

Fulminant Hepatic Failure in an Adult Patient With Giant-Cell Hepatitis

Maqsood Ahmed Khan, MD¹

Joseph Ahn, MD²

Nikunj Shah, MD²

Shriram Jakate, MD²

Ajay Patel, MD²

Meredith Burns, MD³

Stanley M. Cohen, MD²

¹Division of Gastroenterology, Hepatology, & Nutrition, Cleveland Clinic, Cleveland, Ohio;

²Rush University Medical Center, Chicago, Illinois;

³Loyola University Medical Center, Maywood, Illinois

Giant-cell hepatitis is most commonly found in neonates and rarely seen in the adult population. Diagnosis in adult cases is often difficult to make, as the presentation and etiologies vary. The disease can progress to fulminant hepatitis, necessitating liver transplantation, in some cases.

Case Report

A 56-year-old man presented to the emergency room with bilateral knee pain and jaundice and reported having dark orange urine for 3 days along with dark, hard stools and abdominal pain. His past medical history was significant for autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura (ITP), and splenectomy. His medications included prednisone 40 mg daily, fexofenadine, and insulin. His physical examination was negative for chronic liver disease stigmata except for scleral and sublingual icterus and hives over the trunk and extremities.

Initial laboratory tests showed a white blood cell count of $19.0 \times 10^3/\text{UL}$, total bilirubin of 13.2 mg/dL, direct bilirubin of 9.5 mg/dL, albumin of 3.0 g/dL, alkaline phosphatase of 246 U/L, aspartate aminotransferase/alanine aminotransferase levels of 435/758 U/L, international normalized ratio of 1.66, and gamma-glutamyl transpeptidase of 103 U/L. Ultrasound, computed tomography scan of the abdomen, and magnetic resonance cholangiopancreatography were all normal.

Further laboratory evaluation was negative for hepatitis B virus (HBV), hepatitis C virus (HCV), HIV, Lyme disease, antineutrophilic cytoplasmic antibodies, antinuclear antibody, parvovirus, cytomegalovirus, antismooth muscle, and liver/kidney antibodies. Only hepatitis A virus immunoglobulin (Ig)G antibodies and Epstein-Barr virus (EBV) IgG antibodies were positive. A liver biopsy obtained 2 months prior to admission was significant for plasmacytosis and macrovesicular steatosis. However, the current biopsy revealed periportal and lobular grade III hepatitis with lymphoplasmacytosis and rosetting with increasing cholestasis and cholangitis consistent with an autoimmune hepatitis. Interestingly, EBV was negative on tissue evaluation.

The patient's total bilirubin continued to rapidly rise, and mycophenolate mofetil 1 g twice-daily dosing was started in addition to the prednisone 40 mg daily. The patient developed acute renal failure, requiring hemodialysis. One week after admission, the quantitative EBV titer came back as 323,000 copies/mL, and at this time, mycophenolate was discontinued and the patient was placed on acyclovir for presumed EBV-induced hepatitis. The patient had also developed a *Streptococcus pneumoniae* bronchitis and was treated with levofloxacin (Levaquin, Ortho McNeil Janssen). Shortly after this time, the patient developed fulminant hepatic failure, with an international normalized ratio that rose to 2.95 and total bilirubin that rose to 67.4 mg/dL and he thus underwent liver transplantation. The patient's immunosuppressive medications included a taper of intravenous basiliximab (Simulect, Novartis) 20 mg, methylprednisolone sodium succinate (Solu-Medrol, Pharmacia and Upjohn), tacrolimus

Address correspondence to:

Dr. Maqsood Ahmed Khan, Department of Gastroenterology, Hepatology, and Nutrition, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195.

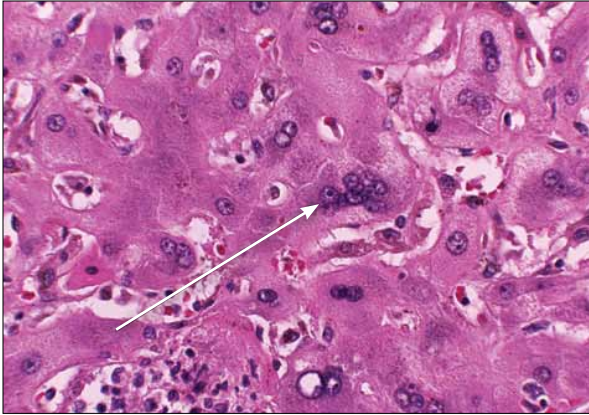


Figure 1. High magnification microphotograph showing giant-cell hepatitis with multinucleated hepatocytes and focal necrosis with inflammation (arrow; hematoxylin and eosin stain; $\times 400$ magnification).

