Original Article

Post-infantile Giant Cell Hepatitis: A Literature Review and Meta-analysis

Jingjing Jiao and Xuchen Zhang*

Department of Pathology and Yale Cancer Center, Yale University School of Medicine, New Haven, CT, USA

Received: June 25, 2022 | Revised: August 5, 2022 | Accepted: August 10, 2022 | Published: August 31, 2022

Abstract

Post-infantile giant cell hepatitis (PIGCH) is a rare disease entity in adults with a multifactorial etiology and widely variable clinical courses and outcomes. The factors associated with the worse outcomes of this disease entity are still unclear. We identified 68 PIGCH patients by searching PubMed and performed meta-analysis. Among the 68 patients, 32% of the cases were associated with autoimmunity disorders, followed by 21% associated with viral infections, 10% with medication, and 7% with malignancy. Twenty-four percent of the patients had more than one etiological factor, and 6% had other uncommon etiologies or an etiology that could not be identified. At the time of this report, 17 patients had died of the disease (poor outcome), and 51 patients remained alive with the disease (good outcome). Compared to the patients with a good outcome, the patients with a poor outcome were characterized by older age, lower levels of platelets and albumin, higher levels of total bilirubin, and a diffuse distribution pattern of giant cells in the liver. There were no differences in gender distribution, aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, etiological distribution, or other histological features, including interface hepatitis, necrosis, lobular inflammation, portal inflammation, cholestasis, or fibrosis. Further studies would be needed to better understand the disease mechanisms and unmask any additional etiological factors and targeted therapies.

Citation of this article: Jiao J, Zhang X. Post-infantile Giant Cell Hepatitis: A Literature Review and Meta-analysis. J Clin Transl Pathol 2022;2(3):100-107. doi: 10.14218/JCTP.2022.00016.

Introduction

Neonatal giant cell hepatitis is a common cause of cholestasis in infants. It is characterized histologically by the formation of syncytial hepatic giant cells (hepatocytes with abundant cytoplasm and more than three nuclei) and hepatitis (lobular disarray, lobular inflammation, Kupffer cell hypertrophy, and hepatocyte spotty necrosis). Etiologies related to neonatal giant cell hepatitis include hypopituitarism, biliary atresia, Alagille syndrome, bile salt defects, and severe hemolytic disease of the newborn. However, a significant number of neonatal giant cell hepatitis remains idiopathic. When the disease entity occurs in adults, it is an extremely rare condition known as post-infantile giant cell hepatitis (PIGCH), or syncytial giant cell hepatitis. Due to the differences in the hepatocyte maturity of the metabolic enzyme systems, regenerative activity, and the spectrum of background liver diseases, giant cell hepatitis in adults is considered a separate disease entity. The clinical course of PIGCH is widely variable ranging from minimal symptoms without major clinical implications to cirrhosis or to liver failure that is often fatal despite standard clinical care. Here we identified 68 cases in the literature and tried to characterize the clinical, laboratory, and histological features by meta-analysis to identify the factors associated with a poor outcome.

Materials and methods

Case identification and selection

We conducted a comprehensive literature search in PubMed in January 2022, using the terms “giant cell hepatitis”, “giant cell change” AND “liver”, and “giant cell transformation” AND “liver”. Only original articles were retrieved and reviewed. A case was selected and included in this study if: (1) the patient’s age at the disease onset was older than or equal to 18 years, (2) the article had information of clinical, laboratory, histology, and disease outcomes, and (3) the article was published in a peer-reviewed journal in English. The excluded criteria included: (1) Important information was missing, (2) no full text was available, and (3) irrelevant articles.

Data extraction

The following data were extracted from the original articles or pathological descriptions, if available: title, journal information, country/region of the corresponding author, age, gender, clinical symptoms and signs, laboratory results, histology, outcome, and length of the follow-up. All of the case entries were assessed by author JJ. The study flow diagram is shown in Figure 1. The meta-analysis was in compliance with the PRISMA guidelines, and a total of 68 patients qualified and were included in this series.
### Statistical analysis

Demographic and clinical parameters were compared between the deceased and living patients at the time of the report using two-tailed student’s t-tests for continuous variables, and Fisher exact or chi-squared tests for the categorical variables as indicated. A *p*-value less than 0.05 was considered statistically significant.

