

CLINICAL PROBLEM-SOLVING

The Unusual Suspects

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In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information by sharing relevant background and reasoning with the reader (regular type). The authors' commentary follows.

A 53-year-old man with Crohn's disease and psoriasis presented to the emergency department with headache, slurred speech, nausea, and vomiting that had persisted for 2 days. His wife reported that he had had yellowing of the skin and eyes and darkening of the urine during the previous 2 weeks. His medications included oral budesonide at a dose of 9 mg daily and intramuscular dupilumab at a dose of 300 mg every 2 weeks; this treatment regimen had remained unchanged for 2 years. He reported no use of tobacco, supplements, or other substances. He consumed four bottles of wine (20 standard drinks) weekly and had maintained this pattern for decades. He lived in New England with his wife. He had traveled to Caribbean islands on two occasions: 4 months before presentation and 3 weeks before presentation. He reported no sick contacts or family history of liver disease.

Neurologic symptoms in an immunocompromised person suggest the possibility of infection, and either liver injury or hemolysis could cause subacute jaundice. Hepatitis may manifest with jaundice and symptoms of elevated intracranial pressure (e.g., headache, slurred speech, or emesis) and could be virus-related or alcohol-induced; on the basis of the patient's travel history, hepatitis A or leptospirosis are possible. Alternatively, malaria or locally acquired babesiosis could cause neurologic symptoms and jaundice due to hemolysis. Evaluation should include careful examination of the nervous system, abdomen, and skin, as well as imaging of the head and liver.

The oral temperature was 36.8°C, the blood pressure 119/79 mm Hg, the heart rate 130 beats per minute and regular, the respiratory rate 18 breaths per minute, and the oxygen saturation 98% while the patient was breathing ambient air. The body-mass index (the weight in kilograms divided by the square of the height in meters) was 31. Scleral icterus and jaundice were present. Cardiovascular examination was notable for a soft, grade 2/6 holosystolic murmur at the apex that radiated to the axilla. The lungs were clear. He had abdominal obesity without tenderness, hepatosplenomegaly, or masses. A nontender papule that measured 5 mm in diameter was present on the left hypothenar eminence, and a tender papule that measured 3 mm in diameter was noted on the left fourth toe. A 2-cm irregular plaque on the right fifth finger was nontender. Two splinter hemorrhages were noted on the right hand (Fig. 1). The patient was alert and oriented. His speech was slurred. Cranial nerves II through XII were intact. Nuchal rigidity, pronator drift, and asterixis were absent. Strength, reflexes, and sensation were normal.

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CME



The tachycardia, systolic murmur, and skin lesions — Osler nodes, a Janeway lesion, and splinter hemorrhages — are suggestive of infective endocarditis with septic emboli.

The white-cell count was 34,000 per microliter, with 79.8% neutrophils, 12.9% bands, and 4.9% metamyelocytes. The hemoglobin level was 12.7 g per deciliter, and the platelet count 130,000 per microliter. The blood level of urea nitrogen was 31 mg per deciliter (11 mmol per liter), and the creatinine level 1.7 mg per deciliter (150 mmol per liter); the estimated glomerular filtration rate was 47.6 ml per minute per 1.73 m² of body-surface area (normal value, >60.0). The remainder of the basic metabolic panel was normal. The aspartate aminotransferase (AST) level was 810 IU per liter (normal range, 10 to 40), and the alanine aminotransferase (ALT) level 1965 IU per liter (normal range, 7 to 56). The alkaline phosphatase level was 178 IU per liter (normal range, 44 to 147), and the total bilirubin level 10.2 mg per deciliter (174 μ mol per liter; normal range, 0.1 to 1.2 mg per deciliter [2 to 21 μ mol per liter]), with a direct bilirubin level of 8 mg per deciliter (137 μ mol per liter; normal value, <0.4 mg per deciliter [<7 μ mol per liter]). The results of these liver-function tests had been normal 9 months earlier. The albumin level was 3.1 g per deciliter (normal range, 3.5 to

5.0), the ammonia level 25 μ mol per liter (43 μ g per deciliter; normal range, 11 to 32 μ mol per liter [19 to 54 μ g per deciliter]), and the lactate level 4.1 mmol per liter (37 mg per deciliter; normal range, 0.5 to 2.2 mmol per liter [5 to 20 mg per deciliter]).

