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CASE REPORT | LIVER

Postinfantile Giant Cell Hepatitis Secondary to Rheumatoid Arthritis

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ABSTRACT

Postinfantile giant cell hepatitis (PIGCH), also known as syncytial giant cell hepatitis, continues to be a poorly defined and rare disease presentation in the adult population. Although a common finding in neonates, there is limited literature on the disease process, causes, and treatment success of PIGCH in adults. A strong association between autoimmune disorders and PIGCH, considerably so in the case of autoimmune hepatitis, has been established. However, there have been limited to no reports of PIGCH secondary to rheumatoid arthritis. Our clinical case aims to bring forth a vignette of PIGCH to spotlight this ill-defined disease in the adult population and highlight some of the proposed causes, treatments, and laboratory markers.

KEYWORDS: post-infantile giant cell hepatitis; giant cell hepatitis; PIGCH; syncytial giant cell hepatitis; adult giant cell hepatitis

INTRODUCTION

While giant cell hepatitis is typically observed in children, postinfantile giant cell hepatitis (PIGCH) is a rare and poorly understood adulthood pathology. There have only been 100 reported cases in the past 30 years.[1] PIGCH presents with large multinucleated hepatocytes in the hepatic parenchyma.[2] Studies have shown that giant cells are most evident in the periportal and periseptal zones and are limited to liver plates with over 15 nuclei.[2] Portal tracts also held inflammatory infiltrates of mature lymphocytes. PIGCH can lead to some degree of periportal fibrosis ending in rapid cirrhosis or acute liver failure.[2,3] PIGCH has multifactorial etiologies including adverse effects of pharmacologic agents, autoimmune disorders, hematologic disorders, and infectious sources.[1–6] PIGCH may also occur idiopathically. Management of PIGCH largely depends on the underlying mechanisms; thus, treatment is often etiology-specific.

CASE REPORT

A 41-year-old woman with a medical history of seronegative rheumatoid arthritis (RA) was being evaluated by her gastroenterologist for iron deficiency anemia and subsequently was found to have elevated liver enzymes: Alkaline phosphatase was 608 U/L; aspartate aminotransferase was 187 U/L; alanine aminotransferase was 228 U/L; and gamma-glutamyl transpeptidase was 536 (Table 1). On review of prior medical records, the patient had had chronically elevated liver enzymes but was lost to follow-up. The patient's RA had been previously diagnosed and managed, but she was not on immunosuppressant therapy at the time of presentation. She reported an unintentional weight loss of 15 lbs within a month-long time frame. She denied abdominal pain, melena, hematochezia, nausea, vomiting, diarrhea, or hematemesis. Current medication reported was ferrous sulfate 250 mg (50 mg iron) extended-release tablets taken twice a day. The patient also denied a history of alcohol use disorder, tobacco use, intravenous drug use, over-the-counter medications (aside from iron supplementation), herbal supplements, sick contacts, or tattoos. Physical examination was unremarkable despite the patient reporting a history of arthralgias.

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Table 1. Laboratory values at presentation

Component	Reference range and units	Value at presentation
Calcium	8.4–10.4 mg/dL	8.1
Total protein	6.1–8.2 gm/dL	6.6
Albumin	3.4–4.7 gm/dL	2.8
Globulin	2.4–4.2 gm/dL	3.8
Bilirubin, total	0.3–1.2 mg/dL	1.5
ALP	38–150 U/L	608
AST (SGOT)	6–58 U/L	187
ALT (SGPT)	14–67 U/L	228
GGT	5–40 U/L	536
Sodium	134–144 mmol/L	139
Potassium	3.5–5.1 mmol/L	3.7
Chloride	98–111 mmol/L	105
CO_2	20–30 mmol/L	26
Anion gap	<15	8
Glucose	60–100 mg/dL	116
BUN	7–31 mg/dL	16
Creatinine	0.50–1.40 mg/dL	0.51
WBC	4.0–11.0 × 10E3/uL	5.6
RBC	4.01–5.47 × 10E6/uL	4.34
Hemoglobin	12.0–16.0 gm/dL	12.1
Hct	35%–48%	39
MCV	81–101 fL	89
MCHC	31.3–35.5 gm/dL	31.4
RDW	11.0–14.5%	22.9
Platelets	150–400 × 10E3/uL	74

ALP, alkaline phosphatase; AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma-glutamyl transpeptidase; CO2, carbon dioxide; BUN, blood urea nitrogen; WBC, white blood cell; RBC, red blood cell; Hct, hematocrit; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width.

