer, or, in young women, Kikuchi's disease (a self-limited, necrotizing lymphadenitis affecting the cervical lymph-node chains). An enlarged left supraclavicular lymph node (referred to as Virchow's node), also observed in this patient, is often pathologic and has historically been described in association with gastrointestinal cancer. In this patient, however, a lymphoproliferative, infectious, or inflammatory disorder seems more likely.

The white-cell count was 11,500 per cubic millimeter, with 30% neutrophils, 31% lymphocytes, 8% monocytes, 2% eosinophils, 1% basophils, and 28% atypical lymphocytes. The hemoglobin level was 13.5 g per deciliter, the hematocrit 38.2%, and the platelet count 553,000 per cubic millimeter. The alanine aminotransferase level was 19 U per liter, the aspartate aminotransferase level 26 U per liter, the alkaline phosphatase level 70 U per liter, and the total bilirubin level 0.6 mg per deciliter (10.3 μmol per liter) (all within normal limits). The lactate dehydrogenase level was 428 U per liter (normal range, 118 to 242). The uric acid level was 8.1 mg per deciliter (482 μmol per liter) (normal range, 2.5 to 6.0 mg per deciliter [149 to 357 μmol per liter]). Levels of blood urea nitrogen, creatinine, serum lipase, albumin, and globulin and results of coagulation studies and urinalysis were normal. The urine was negative for human chorionic gonadotropin. A peripheral-blood smear showed large atypical lymphocytes, red-cell spherocytes, and Howell–Jolly bodies (Fig. 2A, 2B, and 2C). Peripheral-blood flow cytometry showed a small population of gamma–delta and CD3+CD8+ T cells, a finding consistent with a reactive process.

The findings of atypical lymphocytosis and reactive T cells suggest an acute viral illness, whereas the high lactate dehydrogenase level and hyperuricemia raise concern about a possible lymphoproliferative process with rapid cell turnover. Reactive thrombocytosis with platelet counts exceeding 1 million per cubic millimeter may be seen in patients with complete asplenia.
The presence of Howell–Jolly bodies on this patient’s peripheral-blood smear confirms asplenia or hyposplenia, although an accessory spleen or splenule could still be present. Whole-body positron-emission tomography with the use of $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG-PET) in combination with CT might help to characterize the lymphadenopathy and to guide decisions regarding biopsy, because the absence of abnormal $^{18}$F-FDG uptake in the lymph nodes or in the hepatic mass would argue against pathologic involvement of those sites.

Serologic testing for Epstein–Barr virus (EBV) was positive for IgM and IgG antibodies against viral capsid antigen and negative for IgG antibodies against EBV nuclear antigen; a polymerase-chain-reaction (PCR) assay for EBV DNA in peripheral blood showed a quantitative viral load of 8372 genomes per 100,000 white cells. A PCR assay for cytomegalovirus DNA in peripheral blood was negative, as was a serologic test for HIV. An $^{18}$F-FDG-PET–CT scan showed diffuse, intensely hypermetabolic lymph nodes, but the hepatic mass was not hypermetabolic (Fig. 3).

The results of serologic testing are consistent with acute infectious mononucleosis, because IgM and IgG antibodies against viral capsid antigen develop before antibodies against EBV nuclear antigen; this diagnosis is confirmed by the patient’s detectable EBV viral load. The patient has all the cardinal manifestations of infectious mononucleosis, including fever, sore throat, lymphadenopathy, fatigue, atypical lymphocytosis, and, 1 month earlier, elevated liver enzyme levels; however, the duration and magnitude of her weight loss are atypical and are not readily attributable to this diagnosis. The diffuse lymphadenopathy with intense uptake on the $^{18}$F-FDG-PET–CT scan could raise concern about lymphoma, although infection with EBV or other viruses can sometimes result in these findings. The absence of abnormal $^{18}$F-FDG uptake by the liver lesion is surprising and indicates that it is pathophysiologically distinct from the process affecting the lymph nodes. Excisional biopsy of a lymph node with a high maximum standardized uptake value on $^{18}$F-FDG-PET–CT would confirm or rule out lymphoma. Alternatively, serial observation of the patient for spontaneous regression of lymphadenopathy would be an acceptable strategy pending final pathological review of the liver-biopsy specimen.