Blood levels of lipase, thyrotropin, and fibrinogen were normal, as was the partial-thromboplastin time; the international normalized ratio was 1.2. The D-dimer level was 3.62 μ g per milliliter (normal value, <0.50). Urinalysis showed trace blood, 1+ white cells, and 1+ bilirubin; microscopic examination of the sediment revealed 16 to 20 white cells per high-power field (normal value, <5).

An electrocardiogram showed sinus tachycardia. Computed tomography (CT) of the head, performed without the administration of contrast material, revealed acute subdural and subarachnoid hemorrhages overlying the left frontal lobe. CT of the abdomen, also performed without the administration of contrast material, revealed mild hepatic steatosis without cirrhosis or biliary abnormalities and wedge-shaped renal hypodensities that were suggestive of infarcts (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The patient was admitted to the hospital. Blood samples were obtained for culture, treatment with vancomycin and meropenem was initiated, and budesonide therapy was interrupted owing to active infection.



Figure 1. Clinical Photographs.

Skin lesions are present on the left hypothenar eminence (Panel A, arrow), the inferior surface of the left fourth toe (Panel B, arrow), and the dorsum of the right fifth finger (Panel C, black arrow). A splinter hemorrhage is present on the nail of the right fourth finger (Panel C, white arrow).

Although infective endocarditis with systemic septic emboli is the leading diagnosis, it would not explain the disproportionate hepatic dysfunction. It is most likely that the patient has concurrent viral infection. Possibilities include viral hepatitis, cytomegalovirus infection, and Epstein–Barr virus infection, particularly given that the extent of elevation of the ALT level was greater than that of the AST level; other possibilities include herpes simplex virus infection and varicella–zoster virus infection. Owing to the patient's history of Crohn's disease, primary sclerosing cholangitis or primary biliary cholangitis should be considered; autoimmune hepatitis is also possible. Hepatotoxicity is rarely reported in association with dupilumab use. Even if bacteremia is confirmed, septic emboli would not explain his hepatic injury because of the dominance of portal blood flow, which would make it difficult for septic emboli to travel to the liver. Ischemic hepatitis would be a consideration if he had previously unrecognized hypotension, but in such cases, the AST level is typically more elevated than the ALT level. The fact that this patient's ALT level was more elevated than his AST level also argues against alcohol-related injury, which is typically associated with a ratio of AST to ALT approaching 2. The normal levels of coagulation markers make disseminated intravascular coagulation or portal vein thrombosis unlikely, and the near-normal international normalized ratio provides reassurance that acute liver failure is not developing.

His blood cultures grew methicillin-sensitive *Staphylococcus aureus*. Viral serologic testing showed no evidence of infection with hepatitis A, B, or C virus. The results of serologic testing for Epstein–Barr virus included undetectable IgM against the viral capsid antigen (a normal result) and elevated IgG levels against viral capsid and nuclear antigens (>750 IU per milliliter and 600 IU per milliliter, respectively; normal value, <18 for both). Testing for cytomegalovirus IgG and IgM was negative. A polymerase-chain-reaction (PCR) test for herpes simplex virus was negative. The level of varicella–zoster virus IgM was 1.26 IU per milliliter (normal value, ≤0.90). Doppler ultrasonography of the abdomen showed patent hepatic vessels, mild hepatic steatosis, and mild thickening of the gallbladder wall. Magnetic resonance imaging of

the head confirmed the presence of acute hemorrhages in the left frontal lobe and identified acute infarcts of 5 mm in diameter in the left frontal lobe, the left parietal lobe, and both cerebellar hemispheres that suggested an embolic origin (Fig. 2). CT angiography of the head revealed a 2-mm abnormality that was suggestive of a mycotic aneurysm of the left middle cerebral artery, with patent vasculature (Fig. S2). Testing for lupus anticoagulant was negative, as was serologic testing for antiphospholipid antibodies and PCR testing for factor V Leiden and prothrombin variants.

