

Giant Cell Hepatitis: A Rare Form of Liver Disease in Adults

Emily Horn, MD
Department of Internal Medicine
KU Medical Center, Kansas City



Case Presentation

- 23 year old woman
- Flu-like symptoms x 2 months
- Development of jaundice
- Laboratory investigation
 - AST 2284, ALT 1820
 - Total bilirubin 20.5
 - INR 7.35

The case begins with a 23 year old woman who presents to her primary care physician with flu-like symptoms consisting of fatigue, malaise, nausea and vomiting, and fevers and chills of 2 months duration. The development of jaundice several weeks later prompted laboratory investigation, which revealed significantly elevated transaminases and bilirubin, as well as a coagulopathy. She was subsequently transferred to KU Medical Center for further work-up of her hepatic failure.

Case Presentation

- Past Medical History
 - Cesarean section 7/05
- Social History
 - Occasional alcohol, no tobacco or illicit drugs
 - No use of herbal products or over-the-counter drugs
 - Pre-vet student, part-time veterinary technician
- Family History
 - Mother and father with hypertension
 - Brother deceased from alcoholic cirrhosis at age 33

Her past medical history is significant only for a cesarean section. She reports occasional alcohol use without tobacco or illicit drug use. She does not take any medications, including herbal or over-the-counter products. She is a pre-vet student and works part-time as a veterinary technician. Family history is significant for hypertension in both parents, and a brother who died from alcoholic cirrhosis at the age of 33.

Case Presentation

- Physical Exam
 - Afebrile, hemodynamically stable
 - Alert and oriented
 - Mild abdominal distention
 - Jaundice, scleral icterus
 - Negative for asterixis, spider angiomata, palmar erythema, dilated abdominal veins

Physical exam on admission was significant for the presence of jaundice and scleral icterus, as well as mild abdominal distention indicative of ascites. She had no other stigmata of chronic liver disease.

Typical findings: icterus, hepatomegaly, splenomegaly, spider angiomata, palmar erythema, excoriations

Advanced disease: muscle wasting, ascites, edema, dilated abdominal veins, hepatic fetor, asterixis, confusion, stupor, coma

37.8, 112/62, 72, 17, 100% RA

Case Presentation

- Admission labs
 - AST 1255, ALT 1157
 - Albumin 2.1
 - Cholesterol 65
 - INR 5.6
 - Platelets 219
 - Acetaminophen level < 10.0

Admission labs revealed persistently elevated transaminases, as well as some evidence of synthetic dysfunction with low serum levels of albumin and cholesterol, and a persistently elevated INR. She had a normal platelet count and her acetaminophen level was less than ten.

Case Presentation

- Autoimmune titers
 - ANA 320
 - Rheumatoid factor +, titer 16
 - Anti-smooth muscle and anti-mitochondrial antibodies negative
- Viral serologies
 - Hepatitis A IgG + and IgM –
 - Hepatitis B and C serologies negative
 - EBV IgG + and IgM –
 - CMV IgG and IgM –
 - HSV and VZV IgG +, IgM –



Further laboratory investigation to distinguish potential autoimmune versus viral etiologies indicated a non-specific autoimmune process with an elevated ANA and positive rheumatoid factor. Anti-smooth muscle and anti-mitochondrial antibodies, however, were negative. Viral serologies indicated prior exposure to hepatitis A, Epstein-Barr virus, herpes simplex virus, and varicella zoster virus, without current infection.

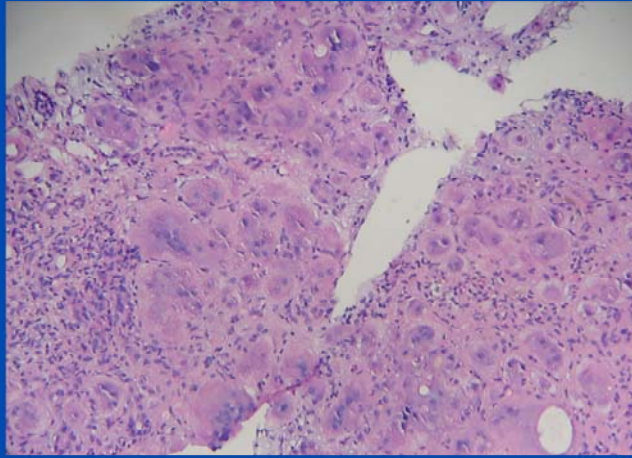
EBV early AgAb and capsid IgG2 +, nuclear AgAb and capsid IgM –

Autoimmune hepatitis:

