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CASE REPORT

Asymptomatic giant cell hepatitis: a subtype of post-infantile giant cell hepatitis?

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Abstract
Giant cell hepatitis in adults is considered a rapidly progressive and life-threatening disease, but there are few descriptions of a prolonged disease course. A 36-year-old Japanese man was referred to our hospital for further evaluation of abnormal liver function test results. Although asymptomatic, he had undergone follow-up for 9 years with these abnormalities. Because the cause of liver injury was not identified despite extensive noninvasive examinations, the patient underwent needle biopsy. He was finally diagnosed with post-infantile giant cell hepatitis (PIGCH) based on the presence of small numbers of giant multinucleated hepatocytes scattered primarily around the portal area. Necroinflammatory changes were very mild in the portal tracts and hepatic parenchyma. According to the histological findings as well as the accepted international diagnostic scoring system for autoimmune hepatitis (AIH), which is closely related to PIGCH, AIH was unlikely, although antinuclear antibody was positive at a titer of 1:160. The present case may describe an unknown subtype of PIGCH, characterized by insidious disease onset and progression with concurrent, mildly active underlying hepatitis, which is in contrast with the well-documented aggressive nature of PIGCH.

Keywords Asymptomatic post-infantile giant cell hepatitis · Giant multinucleated cell · Insidious development · Autoimmune hepatitis · Chronic hepatitis of unknown etiology

Introduction

Giant cell hepatitis is a descriptive disease entity [1–4], histologically denoted by the presence of giant multinucleated cells (GMCs) [5–7], with a wide range of etiologies [8, 9] or clinical presentations and background histology [1, 9–14]. Giant cell hepatitis is commonly found in association with neonatal or infantile liver diseases; however, it is rare in adults [1–3, 5–12, 15–25]. Since the behavior of hepatocytes differs between adults and infants with respect to maturity of metabolic enzyme systems [10], cytoskeleton [8], and regenerative activity [1, 8, 20], and since the spectrum of background liver diseases is different, giant cell hepatitis in adults is considered a separate disease entity, which is termed post-infantile giant cell hepatitis (PIGCH), or syncytial giant cell hepatitis [1, 5, 6, 8, 10, 16, 21, 23]. PIGCH usually manifests with acute hepatitis, acute deterioration of chronic hepatitis, or uncompensated cirrhosis, any of which may potentially progress to life-threatening liver failure [10, 11, 18]. Indeed, some researchers speculate that GMC may reflect rapid cell turnover subsequent to significant hepatocellular death, reflecting the aggressive nature of PIGCH [12, 15, 22].

We describe an unusual PIGCH case with a 9-year history of asymptomatically elevated transaminase levels, in contrast with the well-described aggressive nature of PIGCH. A possible subtype of insidiously progressive PIGCH, about which no information is available to date, is also discussed.

Case report

A 36-year-old Japanese businessman was referred to our hospital to undergo closer examination for persistent abnormal liver function tests. An alanine aminotransferase (ALT) level of 39 IU/L was first documented at the age of