### Results

#### Clinical, laboratory and histological features

Among the 68 patients, the distribution of the patients’ age ranged from 18 to 79 years with a median of 41.5 years. The ratio of male to female was 1.3:1 (male 57.4%; female 42.6%). Of the cases, 44.1% were from Europe, 33.8% were from America, and 22.1% were from Asia. The leading symptoms/signs were jaundice (*n* = 44), followed by fatigue (*n* = 29), hepatomegaly (*n* = 22), abdominal pain/tenderness (*n* = 14), and splenomegaly (*n* = 14).

All the patients with liver functional test data had elevated aminotransferase. The median levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were 500 U/L and 466.5 U/L with a range of 40–5,350 U/L and 39–5,609 U/L, respectively. 91.1% of the patients had elevated total bilirubin with a median value of 10.6 mg/dL (range: 0.7–42 mg/dL). The median level of albumin was 3.0 g/dL (range: 2.2–4.1 g/dL). The percentage of patients with positive antinuclear antibodies, anti-smooth muscle antibodies, and anti-mitochondrial antibodies was 60%, 38.6%, and 20.5%, respectively.

The distribution pattern of the multinoucleated giant cells in the liver was specified in 27 PIGCH patients with eight cases predominantly at Zone 1, one at Zone 2, eight at Zone 3, eight with a diffuse distribution pattern, one at both Zones 2 and 3, and one case with a “no preference” pattern. Those giant cells could contain up to 30 nuclei with an abundant and eosinophilic cytoplasm, which could contain eosinophilic granules, Mallory-Denk bodies, brown granules, and/or bile pigment (Figs. 2a, b).

Acidophilic degeneration and giant cell necrosis were sometimes observed with the neutrophilic reaction as well. Among the 51 cases with information of fibrosis in the liver histology, seven had no fibrosis and 44 had a different degree of fibrosis, among which 11 reached cirrhosis. Portal inflammation and lobular inflammation were mentioned in 34 and 19 cases, respectively. Thirty-seven cases had a variable amount of necrosis. Interface hepatitis was present in 21 cases, and 24 cases had histological features of cholestasis. Ductular reaction (*n* = 8), ballooning (*n* = 7), steatosis (*n* = 5), Councilman (acidophilic) body (*n* = 4), Mallory-Denk body (*n* = 3), and Kupffer cell hyperplasia (*n* = 3) were features infrequently encountered.

#### Distribution of the etiology

With regard to the etiological factors, 32% of the cases were associated with autoimmune disorders, 21% were associated with viral infections, 10% were associated with medication...
Jiao J. et al: Post-infantile giant cell hepatitis

In addition to medications, such as clometacin, diclofenac, doxycycline, amoxicillin/clavulanate, dehydrocholic acid, and testosterone analogue, herbal remedies and dietary supplements were also reported to have an association with PIGCH. The most commonly associated malignancy with PIGCH appeared to be chronic lymphocyte leukemia (CLL). In addition, other malignancies seen in patients with PIGCH included Hodgkin’s lymphoma, papillary thyroid carcinoma, anaplastic carcinoma, and primary myelofibrosis.

Some patients had more than one etiology, including autoimmune disorder and a viral infection, autoimmune disorder and medication, CLL with autoimmune hemolytic anemia, and CLL with a viral infection. Singh et al. reported a case of PIGCH developed in a patient with autoimmune hepatitis in the setting of acute bacterial infection and recent use of hepatotoxic medications amoxicillin/clavulanate. Another case of PIGCH developed in a patient with myelofibrosis and severe autoimmune hepatitis, which was probably triggered by diclofenac administration.

Other rare conditions, which had been seen concomitantly with PIGCH, included Rosai-Dorfman disease, necrobiotic...
Clinical, laboratory, and histological features associated with the worse outcome

Seventeen patients had already passed away at the time of the report, 13 of these died of the deterioration of liver disease, while four died of non-liver related etiology (e.g., complications in CLL, or brain hemorrhage). Some patients had stable disease most of the improvements were based on clinical and/or biochemical improvements. The reduction or elimination of giant cells, decrease inflammation, or even regression of fibrosis was documented to a less extent.