Type 1 (classic) - ANA and/or ASMA

Type 2 - ALKM-1 (liver/kidney microsomes) and/or ALC-1 (liver cytosol antigen)

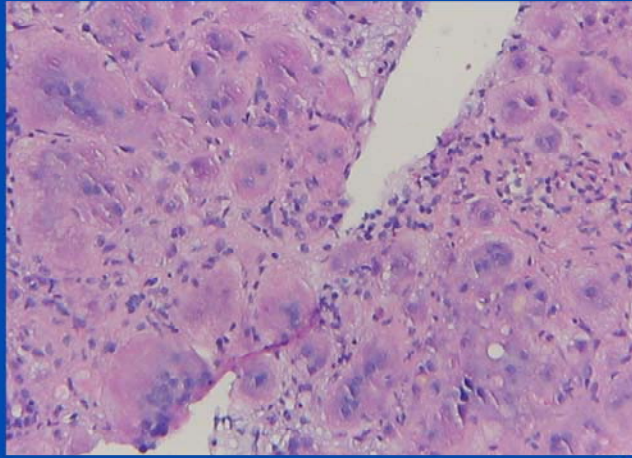
Transjugular Liver Biopsy



KU MEDICAL
CENTER
The University of Kansas

Transjugular liver biopsy was performed, which showed very little normal tissue...

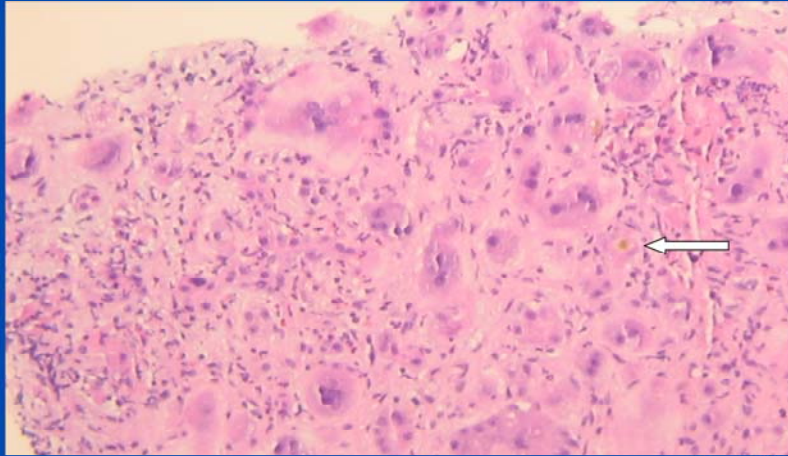
Transjugular Liver Biopsy



KU MEDICAL CENTER
The University of Kansas

...infiltrated with dense areas of multinucleated hepatocytes.

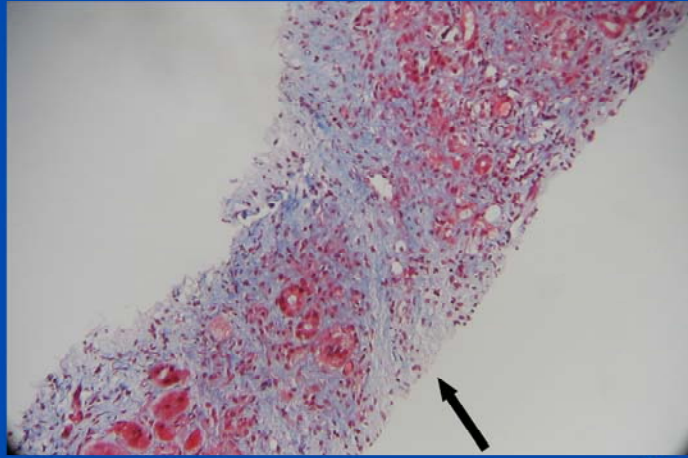
Transjugular Liver Biopsy



KU MEDICAL CENTER
The University of Kansas

There was also evidence of bile stasis, as shown by the arrow on this slide. You can again see several of these multinucleated giant cells.

Transjugular Liver Biopsy



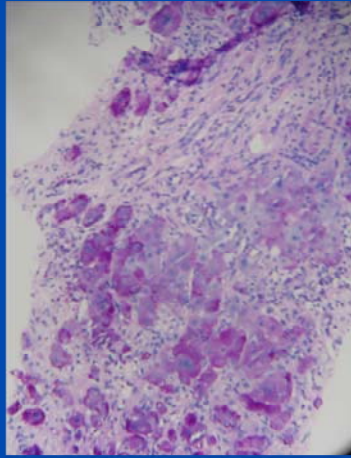
KU MEDICAL CENTER
The University of Kansas

Bridging fibrosis was also present, indicated by the blue color on this trichrome stain.

