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Type I Autoimmune Hepatitis Presenting With Acute Liver Failure in the Setting of Wild Mushroom Ingestion

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Abstract

Type I autoimmune hepatitis usually has an indolent presentation and course, and is classically thought of as a disease of young women, but can in fact occur across all age ranges. Although its etiology remains unclear, it is hypothesized that an environmental antigen may trigger the disease in a genetically susceptible individual. Here, we report the unusual case of a woman in her seventh decade who presented with acute liver failure as her initial manifestation of autoimmune hepatitis, and who had been a long-time ingester of hand-picked, wild mushrooms.

Keywords

autoimmune hepatitis; acute liver failure; mushrooms

PRESENTATION OF CASE

Dr Jason Rogart—A 63-year-old white female presented to the emergency room with worsening jaundice, lethargy, and confusion. She was well until 2 months before admission when she developed mild fatigue. One month before admission, she was hospitalized at another institution for new-onset jaundice and discharged with a diagnosis of “hepatitis,” but no established etiology. She did not complain of abdominal pain, pruritus, fevers, or nausea. She had no sick contacts, no recent antibiotics or medications, and no recent travel except for an annual local outing in rural Connecticut 2 weeks before her initial symptoms, during which she picked wild mushrooms for consumption. The patient’s past medical history included asthma and an unspecified type of arthritis. She had routine laboratories 6 months ago that included liver function tests and serum albumin, all of which were normal. She took no medications or herbal supplements, nor did she use tobacco or alcohol. There was no family history of liver disease.

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Editor’s Note: This is a continuation of Grand Rounds that were published several years ago from the Yale University School of Medicine Digestive Disease Section and its affiliated hospitals Yale/New Haven Hospital, Bridgeport Hospital, St Raphael’s Hospital and Norwalk Hospital.

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On physical examination, she was afebrile with stable vital signs. She was overweight (body mass index, 28) and deeply jaundiced with no stigmata of chronic liver disease. Her abdomen was softly distended with mild right upper quadrant tenderness, and no hepatosplenomegaly. She had trace peripheral edema and mild asterixis. Initial laboratory testing is summarized in Table 1 and is notable for mild renal insufficiency, a marked transaminitis and hyperbilirubinemia, a low albumin, and an International Normalized Ratio of 4.0. Results of laboratory tests from her prior hospitalization are also listed in Table 1 for comparison. As the patient presented to our institution on a weekend, further details of her recent hospitalization were not initially available.

The patient was admitted to the medical intensive care unit and given lactulose, vitamin K, and intravenous albumin. An abdominal ultrasound (Fig. 1A) showed a small amount of ascites (not enough for paracentesis), no biliary ductal dilation, and possible multiple liver masses. An abdominal magnetic resonance imaging (Fig. 1B) showed no enhancing hepatic masses; however, there appeared to be thickening of the omentum that was concerning for possible malignancy. Nonetheless, evaluation for orthotopic liver transplantation was undertaken.

On hospital day 3, the patient's condition acutely worsened with increased abdominal pain, somnolence, and hypoxia. She developed fever and hypotension, worsening renal failure, hypoglycemia, and severe metabolic acidosis. Broad-spectrum antibiotics and vasopressors were initiated for presumed sepsis and she was intubated. Results of laboratory tests, including those faxed to us from her prior hospitalization are summarized in Table 2, and notable for negative viral hepatitis serologies, and positive antinuclear and smooth muscle antibodies.

Pathology

Dr Anita Iyer and Dr Marie Robert—The pathology slides from a liver biopsy performed 11 days before admission were also obtained, and revealed chronic hepatitis consistent with a diagnosis of autoimmune hepatitis (Figs. 2A–D). Portal tracts showed significant lymphoplasmacytic infiltrates and bile ductular proliferation with moderate interface hepatitis. The hepatic architecture was distorted by significant portal-to-portal bridging and sinusoidal fibrosis, confirmed on trichome stain. Moderate to severe lobular hepatitis was noted with scattered acidophil bodies and giant cell transformation of hepatocytes. Centrilobular hemorrhagic necrosis and fatty degeneration characteristic of acute *Amanita phalloides* poisoning was not seen.¹

Dr Jason Rogart—The patient was started on intravenous corticosteroids for presumed type I autoimmune hepatitis; however, her condition continued to worsen with refractory shock, lactic acidosis, hypoglycemia, coagulopathy, and renal failure. Her family ultimately withdrew care and the patient expired less than 72 hours after admission.