Colonoscopy was performed showing terminal ileal ulcers as part of the anemia workup. A liver ultrasound revealed nonenlarged liver size at 13 cm by 11 cm, normal liver vasculature, mild splenomegaly, and fatty liver without enlargement. A noninvasive transient elastography was then performed, with interpretation of S0 steatosis, F3 fibrosis, a controlled attenuation parameter score of 258 dB/m, and a liver stiffness of 10.5 kPa. This revealed that she had severe fibrosis without evidence of nonalcoholic fatty liver disease or cirrhosis.

Workup for autoimmune hepatitis (AIH), including negative smooth muscle IgG, an IgG level of 1,461 mg/dL, and negative liver biopsy, suggested that AIH is unlikely. In addition, antimitochondrial antibody, primary biliary cholangitis, hemochromatosis, Wilson disease, hepatitis B, and hepatitis C were all negative. Human herpes virus-8, Epstein-Barr virus, cytomegalovirus, and herpes simplex virus were negative for staining on pathology.

A needle biopsy of the right liver lobe revealed hepatocyte syncytial giant cell change and diffuse lymphocytic lobular hepatitis with mild-to-moderate portal inflammation, portal lymphoid aggregates, as well as portal and periportal fibrosis indicating F3-stage fibrosis (Figure 1). Bile ducts were present and intact. Giant cells were observed to have up to 25 nuclei. The histopathology was consistent with postinfantile giant cell hepatitis.

After the diagnosis of PIGCH secondary to RA, the patient was referred to a hepatologist and rheumatologist for further management. The patient was placed on ursodeoxycholic acid 500 mg twice daily, daily azathioprine 125 mg, and prednisone 5 mg. The patient was told that she will be on azathioprine lifelong and prednisone will most likely be tapered off as clinically determined by her treating physician.

The course improved on 1-year follow-up. The patient continues to follow up with her rheumatologist for the management of RA. No secondary biopsy has been performed to confirm progression or resolution of giant cells.

DISCUSSION

We highlight a case of PIGCH secondary to RA that has resulted thus far in a good outcome. The mechanism of hepatocyte giant cell transformation in PIGCH is still unclear. However, 2 prevailing theories are fusion of individual hepatocytes forming a giant cell and nuclear proliferation with failure of the cytoplasm to divide with each division.[4,6–8] A case report by Hayashi et al[8] highlighted the possibility that the mechanism of giant cell formation in PIGCH may likely be because of hepatocyte fusion. Immunohistochemical analysis implemented in the patient's workup demonstrated low proliferation potency of giant cells and fewer actively dividing hepatocytes. Despite the mechanism behind the transformation of hepatocytes into giant cells being elusive, a common theme seems to include a variety of etiologies that can cause insult and induce giant cell formation.[4–7,9]

Matta et al identified 50 patients with an established diagnosis of giant cell hepatitis at the University of Pittsburgh. Of these patients, AIH was the most common underlying factor, accounting for 32% of cases.[1] The pathogenesis relating to autoimmune disorders remains relatively unknown. PIGCH secondary to underlying autoimmune disorders presents with variable and nonspecific clinical presentations.

Although we were unable to find reported cases of PIGCH associated with RA in our literature review, there were