(Protopic, Astellas) 2 mg oral, twice daily, and mycophenolate mofetil 500 mg every 12 hours.

The explanted liver showed severe giant-cell hepatitis suggestive of a giant-cell hepatitis variant of autoimmune hepatitis (Figure 1). The patient's renal function and liver function tests continued to improve, with a total bilirubin of 13.3 mg/dL and aspartate aminotransferase/alanine aminotransferase levels of 40/103 U/L at the time of discharge (Table 1). The patient was discharged from the hospital on tacrolimus 4 mg twice daily, mycophenolate 1 g twice daily, and acyclovir 200 mg twice daily.

Discussion

Giant-cell hepatitis is a condition characterized by inflammation and large multinucleated hepatocytes in the parenchyma. Although the formation of giant hepatocytes has been shown to be a common response of the newborn liver to a variety of attacks, its occurrence in adults is very rare (0.1–0.25% of all hepatic diseases).^{1,2} There have been approximately 100 reported cases of adult giant-cell hepatitis within the last two decades.³ The combination of hepatitis and extensive giant-cell transformation in the adult liver has been referred to as postinfantile giant-cell hepatitis or syncytial giant-cell hepatitis.⁴ Cases are variable in both their clinical presentation and etiology. Adult giant-cell hepatitis has been associated with autoimmune disorders, and multiple patients have been found to have antismooth muscle and antinuclear antibody–positive serology.⁵

Viral infections (eg, EBV, paramyxovirus, and viral hepatitis), medications, and cholestatic disorders have

Table 1. Significant Laboratory Findings over Patient Hospital Course

Laboratory values	At admission	Pre-transplant	Post-transplant
Total bilirubin (mg/dL)	13.2	67.4	13.3
Aspartate aminotransferase (U/L)	435	231	40
Alanine aminotransferase (U/L)	758	645	103
International normalized ratio	1.66	2.95	0.92
Creatinine (mg/dL)	0.9	5.3	1.5

also been seen as causes of this disease.^{1,4,6,7} In fact, there have been some reports suggesting a novel paramyxo-like virus as the cause of some cases of adult giant-cell hepatitis.^{4,8} In one of the largest studies to date with 78 patients, the various conditions found to be associated with adult giant-cell hepatitis were as follows: autoimmune hepatitis in 29 (37.2%) patients, HCV infection in 6 (7.7%) patients, HBV infection in 4 (5.1%) patients, HBV and HCV plus HIV infection in 1 (1.3%) patient, EBV infection in 1 (1.3%) patient, and drug-induced hepatitis in 1 (1.3%) patient. No associated possible etiology was found in 36 of the 78 patients (46.2%).⁹ In our case, the patient had a history of ITP as well as a positive serology for EBV.

Adult giant-cell hepatitis has been shown to be a progressive and often fatal disease process, with a survival rate of only approximately 50% without orthotopic liver transplantation (OLT). The high mortality rate is often due to severe liver failure, anemia that is difficult to control, or sepsis in the setting of aggressive use of immunosuppressants.⁸ Indeed, our patient was found to have fulminant hepatic failure with uncontrollable anemia and was diagnosed with a *Streptococcus pneumoniae* bronchitis in the setting of corticosteroid and mycophenolate mofetil immunosuppression.

Corticosteroids have been found to definitively improve the clinical picture in those individuals who are seropositive for autoimmune markers.^{1,2} It has also been shown that in many autoimmune seropositive cases of giant-cell hepatitis, disease recurrence was seen after OLT, and in these cases, transplant is no longer considered appropriate treatment.¹⁰ These patients should continue to be monitored indefinitely for any signs of recurrence

via frequent liver function tests and autoimmune panels as well as serial liver biopsies.