Transthoracic and transesophageal echocardiography revealed a 1.2-cm vegetation on the A2 scallop of the mitral-valve leaflet, perforation of the anterior mitral-valve leaflet, severe mitral regurgitation, and flow reversal in the pulmonary vein (Fig. 3, Fig. S3, and video). The remaining valves were normal, as was biventricular function. Antibiotic therapy was changed to oxacillin.

Infective endocarditis with septic emboli to the posterior left frontal lobe (Broca's area) and to the cerebellum explains the patient's slurred speech with intact cranial nerves. However, additional testing is needed to better explain the liver dysfunction. Heightened susceptibility to liver injury may arise from autoimmune- or alcohol-related subclinical disease. His family history makes inherited disorders (e.g., Wilson's disease, α_1 -antitrypsin deficiency, or hemochromatosis) unlikely. The modestly elevated varicella–zoster virus IgM level probably reflects immune activation rather than new varicella–zoster virus infection, given the absence of a characteristic rash.

The antinuclear antibody (ANA) titer was 1:320 (normal value, <1:40). The F-actin anti-smooth-muscle IgG level, measured by enzyme-linked immunosorbent assay, was 35 units (normal value, <20), with negative tests for antimitochondrial antibodies and anti–liver–kidney microsomal antibodies. The IgG level was 3238 mg per deciliter (normal range, 700 to 1600), and the IgA level 894 mg per deciliter (normal range, 70 to 400), with a normal IgM level. The phosphatidylethanol level, measured on hospital day 12, was 37 ng per milliliter (a level of <20 suggests absent or low alcohol consumption; a level of >200 suggests heavy consumption). The serum ceruloplasmin level was 39 mg per deciliter (normal range, 18 to 36).



A video showing transesophageal echocardiography is available at [NEJM.org](https://www.nejm.org)



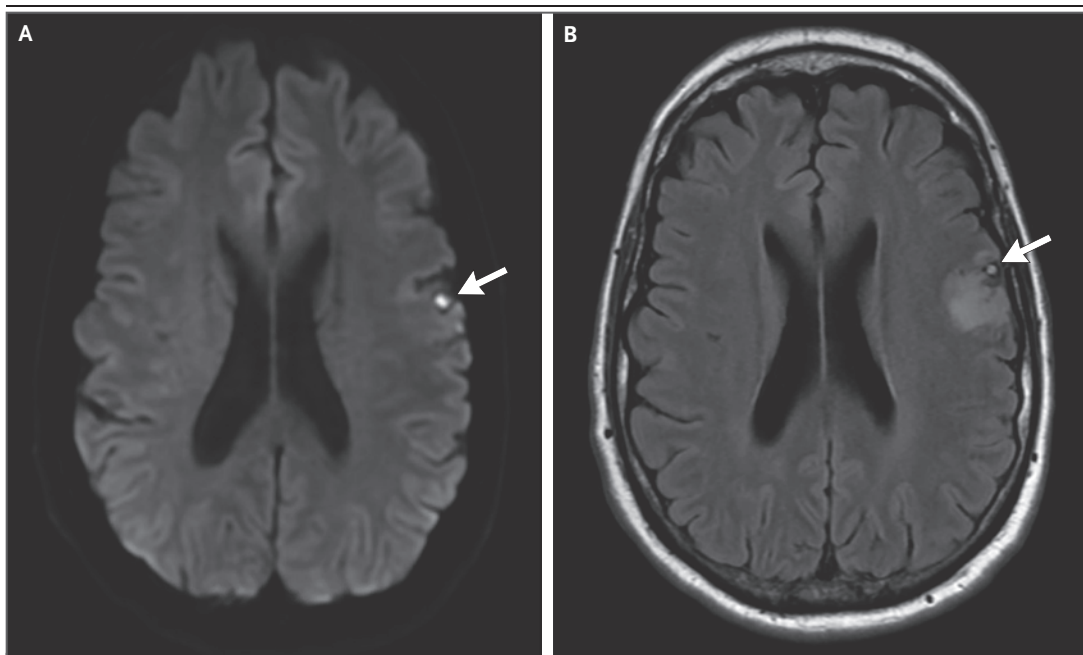


Figure 2. Magnetic Resonance Imaging of the Head.