We compared the clinical, laboratory, and histological features of the PIGCH patients with a good (living) outcome. Patients with a poor outcome had a significantly lower platelet count (median value: 126 × 10^9/L vs 207 × 10^9/L; \( p = 0.04 \)) lower albumin concentration (median value: 2.7 g/dL vs 3.1 g/dL; \( p = 0.012 \)), higher total bilirubin levels (median value: 18.0 mg/dL vs 8.4 mg/dL; \( p = 0.022 \)) and were more likely to have a diffuse distribution pattern of giant cells (80% vs 18.2%; \( p = 0.017 \)) than those of patients with a good outcome. There was also a trend of older age (median value: 60 vs 39 years; \( p = 0.067 \)) and lower total protein level (5.5 g/dL vs 6.8 g/dL; \( p = 0.056 \)) without reaching statistical significance. There were no differ-ences in gender distribution, other liver function tests (aminotransferase, alkaline phosphatase, and gamma-gluta-family) etiological distribution, or other histological features (interface hepatitis, necrosis, lobular inflammation, portal inflammation, cholestasis, or fibrosis) between the two groups. The detailed comparison is summarized in Table 1.

Discussion

PIGCH is a very rare disease entity in adults with an estimated incidence ranging from 0.1% to 0.25% and a multifactorial etiology. Consistent with previous reports, autoimmune conditions, especially autoimmune liver diseases, remained the most common etiology. Many viruses, such as HCV, HIV, HHV-6, CMV, EBV, HSV, and paramyxoviridae-like viruses, were associated with the worse outcome. Patients with a poor outcome had a significantly lower platelet count (median value: 126 × 10^9/L vs 207 × 10^9/L; \( p = 0.04 \)) lower albumin concentration (median value: 2.7 g/dL vs 3.1 g/dL; \( p = 0.012 \)), higher total bilirubin levels (median value: 18.0 mg/dL vs 8.4 mg/dL; \( p = 0.022 \)) and were more likely to have a diffuse distribution pattern of giant cells (80% vs 18.2%; \( p = 0.017 \)) than those of patients with a good outcome. There was also a trend of older age (median value: 60 vs 39 years; \( p = 0.067 \)) and lower total protein level (5.5 g/dL vs 6.8 g/dL; \( p = 0.056 \)) without reaching statistical significance. There were no differences in gender distribution, other liver function tests (aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase), etiological distribution, or other histological features (interface hepatitis, necrosis, lobular inflammation, portal inflammation, cholestasis, or fibrosis) between the two groups. The detailed comparison is summarized in Table 1.

According to clinical and/ or biochemical improvements. The reduction or elimination of giant cells, decreased inflammation, or even regression of fibrosis was documented to a less extent.

We compared the clinical, laboratory, and histological features of the PIGCH patients with a good (living) outcome. Patients with a poor outcome had a significantly lower platelet count (median value: 126 × 10^9/L vs 207 × 10^9/L; \( p = 0.04 \)) lower albumin concentration (median value: 2.7 g/dL vs 3.1 g/dL; \( p = 0.012 \)), higher total bilirubin levels (median value: 18.0 mg/dL vs 8.4 mg/dL; \( p = 0.022 \)) and were more likely to have a diffuse distribution pattern of giant cells (80% vs 18.2%; \( p = 0.017 \)) than those of patients with a good outcome. There was also a trend of older age (median value: 60 vs 39 years; \( p = 0.067 \)) and lower total protein level (5.5 g/dL vs 6.8 g/dL; \( p = 0.056 \)) without reaching statistical significance. There were no differences in gender distribution, other liver function tests (aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase), etiological distribution, or other histological features (interface hepatitis, necrosis, lobular inflammation, portal inflammation, cholestasis, or fibrosis) between the two groups. The detailed comparison is summarized in Table 1.