This case of adult giant-cell hepatitis is unique in that the initial liver biopsy did not provide the appropriate diagnosis. It was not apparent until evaluation of the gross explanted liver specimen that the etiology of the patient's liver failure might be giant-cell hepatitis. A complicating feature of this patient's case was his EBV-positive status. This finding directed his treatment toward a likely EBV-induced hepatitis. When his clinical status continued to deteriorate despite treatment, other more rare causes of hepatitis were investigated. Interestingly, as mentioned above, it has been shown that EBV is a possible etiology of giant-cell hepatitis resulting in fulminant hepatic failure.⁹ It is unclear what role EBV played in this patient's hepatic failure, but this case demonstrates the importance of a thorough immunologic evaluation of possible etiologies for patients with hepatic failure. The diagnosis of giant-cell hepatitis must be considered in cases of apparent idiopathic hepatic failure.

This patient was seen recently for follow-up evaluation in the liver transplantation clinic and was still doing well 3 months post-transplant.

References

1. Johnson SJ, Mathew J, MacSween RN, Bennett MK, Burt AD. Post-infantile giant cell hepatitis: histological and immunohistochemical study. *J Clin Pathol*. 1994;47:1022-1027.
2. Devaney K, Goodman ZD, Ishak KG. Postinfantile giant-cell transformation in hepatitis. *Hepatology*. 1992;16:327-333.
3. Kryczka W, Walewska-Zielecka B, Dutkiewicz E. Acute seronegative hepatitis C manifesting itself as adult giant cell hepatitis: a case report and review of literature. *Med Sci Monit*. 2003;9(suppl 3):29-31.
4. Phillips MJ, Blendis LM, Poucell S, Offerson J, Petric M, et al. Syncytial giant cell hepatitis. Sporadic hepatitis with distinctive pathological features, a severe clinical course, and paramyxoviral features. *N Engl J Med*. 1991;324:455-460.
5. Gorelik M, Debski R, Frangoul H. Autoimmune hemolytic anemia with giant cell hepatitis: case report and review of the literature. *J Pediatr Hematol Oncol*. 2004;26:837-839.
6. Lau JY, Koukoulis G, Mieli-Vergani G, Portmann BC, Williams R. Syncytial giant-cell hepatitis: a specific disease entity? *J Hepatol*. 1992;15:216-219.
7. Fimmel CJ, Guo L, Compans RW, Brunt EM, Hickman S, et al. A case of syncytial giant cell hepatitis with features of a paramyxoviral infection. *Am J Gastroenterol*. 1998;93:1931-1937.
8. Vajro P, Migliaro F, Ruggeri C, Di Cosmo N, Crispino G, et al. Life saving cyclophosphamide treatment in a girl with giant cell hepatitis and autoimmune hemolytic anemia: case report and up-to-date on therapeutical options. *Dig Liver Dis*. 2006;38:846-850.
9. Thaler H. Post-infantile giant cell hepatitis. *Liver*. 1982;2:393-403.
10. Pappo O, Yunis E, Jordan JA, Jaffe R, Mateo R, et al. Recurrent and de novo giant cell hepatitis after orthotopic liver transplantation. *Am J Surg Pathol*. 1994;18:804-813.

Review

Claus J. Fimmel, MD, and

Suzanne Robertazzi, MSN, ANP-BC

Loyola University Medical Center, Maywood, Illinois

Syncytial giant-cell hepatitis is an uncommon form of liver disease in the adult population, whereas giant multinucleated hepatocytes are frequently observed in neonatal hepatitis.¹ The mechanisms by which the characteristic multinucleated hepatocyte syncytia are formed are unknown. Two processes have been proposed: increased hepatocyte nuclear proliferation that is not followed by cell division or the membrane fusion of neighboring hepatocytes.²⁻⁵

The characteristic histologic changes of giant-cell hepatitis have been attributed to a variety of insults. Medications such as methotrexate, 6-mercaptopurine, clometacin, amitriptyline, chlorthalidone, and chlorpromazine have been implicated as potential causes. A variety of autoimmune disorders can be associated with giant-cell hepatitis, including systemic lupus erythematosus, rheumatoid arthritis, ulcerative colitis, autoimmune hemolytic anemia, primary sclerosing cholangitis, and autoimmune hepatitis (AIH).⁶ Finally, several viruses have been detected in the livers of patients with the disease, including hepatitis A, B, C, and E, Epstein-Barr virus (EBV), and a potentially unidentified paramyxovirus.^{3,6-11} Most recently, a study by Potenza and associates suggested that the reactivation of human herpesvirus 6A infection in a liver transplant recipient was a cause of giant-cell hepatitis.¹²