Pink = normal

Blue = fibrosis

Transjugular Liver Biopsy



KU MEDICAL CENTER
The University of Kansas

Staining for viral inclusions was negative, although this stain does highlight the giant cells.

PAS = periodic acid schiff

Hospital Course

- Empiric treatment for an autoimmune etiology
 - Azathioprine
 - Prednisone
- Work-up for liver transplant
- Discharged to home

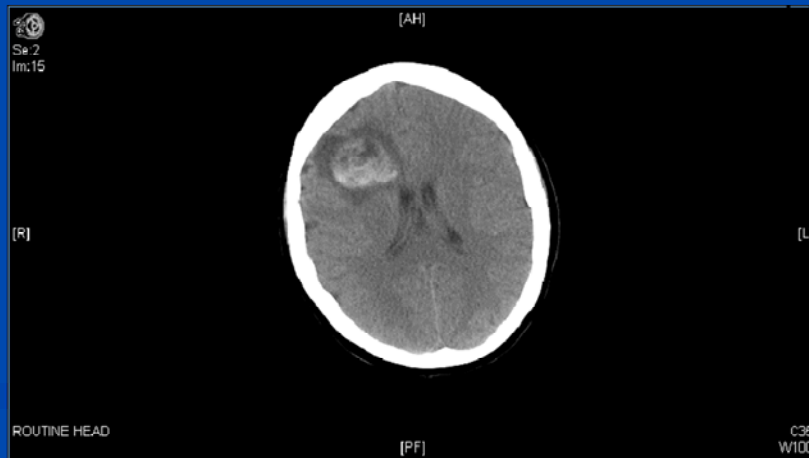
Empiric treatment for a suspected autoimmune etiology was initiated with azathioprine and prednisone, while the work-up for liver transplant began. She was subsequently discharged home to await transplantation. Unfortunately...

Hospital Course

- Re-admitted 2 weeks later for a lower GI bleed secondary to hemorrhoids
- Upper GI bleed from esophageal varices
- Septic shock secondary to E. coli bacteremia
 - Hypotension requiring vasopressor support
 - Acute renal insufficiency requiring hemodialysis
- Mental status changes

...she was re-admitted 2 weeks later for a lower gastrointestinal bleed. She then developed an upper gastrointestinal bleed secondary to esophageal varices as well as septic shock secondary to E. coli bacteremia, requiring the administration of multiple vasopressors for blood pressure support and hemodialysis for acute renal insufficiency. The development of mental status changes prompted CT evaluation...

Hospital Course



...revealing a significant intracranial hemorrhage. There were 4 areas of intraparenchymal hemorrhage noted on this initial CT, the largest shown here in the right frontal lobe with surrounding edema and a small amount of midline shift. A repeat CT 11 hours later...

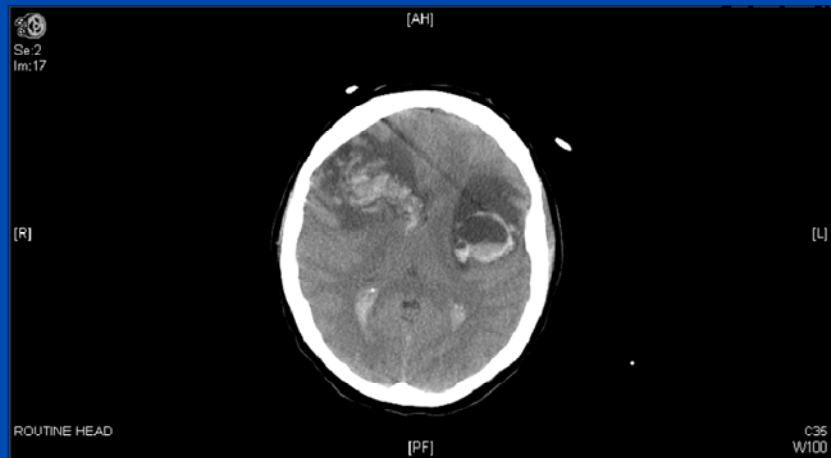
Right frontal: 3.4 x 3.1 cm with a 3 mm right-to-left midline shift, surrounding vasogenic edema

Left posterior corpus callosum: 1.3 cm

Left posterior frontal lobe: 8 mm

Left centrum semiovale: 2.5 mm

Hospital Course



KU MEDICAL CENTER
The University of Kansas

...showed progression of the hemorrhages, as well as several new smaller hemorrhages and evidence of uncal herniation. The goals of care were shifted to comfort measures, and the patient...