Discussion

PIGCH is a very rare disease entity in adults with an estimated incidence ranging from 0.1% to 0.25% and a multifactorial etiology. Consistent with previous reports, autoimmune conditions, especially autoimmune liver diseases, remained the most common etiology. Many viruses, such as HCV, HIV, HHV-6, CMV, EBV, HSV, and paramyxoviridae-like viruses, were associated with the worse outcome. Patients with a poor outcome had a significantly lower platelet count (median value: 126 × 10^9/L vs 207 × 10^9/L; \( p = 0.04 \)) lower albumin concentration (median value: 2.7 g/dL vs 3.1 g/dL; \( p = 0.012 \)), higher total bilirubin levels (median value: 18.0 mg/dL vs 8.4 mg/dL; \( p = 0.022 \)) and were more likely to have a diffuse distribution pattern of giant cells (80% vs 18.2%; \( p = 0.017 \)) than those of patients with a good outcome. There was also a trend of older age (median value: 60 vs 39 years; \( p = 0.067 \)) and lower total protein level (5.5 g/dL vs 6.8 g/dL; \( p = 0.056 \)) without reaching statistical significance. There were no differences in gender distribution, other liver function tests (aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase), etiological distribution, or other histological features (interface hepatitis, necrosis, lobular inflammation, portal inflammation, cholestasis, or fibrosis) between the two groups. The detailed comparison is summarized in Table 1.

Discussion

PIGCH is a very rare disease entity in adults with an estimated incidence ranging from 0.1% to 0.25% and a multifactorial etiology. Consistent with previous reports, autoimmune conditions, especially autoimmune liver diseases, remained the most common etiology. Many viruses, such as HCV, HIV, HHV-6, CMV, EBV, HSV, and paramyxoviridae-like viruses, were associated with the worse outcome. Patients with a poor outcome had a significantly lower platelet count (median value: 126 × 10^9/L vs 207 × 10^9/L; \( p = 0.04 \)) lower albumin concentration (median value: 2.7 g/dL vs 3.1 g/dL; \( p = 0.012 \)), higher total bilirubin levels (median value: 18.0 mg/dL vs 8.4 mg/dL; \( p = 0.022 \)) and were more likely to have a diffuse distribution pattern of giant cells (80% vs 18.2%; \( p = 0.017 \)) than those of patients with a good outcome. There was also a trend of older age (median value: 60 vs 39 years; \( p = 0.067 \)) and lower total protein level (5.5 g/dL vs 6.8 g/dL; \( p = 0.056 \)) without reaching statistical significance. There were no differences in gender distribution, other liver function tests (aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase), etiological distribution, or other histological features (interface hepatitis, necrosis, lobular inflammation, portal inflammation, cholestasis, or fibrosis) between the two groups. The detailed comparison is summarized in Table 1.
Jiao J. et al: Post-infantile giant cell hepatitis