The case described by Khan and colleagues is of particular interest because of the presence of two potentially related etiologies of giant-cell hepatitis: AIH and EBV infection.¹³ A few questions were raised with regard to the patient's prior history. It was noted that the patient underwent a liver biopsy 2 months prior to his admission with severe cholestatic hepatitis. It would have been helpful to discuss the indications for the initial liver biopsy. Similarly, it would have been of interest to review the initial laboratory values, including liver function tests and

Address correspondence to:

Dr. Claus J. Fimmel, Division Director of Gastroenterology, Medical Director of Hepatology, Loyola University Medical Center, 2160 South First Ave, Building 54, Suite 037, Maywood, IL 60153; Tel: 708-216-9230; Fax: 708-216-4113; E-mail: cfimmel@lumc.edu

autoimmune markers, and to know the abnormalities that prompted the liver biopsy and whether the patient was started on prednisone as a result of a new diagnosis of AIH. Or, perhaps prednisone was given to treat autoimmune hemolytic anemia and immune thrombocytopenic purpura, both conditions listed in the patient's past medical history. However, the patient had previously undergone a splenectomy, which typically reduces the need for high-dose steroid therapy.^{14,15}

The initial laboratory values provided in this case study include negative antineutrophil cytoplasmic, antinuclear (ANA), antismooth muscle (ASMA), and anti-liver-kidney-microsome antibodies. At first glance, these findings argue against a diagnosis of AIH. However, although ANA and ASMA titers are typically elevated in AIH, they can be undetectable in up to 20% of patients with histologically proven AIH.¹⁶ Newer autoantibodies are being studied to assist in the diagnosis of AIH and to predict disease progression and relapse after corticosteroid withdrawal.¹⁷ For example, antibodies to soluble liver antigen/liver pancreas reportedly have a 99% specificity for AIH.¹⁸ It would have been interesting to test for this autoantibody in this patient. Serum protein electrophoresis and immunoglobulin analysis would also have been useful to further evaluate this patient for possible AIH.

Later in the patient's course, the focus shifted to a possible causative role of EBV infection in the patient's liver disease. Approximately 90% of the world's adult population is infected with EBV, a member of the herpes virus family.¹⁹ The infection persists for life. Based upon this patient's high EBV titer of 323,000 copies/mL, a reactivation of latent EBV or a de novo infection with liver involvement is possible. EBV hepatitis in immunocompetent patients is uncommon.²⁰ On liver biopsy, EBV hepatitis is characterized by moderate-to-marked mixed inflammatory cell infiltrates in the portal tract along with scattered foci of interface activity. In addition, infiltration of the liver with atypical lymphocytes is typically present and results in a characteristic beaded sinusoidal pattern.¹⁹ It is unknown whether these features were present in either of the patient's biopsies. With regard to the direct virologic examination of liver tissues for EBV, commercially available techniques include immunohistochemical staining, in-situ hybridization (ISH), and polymerase chain reaction (PCR). Of these methods, immunohistochemical staining was found to be the least sensitive, whereas better results were obtained with ISH and PCR.¹⁸ It would have been helpful to know which method was used in this case to interpret the reported negative results.

This case report rekindles the ongoing discussion in the literature regarding the possible causative relationship between EBV infection and AIH.²¹

To further complicate matters, both of the entities can be associated with giant-cell transformation.^{5,8} Based upon the evidence presented, we suggest that this patient developed AIH and that the reactivation of his latent EBV infection did not play a causative role in his liver failure. This impression is based upon the absence of additional clinical features suggesting primary EBV infection and upon the lack of suggestive liver biopsy findings.

The authors' observation that giant-cell changes can be missed on percutaneous liver biopsy is important and reinforces the need for a careful analysis of the explanted liver, particularly in patients with acute liver failure. It will be interesting to follow this patient's post-transplant course, as giant-cell hepatitis can reoccur in the hepatic allograft.^{4,22}