Progression of existing hemorrhages with several new smaller intraparenchymal hemorrhages with diffuse intraventricular hemorrhage and interval effacement of the basilar cisterns and 4th ventricle consistent with the development of downward uncal herniation.

Hospital Course

- Goals of care shifted to comfort measures
- Patient death, approximately 4 months following symptom onset

...died soon thereafter, approximately 4 months following the onset of her symptoms.

Giant Cell Hepatitis

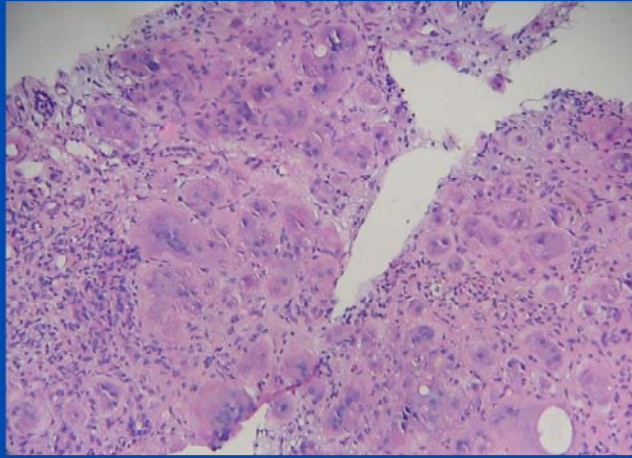
- Synonyms
 - Post-infantile giant cell hepatitis
 - Syncytial giant cell hepatitis
- Descriptive term, denoted by the presence of multinucleated hepatocytes on biopsy
- Heterogenous group of disorders in terms of clinical, serological, and histological features

Labowitz J, et al. Am J Gastroenterol. 2001;96(4):1274-6.
Cairns A, et al. J Clin Pathol. 1996;49:183-4.



Giant cell hepatitis, also known as post-infantile giant cell hepatitis and syncytial giant cell hepatitis, is a rare form of liver disease in adults. It is a descriptive diagnosis based on the pathology found at biopsy, representing a heterogenous group of disorders in terms of clinical, serological, and histological features with the common characteristic of multinucleated hepatocytes on biopsy.

Pathology



KU MEDICAL CENTER
The University of Kansas

The presence of multinucleated giant cells on liver biopsy is the distinguishing diagnostic feature of giant cell hepatitis. There are often other non-specific findings consistent with inflammation or cirrhosis such as fibrosis, bile stasis, portal edema, and infiltration of inflammatory cells.

Etiology

- Non-specific reaction pattern, idiosyncratic regenerative response to hepatic stimuli
 - Viral infection: paramyxovirus, HIV, EBV, hepatitis A, B, and C
 - Drugs and chemicals: MTX, 6-MP, chlorpromazine, vinyl chloride
 - Autoimmune disease: inflammatory bowel disease, SLE, Graves disease

Anagnostopoulos GK, et al. J Gastroenterol Hepatol. 2006;21:1863-4.
Johnson SJ, et al. J Clin Pathol. 1994;47:1022-7.



Giant cells are frequently present in neonatal and infantile liver disease, but are rare in the adult population. In infants, giant cell formation is thought to be a response of immature hepatocytes to a variety of insults, most commonly cholestasis. In adults, the formation of giant cells is thought to be an idiosyncratic regenerative response of hepatocytes. Giant cell hepatitis has been associated with viral infection (including paramyxovirus, HIV, Epstein-Barr virus, and hepatitis A, B, and C); drugs, chemicals, and herbals; as well as autoimmune diseases such as inflammatory bowel disease, systemic lupus, and Graves disease. Giant cell hepatitis is therefore a non-specific reaction pattern rather than a distinct disease process.

Other drugs: clomethacin, p-aminosalicylic acid

Other diseases: sickle cell, hypoparathyroidism

Proposed Mechanisms

- Fusion of mononuclear hepatocytes to form a syncytium
- Failure of the cytoplasm to divide during nuclear division
- Reticuloendothelial origin
 - Circulating macrophages
 - Transformed Kupffer cells

Labowitz J, et al. Am J Gastroenterol. 2001;96(4):1274-6.

KU MEDICAL
CENTER
The University of Kansas

So why does this regenerative response occur? There are several proposed mechanisms for giant cell formation including fusion of mononuclear hepatocytes, failure of the cytoplasm to divide during nuclear division, and arising from reticuloendothelial cells such as circulating macrophages and Kupffer cells.