|                  | Deceased (n = 17) | Living (n = 51) | p      |
|------------------|-------------------|----------------|--------|
| Age (n = 68)     | 60.0 (25–76)      | 39.0 (18–79)   | 0.067  |
| Gender (n = 68)  |                   |                |        |
| male             | 9 (52.9%)         | 30 (58.8%)     | 0.779  |
| female           | 8 (47.1%)         | 21 (41.2%)     |        |
| Region (n = 68)  |                   |                | 0.568  |
| America          | 4 (23.5%)         | 19 (37.3%)     |        |
| Europe           | 9 (52.9%)         | 21 (41.2%)     |        |
| Asia             | 4 (23.5%)         | 11 (21.6%)     |        |
| Hg (g/dL) (n = 17) | 11.1 (4.8–12)    | 11.8 (8.4–14)  | 0.209  |
| WBC (x10^9/L) (n = 20) | 9.8 (2.4–35) | 12.8 (2.61–237.8) | 0.135 |
| IgG (g/L) (n = 30) | 26.9 (17.6–38.76)| 23.2 (4.93–47.1) | 0.543  |
| Elevated IgG     | 7 (100.0%)        | 16 (69.6%)     | 0.154  |
| AST (U/L) (n = 61) | 406.0 (56–2,385) | 529.0 (40–5,350) | 0.551  |
| ALT (U/L) (n = 66) | 216.0 (39–5,609) | 469.0 (55–4,670) | 0.934  |
| ALP (U/L) (n = 49) | 266.0 (47–727)  | 231.0 (57–828) | 0.795  |
| GGT (U/L) (n = 29) | 159.5 (10–320)   | 190.0 (22–1,500) | 0.218  |
| TB (mg/dl) (n = 56) | 18.0 (1–42)      | 8.4 (0.7–33.6) | 0.022  |
| Elevated TB      | 14 (93.3%)        | 37 (90.2%)     | >0.9999|
| DB (mg/dl) (n = 26) | 13.5 (1.92–34.4)| 9.0 (2–21.4)  | 0.430  |
| Elevated DB      | 11 (100.0%)       | 15 (100.0%)    | >0.9999|
| INR (n = 19)     | 1.6 (1.1–2.32)    | 1.5 (0.9–6.2)  | 0.668  |
| Albumin (g/dL) (n = 25) | 2.7 (2.2–3.3) | 3.1 (2.4–4.1) | 0.012  |
| Total protein (g/dL) (n = 16) | 5.6 (4.5–7)   | 6.8 (5.4–10)  | 0.056  |
| Positive ANA (n = 55) | 8/14 (57.1%)     | 25/41 (61.0%) | 0.758  |
| Positive SMA (n = 44) | 5/10 (50.0%)    | 12/34 (35.3%) | 0.473  |
| Positive AMA (n = 39) | 2/11 (18.2%)    | 6/28 (21.4%)  | >0.9999|
| Etiology (n = 68) |                   |                | 0.923  |
| Autoimmune       | 5 (29.4%)         | 17 (33.3%)     |        |
| Viral            | 5 (29.4%)         | 9 (17.6%)      |        |
| Medication       | 1 (5.9%)          | 6 (11.8%)      |        |
| Malignancy       | 1 (5.9%)          | 4 (7.8%)       |        |
| Combined etiologies | 4 (23.5%)   | 12 (23.5%)     |        |
| Others           | 1 (5.9%)          | 3 (5.9%)       |        |
| Histology        |                   |                |        |
| Interface hepatitis (n = 24) | 6/6 (100.0%) | 15/18 (83.3%) | 0.546  |
| Necrosis (n = 39) | 11/11 (100.0%)   | 26/28 (92.9%) | >0.9999|
| Lobular inflammation(n = 20) | 5/5 (100.0%) | 14/15 (93.3%) | >0.9999|
| Portal inflammation (n = 34) | 10/10 (100.0%) | 24/24 (100.0%) | >0.9999|
| Cholestasis (n = 27) | 10/11 (90.9%)   | 14/16 (87.5%) | >0.9999|
| Steatosis (n = 9) | 2/3 (66.7%)      | 3/6 (50.0%)    | >0.9999|
| Fibrosis (n = 51) | 13/15 (86.7%)    | 31/36 (86.1%)  | >0.9999|
| Cirrhosis (n = 51) | 4/15 (26.7%)    | 7/36 (19.4%)   | 0.711  |
| Distribution of giant cells (n = 27) | 4/5 (80.0%) | 4/22 (18.2%) | 0.017  |

The data are presented as a median (range) or number (%). Hg, hemoglobin; WBC, white blood cells; Pt, platelet; IgG, immunoglobulin G; AST, aspartate aminotransferase; ALP, alkaline phosphatase; TB, total bilirubin; DB: direct bilirubin; INR, international normalized ratio; ANA, antinuclear antibodies; SMA, smooth muscle antibody; AMA, antimitochondrial antibody.
combination of immunosuppression (e.g., corticosteroids, cyclophosphamide, and azathioprine) and CLL directed therapy (anti-CD20 antibody, chemotherapy and/or ibrutinib). For patients with rapid progression and a fatal process, liver transplantation is the last resort.

Our analysis was the first to comprehensively characterize the clinical, laboratory, and histological features associated with the outcome of PIGCH. In contrast to previous studies indicating that the prognosis of PIGCH was dictated by the underlying etiology, we did not find any differences between the etiological composition between the patients with a poor or good outcome. Instead, the patients with a poor outcome were characterized by older age, lower levels of platelets and albumin, higher level of total bilirubin, and diffuse distribution pattern of giant cells in the liver. Nevertheless, there are still unanswered questions about PIGCH. One enigmatic issue is the recurrence after liver transplantation. In cases of rapid progression to liver failure, liver transplantation was used as a rescue treatment. However, the transplant was still burdened by the risk of the recurrence of disease. The recurrence of giant cell hepatitis after one or two liver transplantsations were documented. In some patients, no etiology could be identified. Interestingly, Shah et al. reported a patient receiving a liver transplantation for giant cell hepatitis at the age of 10 months. Following the transplantation, the patient did well on a maintenance regimen of prednisone, azathioprine, and cyclosporine until aged 18 years when the patient developed recurrent giant cell hepatitis that was then successfully treated with ribavirin. It was hypothesized that the recurrence of the disease after transplantation was due to a viral etiology located in the extrahepatic sites. Ribavirin has since demonstrated to be successful in treating recurrent diseases leading to normalization of the liver enzyme, reduced inflammation and number of giant cells, and even normalized liver histology in some cases. Nonetheless, this regimen was not always successful. Next-generation sequencing (NGS) based metagenomics has been successfully used to detect novel and rare infections and may open a new chapter in identifying viral etiologies associated with PIGCH.