References

1. Johnson SJ, Mathew J, MacSween RN, Bennett MK, Burt AD. Post-infantile giant cell hepatitis: histological and immunohistochemical study. *J Clin Pathol.* 1994;47:1022-1027.
2. Ben-Ari Z, Broida E, Monselise Y, Kazatsker A, Baruch J, et al. Syncytial giant-cell hepatitis due to autoimmune hepatitis type II (LKM1+) presenting as subfulminant hepatitis. *Am J Gastroenterol.* 2000;95:799-801.
3. Devaney K, Goodman ZD, Ishak KG. Postinfantile giant-cell transformation in hepatitis. *Hepatology.* 1992;16:327-333.
4. Estradas J, Pascual-Ramos V, Martínez B, Uribe M, Torre A. Autoimmune hepatitis with giant-cell transformation. *Ann Hepatol.* 2009;8:68-70.
5. Lau JY, Koukoulis G, Mieli-Vergani G, Portmann BC, Williams R. Syncytial giant-cell hepatitis—a specific disease entity? *J Hepatol.* 1992;15:216-219.
6. Gabor L, Pal K, Zsuzsa S. Giant cell hepatitis in adults. *Pathol Oncol Res.* 1997;3:215-218.
7. Fimmel CJ, Guo L, Compans RW, Brunt EM, Hickman S, et al. A case of syncytial giant cell hepatitis with features of a paramyxoviral infection. *Am J Gastroenterol.* 1998;93:1931-1937.
8. Koskinas J, Deutsch M, Papaioannou C, Kafiri G, Hadziyannis S. Post-infantile giant cell hepatitis associated with autoimmune hepatitis and polyarteritis nodosa. *Scand J Gastroenterol.* 2002;37:120-123.
9. Moreno A, Moreno A, Pérez-Eliás MJ, Quereda C, Fernández-Muñoz R, et al. Syncytial giant cell hepatitis in human immunodeficiency virus-infected patients with chronic hepatitis C: 2 cases and review of the literature. *Hum Pathol.* 2006;37:1344-1349.
10. Micchelli ST, Thomas D, Boitnott JK, Torbenson M. Hepatic giant cells in hepatitis C virus (HCV) mono-infection and HCV/HIV co-infection. *J Clin Pathol.* 2008;61:1058-1061.
11. Phillips MJ, Blendis LM, Poucell S, Offerson J, Petric M, et al. Syncytial giant-cell hepatitis. Sporadic hepatitis with distinctive pathological features, a severe clinical course, and paramyxoviral features. *N Engl J Med.* 1991;324:455-460.
12. Potenza L, Luppi M, Barozzi P, Rossi G, Cocchi S, et al. HHV-6A in syncytial giant-cell hepatitis. *N Engl J Med.* 2008;359:593-602.
13. Khan MA, Ahn J, Shah N, Jakate S, Patel A, et al. Fulminant hepatic failure in an adult patient with giant-cell hepatitis. *Gastroenterol Hepatol.* 2009;5:502-504.
14. Gehrs BC, Friedberg RC. Autoimmune hemolytic anemia. *Am J Hematol.* 2002;69:258-271.
15. Kojouri K, Vesely SK, Terrell DR, George JN. Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systematic review to assess long-term platelet count responses, prediction of response, and surgical complications. *Blood.* 2004;104:2623-2634.
16. Mehendiratta V, Mitroo P, Bombonati A, Navarro VJ, Rossi S, et al. Serologic markers do not predict histologic severity or response to treatment in patients with autoimmune hepatitis. *Clin Gastroenterol Hepatol.* 2009;7:98-103.

17. Czaja AJ, Shums Z, Norman GL. Nonstandard antibodies as prognostic markers in autoimmune hepatitis. *Autoimmunity*. 2004;37:195-201.
18. Czaja AJ, Shums Z, Norman GL. Frequency and significance of antibodies to soluble liver antigen/liver pancreas in variant autoimmune hepatitis. *Autoimmunity*. 2002;35:475-483.
19. Suh N, Liapis H, Misdraji J, Brunt EM, Wang HL. Epstein-Barr virus hepatitis: diagnostic value of in situ hybridization, polymerase chain reaction, and immunohistochemistry on liver biopsy from immunocompetent patients. *Am J Surg Pathol*. 2007;31:1403-1409.
20. Maeda E, Akahane M, Kiryu S, Kato N, Yoshikawa T, et al. Spectrum of Epstein-Barr virus-related diseases: a pictorial review. *Jpn J Radiol*. 2009;27:4-19.
21. Cabibi D, Scaduti S, Cacciatore M, DiGaudio F. Epstein-Barr virus infection as a trigger of autoimmune hepatitis: case report. *Am J Infect Dis*. 2008;4:200-203.
22. Lerut JP, Claeys N, Ciccarelli O, Pisa R, Galant C, et al. Recurrent postinfectious syncytial giant cell hepatitis after orthotopic liver transplantation. *Transpl Int*. 1998;11:320-322.