A diffusion-weighted image (Panel A) shows signal hyperintensity with reduced diffusivity, susceptibility artifact, and heterogeneous enhancement in the left posterior frontal lobe and frontal operculum (arrow). A T2-weighted image (Panel B) shows hyperintensity and associated susceptibility in the left posterior frontal lobe and frontal operculum (arrow), findings that indicate a subacute infarct.

The α_1 -antitrypsin level was normal. The ferritin level was 1288 μg per liter (normal range, 30 to 300), and the iron level 167 μg per deciliter (normal range, 60 to 170); the presence of hyperbilirubinemia prevented calculation of the transferrin saturation. Three days after initiation of empirical antibiotic therapy with vancomycin and meropenem, the AST level had decreased to 445 IU per liter, the ALT level to 480 IU per liter, the total bilirubin level to 6.9 mg per deciliter (118 μmol per liter), and the white-cell count to 15,100 per microliter.

Given the rapid improvement with appropriate antibiotic therapy, at least some component of his liver injury appears to be related to bacteremia or unwitnessed hypotension. Elevated levels of ANA and anti-smooth-muscle antibodies, even in the absence of anti-liver-kidney microsomal antibodies, suggest autoimmune hepatitis but require interpretation in context; although anti-smooth-muscle antibodies have higher specificity for autoimmune hepatitis than ANA, false posi-

tive results for both antibodies are well described in patients with acute bacterial infection, chronic inflammatory bowel disease, metabolic-associated steatotic liver disease, and alcohol-related liver disease. A liver biopsy could provide a definitive pathological diagnosis. Concomitant hepatic steatosis that is possibly associated with alcohol consumption or metabolic disease may delay resolution of his acute liver injury. Although the phosphatidylethanol level suggests moderate alcohol consumption in the 2 to 4 weeks before presentation, this biomarker does not reliably quantify the amount consumed. The slightly elevated ceruloplasmin level is probably a result of inflammation; the level of ceruloplasmin would be low if Wilson's disease were present.

Between hospital days 6 and 14, the AST and ALT levels increased again; the AST level rose to a peak of 984 IU per liter, and the ALT level to a peak of 674 IU per liter. The bilirubin and alkaline phosphatase levels trended downward. The leukocytosis decreased. Blood cultures showed no growth

after hospital day 7. Repeat echocardiography showed valvular function that was similar to that seen on the initial study.

The rising aminotransferase levels suggest hepatocellular liver injury unrelated to infection. In the context of elevated ANA and anti-smooth-muscle antibody titers, autoimmune hepatitis — which may have been exacerbated by the temporary cessation of glucocorticoids during bacteremia — is the most likely diagnosis; the decreasing levels of bilirubin and alkaline phosphatase argue against primary sclerosing cholangitis. Drug-induced liver injury could explain the additional rise in aminotransferase levels but would not explain the patient's abnormal results on liver-function tests at presentation. Of his medications, oxacillin is the most likely to have contributed to liver injury. Liver biopsy is necessary to differentiate the causes of liver dysfunction in this case, including autoimmune hepatitis, drug-induced liver injury that exacerbated the initial infection-related injury, or less likely, small-duct primary sclerosing cholangitis.

Treatment with oral budesonide was restarted on hospital day 8; oxacillin was replaced with cefazolin on hospital day 11. Repeat abdominal imaging confirmed the presence of renal infarcts without intraabdominal abscess or thrombus. A liver biopsy revealed severe portal and lobular hepatitis; findings included infiltrate containing approximately 40% mononuclear immune cells with numerous clusters of more than 5 plasma cells, severe interface activity, and focal portal–central bridging necrosis without evidence of other liver disease (Fig. 4). Together with the patient's laboratory test results, these findings met the criteria for definite autoimmune hepatitis on the basis of a scoring system (the Simplified Autoimmune Hepatitis Score) for diagnosis of autoimmune hepatitis that was developed by the International Autoimmune Hepatitis Group. Budesonide treatment was changed to prednisone at a dose of 40 mg daily; a medication review revealed that the budesonide dose of 9 mg that the patient had previously been taking had been inadvertently restarted at a dose of 3 mg daily. The levels of liver enzymes decreased during hospital days 15 through 23. The patient was discharged home on hospital