Excisional biopsy of a left axillary lymph node showed architectural distortion due to an interfollicular expansion of reactive T cells, with preservation of follicular structures, and in situ hybridization positive for EBV-encoded small RNA. These findings are consistent with EBV infection (Fig. 4A, 4B, and 4C).

Abdominal discomfort in infectious mononucleosis may be due to splenomegaly resulting from lymphoid proliferation in the spleen; one possibility in this case is that the right-sided abdominal pain is the result of reactive splenic tissue...
outside the native splenic bed. Intrahepatic splenosis, which may occur in the context of splenic trauma or after an incomplete splenectomy, could explain the hematopoietic elements seen on biopsy of the liver mass. Alternatively, extramedullary hematopoiesis in the form of an extranodal mass can occur in chronic hemolytic disorders, but it is rare in hereditary spherocytosis. Red-cell uptake on a radionuclide scan obtained after injection of $^{99m}$Tc-labeled red cells denatured by heat would confirm the presence of residual or accessory splenic tissue.

On questioning, the patient’s mother reported that the previous laparoscopic splenectomy had been a “tough” procedure, given the large size of the spleen, and that “a small piece” had been left behind. A $^{99m}$Tc-labeled, heat-damaged red-cell scan showed focal uptake in the inferior right hepatic lobe and the left upper abdomen, findings that were consistent with both intrahepatic splenosis and a residual splenule (Fig. 5). Final review of the core-needle biopsy specimen of the liver revealed islands of mature red cells and other hematopoietic elements without liver parenchyma (Fig. 6A). Electron microscopy showed heterogeneous hematopoietic cells, a finding compatible with the presence of splenic tissue (Fig. 6B and 6C).

**COMMENTARY**

Splenosis is the development of ectopic splenic tissue after trauma or iatrogenic injury to the spleen. In contrast to true accessory spleens, splenosis is found in anatomical areas outside those supplied by the splenic artery and is postulated to arise from intravascular migration of ruptured spleen pulp, which becomes embedded in vascularized surfaces of peritoneal and extra-
peritoneal tissue. Historically, a decrease in the percentage of pitted red cells, as determined manually with the use of light microscopy, was used as a marker of the return of splenic function and the development of splenosis in patients who had undergone splenectomy.\(^1\) In the era of nuclear medicine, \(^{99m}\)Tc-labeled, heat-damaged red-cell scanning, with or without single-photon PET, has emerged as the diagnostic study of choice for splenosis,\(^2-4\) although \(^{99m}\)Tc sulfur-colloid liver-spleen scanning and \(^{111}\)In-labeled platelet scanning are alternatives. Each of these imaging techniques involves injection of a radiolabeled substrate that localizes to splenic tissue, with a level of radiation exposure that is intermediate between the exposure with standard chest radiography and that with abdominal CT.

Splenosis develops in 15 to 70% of patients
after traumatic splenectomy and is usually identified coincidentally on routine imaging or laparotomy, although complications can occur. In rare cases, splenic implants have been reported to cause bowel obstruction or gastrointestinal bleeding. In patients who have undergone splenectomy because of a chronic hemolytic disorder or immune thrombocytopenia, splenosis may result in recurrence of hemolysis or thrombocytopenia, which resolves after resection of the ectopic splenic tissue. The degree of splenic function due to splenosis is dependent on the amount of retained spleen, which in most cases is insufficient to restore full function, resulting in the presence of Howell–Jolly bodies on a peripheral-blood smear.

In case reports of infectious mononucleosis in which modern imaging studies such as 18F-FDG-PET–CT have been performed, diffuse lymphadenopathy with intense 18F-FDG uptake, an increased lactate dehydrogenase level, and hyperuricemia have been observed, essentially mimicking the presentation of aggressive or highly aggressive lymphomas. Subtle clinical features can help to distinguish between lymphoma and infectious mononucleosis, although, as illustrated by the present case, a close collaboration among clinicians, pathologists, surgeons, and radiologists may be required in the case of a common disease in a patient with an uncommon coexisting condition.

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

We thank Lisa Rivera and Drs. Bryan Young, Anthony Zaldonis, Dennis L. Cooper, and Thomas P. Duffy for their contributions to the evaluation of the patient.

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