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27. While abnormal liver function tests were followed up in an annual medical checkup at his workplace, the levels of ALT and aspartate aminotransferase (AST) gradually increased without symptoms (Fig. 1). At presentation, the patient did not report any symptoms. His past medical history was unremarkable except for appendectomy at the age of 20. He was neither a smoker nor an alcohol consumer. He denied using any drugs, herbal medicines, or supplements. Physical examination was unremarkable. Blood biochemistry showed the following (normal ranges in parentheses): AST 74 IU/L (13–33) and ALT 185 IU/L (8–42); however, levels of alkaline phosphatase, gamma-glutamyl transpeptidase, and total bilirubin were all in normal range. Viral markers including immunoglobulin (Ig) M-hepatitis A virus antibody, IgM-hepatitis B virus (HBV) core antibody, hepatitis C virus (HCV) antibody, and IgA-hepatitis E virus antibody were negative. Tests for HBV DNA and HCV RNA by polymerase chain reaction were negative. Positive antibody to Epstein–Barr virus (EBV) nuclear antigen (1:320), negative IgM-EBV viral capsid antigen (VCA) antibody, and IgG-EBV early antigen-diffuse and restricted complex (EA-DR) antibody suggested past EBV infection. Similarly, negative IgM-cytomegalovirus (CMV) antibody but positive IgG-CMV antibody suggested past CMV infection. Antibodies to paramyxoviruses including parainfluenza virus type 1–3, respiratory syncytial virus, measles virus, and mumps virus, which are suspected as one of the causes of giant cell hepatitis [13], were negative or weakly positive. Inflammatory reactions were normal as follows: C reactive protein 0.04 mg/dl, erythrocyte sedimentation rate 2.4 mm/h. Markers for autoimmune disease tested positive for antinuclear antibody (ANA) at a titer of 1:160, but rheumatoid factor, anti-DNA antibody, anti-smooth muscle antibody, anti-M2 mitochondrial antibody, and anti-kidney liver microsome-1 antibody tests were negative. Levels of gamma globulin, immunoglobulin, and complement proteins were normal: gamma globulin, 1.2 g/dL; IgG, 1488 mg/dL; IgM, 126 mg/dL; IgA, 309 mg/dL; C3, 97 mg/dL; C4, 22.0 mg/dL; and CH50, 30 U/mL. Thyroid function test results and test results for glucose, lipid, iron, and copper were normal. Ultrasonography revealed no significant morphological abnormalities including steatosis, but shear wave elastography suggested mild hepatic fibrosis as shown by shear wave velocity (V_s) of 1.71 m/s. Liver scintigraphy with technetium-99m galactosyl human serum albumin also suggested mild liver dysfunction, with a clearance index of 0.568 (normal 0.50–0.57, mild dysfunction 0.55–0.71) and receptor index of 0.939 (normal 0.93–0.96, mild dysfunction 0.87–0.95) [26]. These non-invasive examinations suggested of mild liver dysfunction with fibrous changes, but the cause could not be determined. A needle biopsy was then performed.

Histological examination showed scattered giant hepatocytes with 3–5 nuclei in the periportal hepatic parenchyma (Fig. 2). Mild sclerotic portal fibrosis, very mild portal inflammation, spotty necrosis, perivenular fibrosis, and minimal centrilobular microvesicular fatty changes were also observed (Fig. 2). Interface hepatitis; prominent plasma cell infiltration; rosette formation; and emperipolesis, representative of AIH [16, 27], were not seen. A diagnosis of PIGCH was finally established based on these histological findings.

Autoimmune hepatitis (AIH), which accounts for approximately 40% of concomitant autoimmune disease associated with PIGCH [9, 23], was unlikely, because the overall score using the accepted international diagnostic scoring system for AIH [27] was 6 points. Further, hepatitis activity was mild on histological examination, so treatment with 600 mg/day of ursodeoxycholic acid (UDCA) was initiated for its cytoprotective effect on hepatocytes [28]. However, UDCA did not ameliorate the abnormal transaminase values and UDCA treatment was discontinued 4 months later (Fig. 1). The patient is being carefully monitored without any medication, including immunosuppressive therapy.

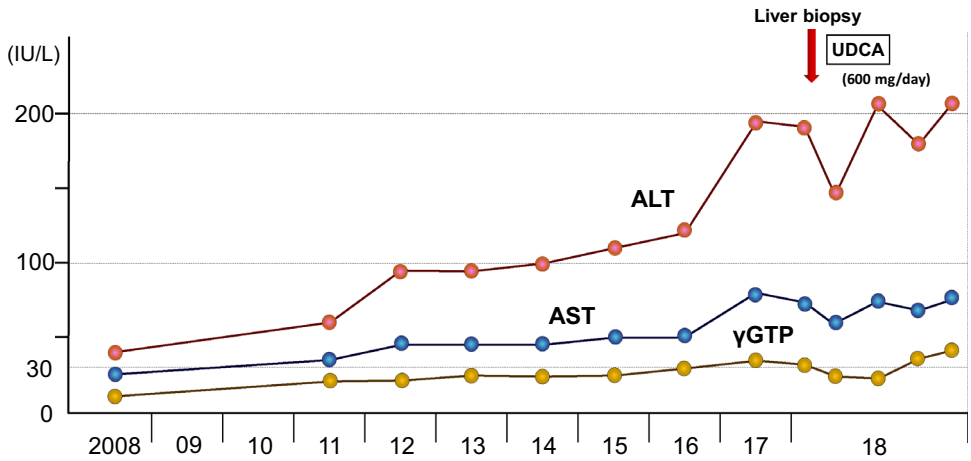

Fig. 1 Transition of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transpeptidase (γGTP). Transferases had asymptomatically but consistently increased with ALT dominance since the age of 27