Pathology

Dr Gillian Levy—At autopsy 1600 mL of ascitic fluid was present. The spleen was enlarged (310 g). Petechial hemorrhages were seen in virtually every organ consistent with the patient's coagulopathy. No hepatic masses or peritoneal seeding was noted. The liver showed wrinkling of the capsule and a diffuse mottled appearance (Fig. 3A).

Dr Anita Iyer and Dr Marie Robert—Microscopic examination of the liver revealed extensive hepatocyte necrosis with residual portal tracts that contained nodular lymphoplasmacytic infiltrates and proliferating bile ductules (Fig. 3B). A Klatskin stain showed bridging fibrosis as was present in the previous biopsy. In addition, areas of

hepatocellular collapse revealed early fibrosis, typically found in subfulminant acute necrosis (Fig. 3C). More laboratory results became available postmortem and are summarized in Table 2.

DISCUSSION

Dr Jason Rogart and Dr Mario Strazzabosco

Autoimmune hepatitis is a chronic liver disease that is classified into 2 main types depending on the pattern of autoantibodies present. Type I is characterized by the presence of antinuclear and smooth muscle antibodies, although additional antibodies such as those to double-stranded DNA and soluble liver antigens may also be seen. Type I autoimmune hepatitis usually has an indolent presentation and course; however, acute presentations occur in 9% to 25% of patients.²⁻⁴ In 1 review of patients who presented acutely, 80% satisfied criteria for fulminant hepatic failure, with an average interval between jaundice and encephalopathy of 2.7 weeks.³ Although our patient presented acutely, she in retrospect likely had a “flare” of chronic disease given the findings of fibrosis and chronic inflammation on her initial liver biopsy. Nonetheless, it is still clinically accurate to characterize her presentation as acute liver failure despite the presence of preexisting disease, as some authors do for similar presentations of other chronic liver diseases such as Wilson disease in which cirrhosis is often present at the time of initial diagnosis.^{5,6} Whether or not acute presentations of chronic autoimmune hepatitis should be considered a distinct clinical entity remains debatable. In 1 retrospective review, Kessler et al³ suggests that patients presenting acutely are different with respect to their comorbidities, biochemical parameters, and liver histology. He found a higher prevalence of coexistent autoimmune thyroid disease, lower serum albumin, higher serum bilirubin, and a pattern of centrilobular (zone III) hepatocyte injury despite overall less hepatic fibrosis.

Audience

Was the patient's older age a significant factor in her disease presentation?

Dr Jason Rogart

It is unclear why, at age 63, our patient presented acutely with autoimmune hepatitis. There is conflicting data regarding the role of age in fulminant presentations, probably because of the limited number of patients studied. One recent review, for example, noted no difference in age between patients with acute and chronic presentations (mean age 40 y),³ whereas another did find a statistically significant difference demonstrating that those with acute presentations are older (mean age 56 vs. 45.5 y, $P<0.05$).⁷ It is clear, however, that patients such as ours who are diagnosed at older ages have more advanced histologic stages of disease and progress more rapidly to cirrhosis, with up to 70% of patients presenting with icterus.^{2,7} In a recent retrospective study of 205 patients with type I autoimmune hepatitis, Czaja et al proposes that patients diagnosed after age 60 may have a distinctive clinical phenotype which, in addition to the above, includes a greater prevalence of coexistent autoimmune thyroid and rheumatic diseases, a better response to corticosteroid treatment, and a higher frequency of HLA DR4 compared with patients younger than 30 who were more likely to have HLA DR3.²

Audience

What role did the consumption of wild mushrooms play?

Dr Jason Rogart

HLA DR4 is associated with double the number of alleles as HLA DR3, and can present a more diverse array of antigens.⁸ This may have implications in the genetic susceptibility of older patients to certain etiologic factors contributing to autoimmune hepatitis. One hypothesis for our patient's sudden, dramatic presentation is that her disease was triggered by an environmental agent through a mechanism of molecular mimicry,⁹ a phenomenon which has been implicated in other autoimmune diseases including primary biliary cirrhosis.^{10,11} Although hepatotropic viruses have received the most attention in this regard, there have been reports of certain medications and herbs inducing or exacerbating autoimmune hepatitis.^{9,12–14} Interestingly, our patient was for years a habitual consumer of wild mushrooms which she picked on her own and stored in her freezer; in fact, just 2 weeks before her initial illness she had picked a fresh crop. Is it possible that there existed a cross-reactivity between mushroom epitopes and liver antigens that resulted in a triggering or exacerbation of our patient's autoimmune hepatitis? A review of the literature reveals only 1 case reported of mushroom poisoning inducing a flare of known, underlying chronic autoimmune hepatitis.¹⁵ However, there have been 2 series reporting the development of chronic liver disease in 20% of patients with mild *Amanita phalloides* poisoning, and in 75% of those with severe intoxication.^{16,17} Eighty percent of survivors of severe intoxications were found to have antismooth muscle antibodies, suggesting that they had perhaps developed autoimmune liver disease.¹⁶ It has been hypothesized that toxic compounds could eventually modify the structure of some hepatocellular proteins, triggering, via a process of molecular mimicry, the generation of autoantibodies and an immune response responsible for the development and sustention of chronic autoimmune hepatitis.¹⁸ We suspect this may have been the case with our patient. Unfortunately, we were unable to perform speciation of the consumed mushrooms.