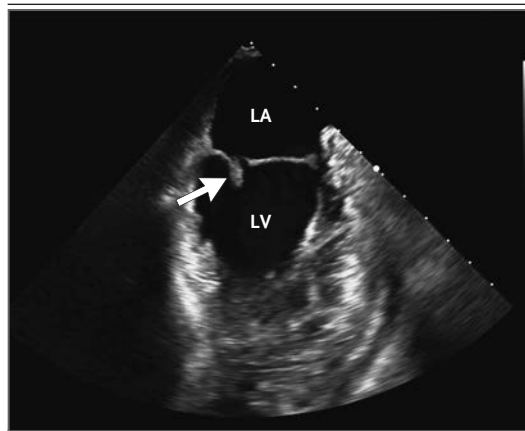


Figure 3. Transesophageal Echocardiogram.

A two-chamber view shows a 1.2-cm, nonmobile vegetation on the body of the anterior leaflet of the mitral valve (arrow). LA denotes left atrium, and LV left ventricle.

day 23 with a prescription for an 8-week course of cefazolin and with a plan to taper the dose of prednisone to 20 mg daily during the subsequent week.

Treatment with azathioprine was added to the prednisone regimen 1 week after hospital discharge and was increased to a dose of 100 mg daily over the course of 1 month. Owing to planned mitral-valve surgery and concerns about the risks associated with glucocorticoids in the context of surgery, the dose of prednisone was rapidly tapered over a period of 2 months and was discontinued 1 week after the levels of liver enzymes had normalized. Bioprosthetic mitral-valve replacement was performed soon after the dose of prednisone was tapered to discontinuation; the patient had no complications from the procedure. The levels of liver enzymes remained normal at a follow-up visit 16 months later.

COMMENTARY

This patient presented with jaundice, headache, slurred speech, and emesis and received a diagnosis of staphylococcal endocarditis and liver injury that incompletely abated with antibiotics. Liver biopsy ultimately led to a diagnosis of autoimmune hepatitis, which had been unmasked by bacterial infection and temporary discontinuation of budesonide therapy for Crohn's disease,

followed by resumption of budesonide at a reduced dose.

Among patients with infective endocarditis, the mitral valve is the most commonly affected site, *S. aureus* is the most prevalent causative organism, and more than half of patients have no previously diagnosed cardiac disease.¹ Limited data suggest that inflammatory bowel disease is associated with an increased risk of infective endocarditis. In one study involving 213 patients with infective endocarditis, the prevalence of

inflammatory bowel disease was 2.8%, as compared with 0.06% in the general population; however, the study lacked matched controls.² Mechanisms that are hypothesized to contribute to an increased risk of infective endocarditis include mucosal inflammation facilitating entry of bacteria into the bloodstream, the use of immunosuppressive medications, and frequent instrumentation.

Autoimmune hepatitis is an immune-mediated inflammatory liver disease with a prevalence of