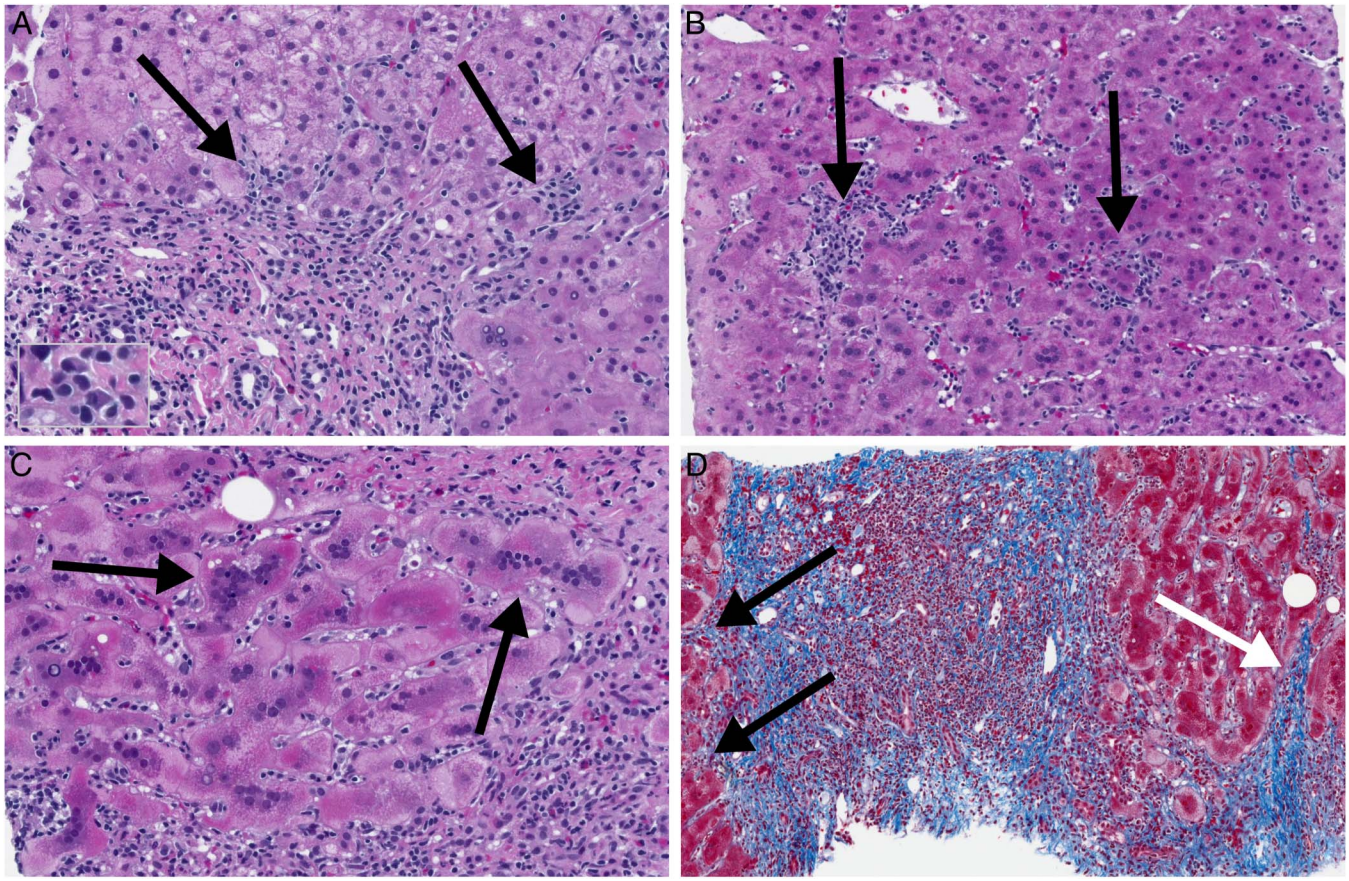

Figure 1. Right liver lobe needle core biopsy with chronic hepatitis, giant cell change, and marked fibrosis: (A) Marked portal inflammation with interface activity (black arrows) and rare plasma cells (inset on the lower left) (H&E, ×11). The inset photograph is of high magnification. (B) Multiple foci inflammation (black arrows) in lobules consistent with lobular hepatitis (H&E, ×7). (C) Numerous markedly enlarged periportal hepatocytes (black arrows) with abundant pink and pale pink cytoplasms with numerous nuclei (ranging up to approximately 25 nuclei) consistent with giant cell change (H&E, ×9). (D) Portal tract shows marked fibrosis with periportal fibrosis (black arrows) and bridging fibrosis (white arrow) (Masson trichrome, ×4). H&E, hematoxylin and eosin.

similar cases of untreated or poorly managed autoimmune etiologies, including AIH, ulcerative colitis, and systemic lupus erythematosus, leading to hepatocyte giant cell transformation.[7,10–12] Of the various autoimmune etiologies, AIH seems to be the most associated underlying factor and often confers a poor prognosis, which included liver failure and death.[1,7]

PIGCH can demonstrate a variety of clinical presentations and can be caused by various underlying etiologies. Treatment targeted toward the identified underlying condition may improve symptoms, leading to improved outcomes. PIGCH should be considered on the differential diagnosis if no obvious source for elevated liver enzymes is apparent and there is a co-occurring autoimmune disease presence because prompt or early recognition and treatment can prevent cirrhosis of the liver.

DISCLOSURES

Author contributions: All coauthors have seen and agree with the contents of the manuscript. We certify that the submission is an original work and is not under review at any other publication. ML Martinez-Moad is the article guarantor.

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