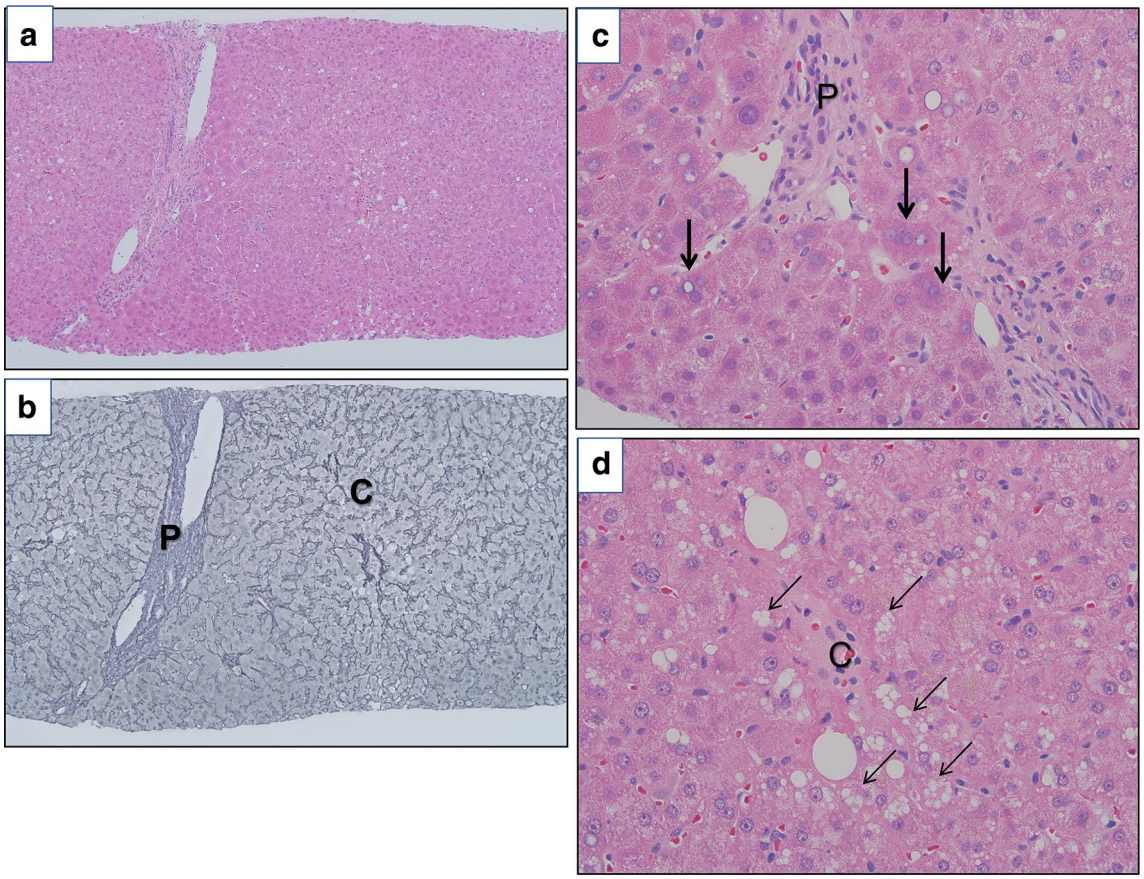

Fig. 2 **a, b** Lobular architecture is slightly distorted and mild sclerotic portal fibrosis, very mild portal inflammation, spotty necrosis, and perivenular fibrosis are seen. Original magnification (×40). *P* portal tract, *c* central vein. **C** Giant hepatocytes with 3–5 nuclei are seen in the periportal hepatic parenchyma (arrows). Original magnification (×400). *P* portal tract. **d** Minimal microvesicular fatty change is seen in centrilobular area (arrows). Original magnification (×400). *C* central vein. **a, c, d** Hematoxylin and eosin (H&E) stain, **b** reticulin stain

Discussion

The most noticeable aspects in the present case were that GMCs coexisted with mildly active hepatitis and that the PIGCH had been traced asymptomatically for 9 years, probably from the time of insidious disease onset. As persistency for more than 1 year is extremely rare [12, 29, 30], little is known about chronic asymptomatic PIGCH. This is partially because PIGCH often manifests as severe hepatitis and progresses rapidly to a poor outcome [3, 8–10, 12, 13, 15, 18–20, 22–24, 29].