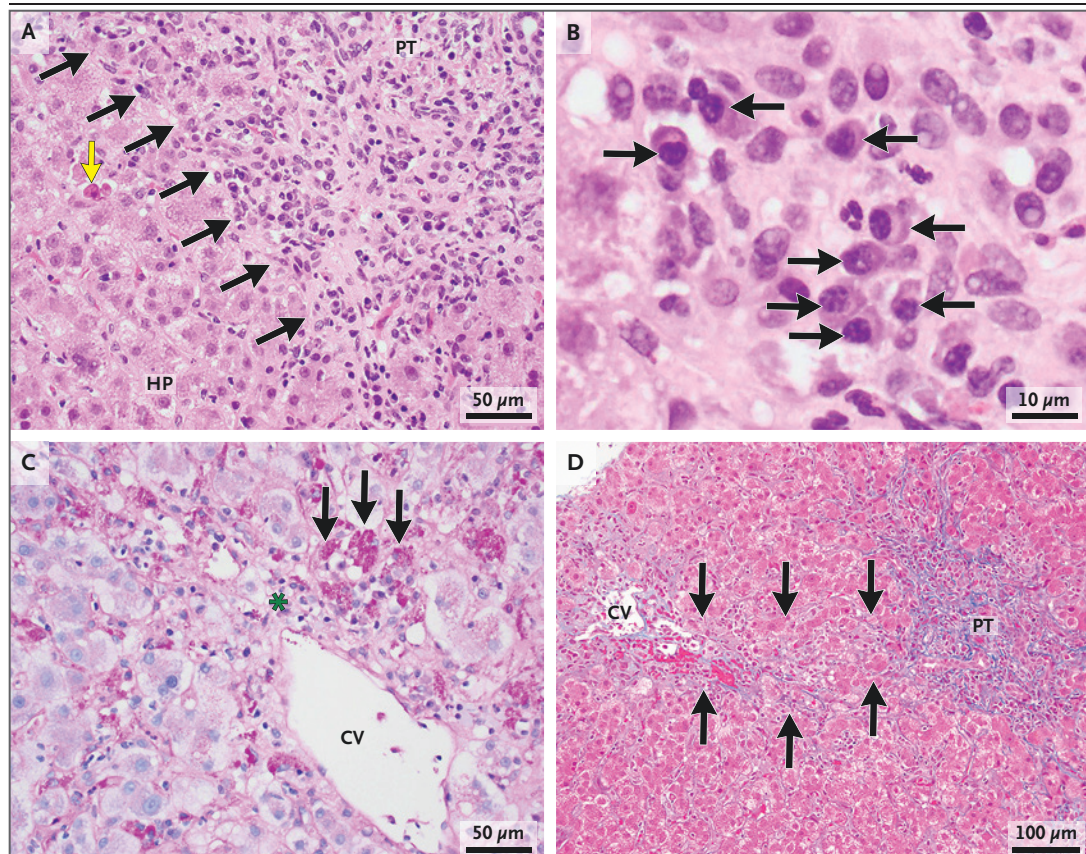


Figure 4. Biopsy Specimens of the Liver.

Hematoxylin and eosin staining (Panel A) shows a moderate-to-marked portal lymphoplasmacytic infiltrate involving most of the portal tracts (PT) with severe interface activity (black arrows; modified Hepatic Activity Index [mHAI] Interface Hepatitis score, 4/4) at the junction with the hepatic parenchyma (HP) and lobular hepatocellular necrosis (yellow arrow; mHAI Focal Necrosis score, 4/4). Higher magnification (Panel B) shows numerous portal and interface plasma cells (comprising approximately 40% of the mononuclear immune cells, including many clusters of >5 plasma cells; arrows) characterized by clumped nuclear chromatin (known as “clockface nuclei”) and abundant eccentric cytoplasm with a perinuclear hof (perinuclear clearing). Interface plasma cells are a characteristic feature of autoimmune hepatitis. Periodic acid–Schiff staining with diastase (Panel C) highlights debris-laden Kupffer cells in magenta (arrows) within a region of confluent necrosis (asterisk) around a central vein (CV). Trichrome staining (Panel D) highlights collagen fibers (in blue), showing bridging necrosis and parenchymal collapse (with fine collagen fibers visible between the arrows) between a central vein and a portal tract (mHAI Confluent Necrosis score, 4/6), without substantial fibrosis that would appear as dense collagen bands. For all three mHAI scales, a higher score indicates more severe disease.

31.2 cases per 100,000 persons in the United States and female predominance, occurring three times as often in women as in men.³ The peak age at presentation is between 40 and 60 years; the prevalence is slightly higher in White populations than in Hispanic, Asian, or Black populations.^{3,4} Other autoimmune diseases are common in patients with autoimmune hepatitis.^{3,5} In a large retrospective cohort study, the odds of having Crohn's disease were 7.2 times as high among adults with autoimmune hepatitis as among those without autoimmune hepatitis.³ In the same cohort study, autoimmune hepatitis was associated with odds of psoriasis — which this patient also had — that were 3.5 times as high among patients with autoimmune hepatitis as among those without the disease.³ Another large retrospective cohort study identified incidence rates of 8.9 cases of autoimmune hepatitis per 100,000 person-years among patients with mild psoriasis and 10.6 cases per 100,000 person-years among patients with severe psoriasis, as compared with 3.0 cases per 100,000 person-years in the general population.⁶

Although the pathogenesis of autoimmune hepatitis is incompletely understood, data suggest that a trigger (e.g., a toxin, infection, or drug) drives aberrant immunologic targeting of hepatocytes in a host with a genetic predisposition to the disease.^{7,8} Normal liver immune tolerance is lost owing to a cycle of impairment of regulatory T-cell function, activation of adaptive immune cells by autoantigens, and production of proinflammatory cytokines that promote hepatocyte injury.⁷