Dr Mario Strazzabosco

In summary, this case serves as a reminder that a diagnosis of autoimmune hepatitis should be considered in patients presenting with acute liver failure that is otherwise unexplained, as prompt treatment with steroids and liver transplantation may be lifesaving. Furthermore, this report again raises the question of a role for environmental antigens in the development of autoimmune hepatitis, and deserves additional attention.

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FIGURE 1.

Initial abdominal imaging. A, Abdominal ultrasound demonstrating ascites and possible hepatic masses. B, Abdominal magnetic resonance imaging did not reveal any enhancing hepatic masses, but showed an abnormally thickened, nonenhancing omentum that raised the possibility of malignancy with peritoneal seeding.

FIGURE 2.

The initial liver biopsy from the previous hospitalization shows the features consistent with autoimmune hepatitis. A, Trichome stain shows periportal, bridging, and sinusoidal fibrosis (stage III) (trichome, 200×). B, Moderate portal and lobular inflammatory activity with dense portal mononuclear infiltrates (arrows) [hematoxylin and eosin (H&E), 200×]. C, High power view of portal tract with significant plasma cell infiltrates (arrows) and proliferating bile ductules (H&E, 600×). D, Giant cell transformation of hepatocytes (arrow) (H&E, 600×).

FIGURE 3.

Postmortem liver. A, The gross appearance of the liver showed a mottled appearance. B, Lack of viable hepatocytes in the lobules. A portal tract with areas of bile duct proliferation and residual inflammation is present (arrows) (H&E, 600 $\times$). C, Klatskin stain reveals extensive bridging fibrosis with nodules of dying hepatocytes, typical of the early fibrous deposition seen in subacute fulminant necrosis. This is likely superimposed on the existing bridging fibrosis seen in the prior liver biopsy (Klatskin, 100 $\times$).

TABLE 1

Routine Laboratory Results at Admission and During Previous Outside Hospitalization

	Admission, t = 0	Discharge, t = 6	Admission, t = 26
AST (IU/L)	1090	2155	2975
ALT (IU/L)	680	1305	2130
Bilirubin, total (mg/dL)	34.7	31.3	10.9
Bilirubin, direct (mg/dL)	23	n/a	9.9
Alk phos (IU/L)	219	232	207
Albumin (gm%)	2.4	3.1	3.5
INR	4.0	2.5	n/a
Platelets ($\times 10^3/\text{mm}^3$)	114	98	207
WBC ($\times 10^3/\text{mm}^3$)	9.8	5.8	4.4
Hematocrit (%)	49.5	43	48.9
Creatinine (mg/dL)	1.4	n/a	0.6
Sodium (mmol/L)	134	n/a	138

Alk phos indicates alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; n/a, not available; WBC, white blood cell.

TABLE 2

Laboratories Available Before and After Death, and those Obtained From Outside Institution During Previous Hospitalization

	Before Death	After Death	Outside Hospital
Hepatitis C Ab	Negative		Negative
Hepatitis B surface Ab	Negative		Negative
Hepatitis B surface Ag	Negative		Negative
Hepatitis A IgM Ab	Negative		Negative
HBV DNA PCR	Not detected		
CMV IgM Ab			Negative
CMV PCR		Negative	
EBV IgM Ab		Negative	
Ceruloplasmin (mg/dL)		24 (normal)	
α -1 antitrypsin (mg/dL)		113 (normal)	
Antinuclear antibody		1:40	1:80
Anti-DS DNA (IU/mL)		1420	
Antimitochondrial Ab			Negative
Antismooth muscle Ab			1:40
Serum protein electrophoresis			Polyclonal increase in γ -globulins
Blood cultures		E. coli	

Ab indicates antibody; Ag, antigen; EBV, Epstein-Barr virus; HBV, hepatitis B virus; n/a, not available; PCR, polymerase chain reaction.