Giant multinucleated cells are commonly found in association with various neonatal or infantile liver diseases, such as biliary atresia, conjugated hyperbilirubinemia, metabolic liver disease, and viral or neonatal hepatitis [1, 3, 8, 11–13, 23]. In contrast, hepatitis with GMCs in adults is rare accounting for 0.1–0.25% of all liver diseases [2, 3, 8, 10, 20, 21, 23] and only approximately 100 cases have been documented in the English literature in the past several decades [7, 9, 16, 23].

Although the mechanism of development in adults has not been fully clarified [1, 3–6, 9, 11, 15, 17, 22, 25], GMC is best regarded as an idiosyncratic response of regenerative or degenerative hepatocytes to noxious stimuli [3–9, 11, 12, 17, 19, 22–25]. The most common causes of PIGCH are viral pathogens, drug toxicity, autoimmune disorders, and a combination of these factors [1–9, 11, 12, 15–25, 29]; however, various other causes include post-transplantation status [9, 17, 20], malignancy [7, 9, 23], metabolic disease [19], and others [8, 9]. However, as often occurs in many PIGCH patients [3, 4, 6, 11, 12, 16, 20, 24, 25], no etiology was identified in our case.

Two major hypotheses regarding GMC development include: (i) nuclear proliferation without cytoplasmic hepatocyte division [1–9, 11, 12, 15, 18–20, 22, 23, 30] and (ii) cytoplasmic fusion of several nonnuclear hepatocytes exposed to noxious stimuli [1–12, 15, 18–20, 22, 23, 30]. The former hypothesis is supported by rapid cell turnover, i.e., hyperproliferation of regenerative hepatocytes subsequent to major hepatocellular death [12, 15, 22], and reflects

the aggressive nature of PIGCH. In the latter mechanism involving hepatocyte fusion, the effect of cytokines produced by infiltrating inflammatory T cells, Kupffer cells, or full-blown syncytial hepatocytes [21], and membrane instability due to microtubular impairment caused by noxious stimuli, such as viral infection [10, 11, 13, 15], have been considered. Although the number of GMCs demonstrated in an initial liver biopsy do not appear to correlate with the outcome [11, 14], a decreasing number [11, 15, 18] or disappearance [4, 10] of GMCs after treatment suggests that GMC counts may reflect concurrent hepatitis activity.

Although it would be important to determine how long GMCs had been present, our patient at least demonstrated that GMCs asymptomatically coexist with mildly active hepatitis. Mild liver tissue damage despite 9 years of elevated transaminase levels with a relatively small number of GMCs suggest that the pathogenic stimulus is weak but persistent, and is probably different from that of PIGCH with an aggressive disease course [3, 8, 9, 12, 13, 15, 19, 20, 22–24, 29]. Furthermore, an insidious course may be more common than realized [20], because PIGCH may be diagnosed as chronic hepatitis of unknown cause, particularly when the number of GMCs is small.

Despite vigorous therapeutic attempts including orthotropic liver transplantation as the only established therapeutic option [15], the overall survival rate of PIGCH remains as low as 50% [3, 9, 11, 15, 17–19, 21, 23, 25, 29]. As approximately half of patients with PIGCH exhibit some autoimmune features such as positive ANA, anti-smooth muscle antibody, or anti-M2 mitochondrial antibody tests, or the presence of hypergammaglobulinemia and high levels of IgG, a close association between PIGCH and autoimmunity [2, 10, 16, 18] and the effectiveness of glucocorticoid therapy for PIGCH with autoimmune features, especially in cases of AIH, has been suggested [1–4, 6, 7, 9–12, 15, 16, 21–23, 25, 30]. Although our patient was positive for ANA, which occurs in 40% of PIGCH patients [6, 12], no other autoimmune features were evident. Furthermore, histology as well as clinical scoring suggested that AIH was unlikely. Based on the benign prior disease course and mild liver tissue damage, we speculate that the patient's prognosis may not be ominous, even without prompt initiation of immunosuppressive therapy [16]. However, long-term monitoring for PIGCH progression or acute exacerbation, or transformation to AIH is certainly necessary.

In summary, the present case may suggest a subtype of PIGCH characterized primarily by insidious disease onset and progression, with GMC development despite mild underlying active hepatitis. To define such a subtype in a heterogeneous disease entity of PIGCH, accumulation of similar cases, including pathological reevaluation of previous cases diagnosed as chronic hepatitis of unknown cause, is required.

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Compliance with ethical standards

Conflict of interest All authors (Takahiro Zenda, Ichiro Araki, and Motoko Sasaki) declare that they have no conflict of interest.

Human/animal rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from the patient for being reported in this journal.

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