Autoimmune hepatitis is diagnosed on the basis of specific serologic and histologic features rather than on the basis of symptoms. In a cohort of 126 patients with autoimmune hepatitis, 31 (25%) were asymptomatic at diagnosis and had been identified through evaluation of incidental abnormal findings on liver-function tests, whereas 94 (75%) were symptomatic and had most commonly presented with fatigue, arthralgias, or jaundice.⁴ Beyond elevated aminotransferase levels, autoimmune hepatitis is typically associated with antibodies to nuclear antigens, smooth-muscle antigens, liver-kidney microsomal type 1, soluble liver antigens, and liver-pancreas antigens.⁸ Even with compatible laboratory findings, including elevated levels of liver enzymes and biomarkers, liver biopsy remains essential

for diagnosis.^{8,9} In the current case, histopathological examination of liver-biopsy specimens revealed two hallmarks of autoimmune hepatitis^{9,10}: interface hepatitis (characterized by inflammation extending from the portal tract into the periportal zone with necrosis of periportal hepatocytes and disruption of the limiting plate) and plasma-cell infiltration of the portal tracts. The Simplified Autoimmune Hepatitis Score for diagnosis of autoimmune hepatitis, developed in 2008 by the International Autoimmune Hepatitis Group, provides a practical and validated diagnostic framework that incorporates autoantibody profiles, IgG levels, liver histologic features, and the ruling out of viral hepatitis.¹¹

Early diagnosis and treatment are critical to preventing complications of autoimmune hepatitis, which include cirrhosis, hepatocellular carcinoma, gastrointestinal bleeding, liver failure resulting in transplantation, and death. Treatment for autoimmune hepatitis involves the use of immunosuppressive agents to prevent disease progression, with dose adjustment to achieve normalization of liver-function test results and resolution of symptoms. Data from randomized, placebo-controlled trials show reductions in the incidence of death¹² and increases in the percentages of patients having clinical and histologic remissions¹³ with the use of prednisone; the latter trial also showed similar benefits with the combination therapy of prednisone and azathioprine.¹³ In a trial in which budesonide (at a dose of 3 mg three times daily, with a reduction to two times daily) plus azathioprine was compared with prednisone (at a dose of 40 mg daily, tapered to 10 mg daily) plus azathioprine in patients with autoimmune hepatitis, treatment with budesonide plus azathioprine resulted in a higher incidence of biochemical remission at 6 months than prednisone plus azathioprine (60% vs. 39%) and less frequently resulted in side effects from glucocorticoids.¹⁴

Expert guidelines recommend that patients without cirrhosis or acute severe autoimmune hepatitis receive prednisone (or prednisolone) and azathioprine, or budesonide and azathioprine, as first-line therapy; the use of budesonide should be avoided in patients with cirrhosis because of impaired first-pass metabolism.³ A prednisone taper is recommended once the levels of liver enzymes and IgG normalize.⁹ In this case, the patient's use of budesonide for Crohn's

disease may have also inadvertently treated undiagnosed autoimmune hepatitis, and the withdrawal and subsequent resumption of this medication at a lower dose may have contributed to the disease presentation.

Discontinuation of treatment for autoimmune hepatitis may be considered in patients with sustained biochemical remission, defined as normal or near-normal serum aminotransferase and IgG levels for at least 2 years, ideally supported by histologic resolution of hepatitis.⁹ However, relapse remains common. In a prospective study involving 28 adults with autoimmune hepatitis that had been in remission for at least 2 years, only 54% had disease that remained in biochemical remission after cessation of treatment after a median of 28 months.¹⁵ Among 11 patients in the study who had both normal results on liver-function tests and normal liver histologic features before discontinuation of treatment, 46% still had relapse.

The current case highlights the need for a high index of suspicion for autoimmune hepatitis in patients with elevated aminotransferase levels and previous autoimmune disease, as well as the importance of maintaining a broad differential approach to liver injury — serving as a reminder that multiple causes of liver injury are possible. Early recognition and treatment of autoimmune hepatitis are critical to improving outcomes.

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

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