Prognosis

- Determined by underlying disease
- Unfavorable prognosis
- Variable clinical course
 - Normalization of hepatic histology
 - Spontaneously
 - With treatment of underlying disorder
 - Rapid progression to end-stage cirrhosis requiring transplant or resulting in death

Labowitz J, et al. Am J Gastroenterol. 2001;96(4):1274-6.
Ben-Ari Z, et al. Am J Gastroenterol. 2000;95(3):799-801.

KU MEDICAL
CENTER
The University of Kansas

The prognosis of giant cell hepatitis is determined in large part by the underlying disease, although oftentimes the etiology is unknown. In general, it carries an unfavorable prognosis with rapid progression to cirrhosis in about half of the cases. The reported cases DO indicate variability in the clinical course, ranging from normalization of hepatic histology (either spontaneously or with treatment of the underlying disorder) to rapid progression to end-stage cirrhosis, as seen in this case.

Treatment

- Treatment of the underlying cause
 - Immunosuppressants
 - Antivirals
- Transplantation

Treatment focuses on treating the underlying cause, with immunosuppressants for suspected autoimmune etiology, antivirals for suspected viral etiology, and removal of the offending agent for drug- or chemical-induced disease. Many cases, however, require transplantation.

Immunosuppressants or immunomodulators: prednisone, Imuran, CSA, IFN
Antivirals: ribavirin, ACV

GCH After Transplantation

- Case series of 7 patients
 - 5 patients with GCH as native disease
 - 2 died
 - 2 with re-transplantation, 1 of whom with recurrence in a second allograft
 - 1 alive 6 years after transplant
 - 2 patients with de novo GCH after transplant

Pappo O, et al. Am J Surg Pathol. 1994;18(8):804-13.



There have, however, been case reports of giant cell hepatitis FOLLOWING transplantation. A case series of 7 patients published in the American Journal of Surgical Pathology describes 5 patients with recurrent disease following transplant and 2 patients with de novo giant cell hepatitis after transplantation for other indications. This suggests that the formation of giant cells may be related to a transmissible agent, or that a particular recipient may injure livers in a way that elicits a giant cell reaction. Although it would be helpful to be able to predict this type of response in potential transplant recipients, giant cell hepatitis is a rare entity whose mechanism is poorly understood.

GCH as native disease: recurrent GCH 1-21 months after transplant

De novo GCH: 8 months and 24 months after transplant

Giant Cell Hepatitis

- Diagnosis defined by multinucleated hepatocytes on biopsy
- In adults, an idiosyncratic regenerative response to various hepatic insults
- Viral, drug-induced, and autoimmune etiologies reported
- Variable clinical course
- May recur after or result from transplantation

In summary, giant cell hepatitis is a rare form of liver disease in adults, the diagnosis of which is based on biopsy pathology. Giant cell formation in adults is thought to represent an idiosyncratic regenerative response of hepatocytes to various insults including viruses, drugs, and autoimmune disease. Although this is a common and generally benign response of immature hepatocytes in infants with cholestasis, it is an unusual and detrimental response in adults. Prognosis is generally poor, although patients with giant cell hepatitis have a variable clinical course and the disease may recur after, or result from transplantation.

References

- Labowitz J, et al. Postinfantile giant cell hepatitis complicating ulcerative colitis: a case report and review of the literature. *Am J Gastroenterol*. 2001;96(4):1274-6.
- Cairns A, et al. Giant cell hepatitis associated with systemic lupus erythematosus. *J Clin Pathol*. 1996;49:183-4.
- Anagnostopoulos GK, et al. Postinfantile giant-cell hepatitis associated with ulcerative colitis and autoimmune hepatitis. *J Gastroenterol Hepatol*. 2006;21:1863-4.
- Johnson SJ, et al. Post-infantile giant cell hepatitis: histological and immunohistochemical study. *J Clin Pathol*. 1994;47:1022-7.
- Ben-Ari Z, et al. Syncytial giant-cell hepatitis due to autoimmune hepatitis type II presenting as subfulminant hepatitis. *Am J Gastroenterol*. 2000;95(3):799-801.
- Pappo O, et al. Recurrent and de novo giant cell hepatitis after orthotopic liver transplantation. *Am J Surg Pathol*. 1994;18(8):804-13.

Acknowledgements

- Sally Rigler, MD; Division of General and Geriatric Medicine, Department of Internal Medicine, University of Kansas School of Medicine, Kansas City, KS.
- John Bonino, MD; Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Kansas School of Medicine, Kansas City, KS.
- Jamie Porter, MD; Department of Pathology, University of Kansas School of Medicine, Kansas City, KS.