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 syncitia 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 hepatoyctes.[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, chlordiazepoxide, 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 paramyxo-like virus.[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-Elías 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, Offterson 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 postinfantile syncytial giant cell hepatitis after orthotopic liver transplantation. *Transpl Int.* 1998;11:320-322.