The limitations of our meta-analysis included the quality of the case report and possible publication bias. For example, the detailed histological description was not always provided in the case reports. The distribution pattern of giant cells was mentioned in only 27 patients. Moreover, only 36 patients had follow-up data. Regarding publication bias, the cases of PIGCH without a clear etiology identified might be underreported due to the fact that cases without a clear etiology might not have been reported in the publication. Thus, caution should be used when interpreting and applying the related findings.

Conclusions

PIGCH is a rare, heterogenous disease entity with a variable clinical course and prognosis. Poor outcome was associated with old age, low levels of platelets and albumin, high level of total bilirubin, and diffuse distribution pattern of giant cells in the liver. Further studies would be needed to better understand the disease mechanisms and unmask any additional etiological factors and targeted therapies.

Acknowledgments

The authors thank Hannah Wang for the language editing and proofreading of this article.
Aikat BK, Bhattacharya T, Datta D. Giant cell hepatitis with cytomegalovirus inclusion in an adult. A case report. J Assoc Physicians India 2017;65(3):246-248.

Apostolou A, Dejaco-Chambers J, Delledattes JK, Marinos E, Kapranos N, et al. A fatal case of postinfantile giant cell hepatitis in a patient with chronic lymphocytic leukemia. J Clin Exp Hematol 2013;5(1):551-555. doi:10.1016/j.jceh.2013.04.026.33459.7c, PMID:12709215.

Aroztegui N, Boyle E, Haley M, Reddy A, Forouhar F, Clement J. CLL associated giant cell hepatitis. Leuk Res Rev 2019;82:43-45. doi:10.1016/j.lrr.2019.05.011. PMID:31760611.

Bottini M, Guo L, Brant R, Hickman S, Perrillo RR, et al. The role of hepatitis C virus and hepatitis B virus in induced giant cell hepatitis. Liver Int 2011;31(2):237-244. doi:10.1111/j.1478-3231.2010.02328.x, PMID:20978258.

Bharti C, Rastogi A, Srin S. Postinfantile giant cell hepatitis: an etiological and prognostic perspective. Hepat Res Treat 2013;2013:612090. doi:10.1155/2013/612090. PMID:23555054.

Hammarci O, Oral KJ, Ergen O, Gur B, Solmucuer S, Bayraktar Y. Postinfantile giant cell hepatitis due to hepatitis E virus along with the presence of autoantibodies. Dig Dis Sci 2017;62(12):3521-3523. doi:10.1007/s10620-016-4266-x, PMID:27144055.

Vu CH, Ho CM, Tsai JH, Sun HY, Hu RH, Lee PH. First Case Genotype 4 Hepatitis E Infection After a Laparoscopic Liver Resection. J Clin Liver Dis 2017;15(2):229-230. doi:10.6021/5152017.2017.622171.

Pessaye D, Degos F, Feldmann G, Degot C, Benua JM, Berhamou JP. Chronic active hepatitis and giant cells in adults treated with glucocorticoids. J Hepatol 2011;55(3):577-583. doi:10.1016/j.jhep.2011.02.027, PMID:21470349.

Tan YW, Wang JM, Chen L. Is simultaneous presence of IgG4-positive plasmacytoma cells and giant-cell hepatitis a coincidence in autoimmune hepatitis? A case report. World J Clin Cases 2021;9(25):7527-7534. doi:10.12998/wjcc.v9.i25.7527, PMID:34575674.

Umedama T, Zeng Y, Hamano H, Ichijo T, Sawa K, Nakamura Y, et al. Giant cell hepatitis: a differential diagnosis for classical autoimmune hepatitis. Gastroenterology 2007;132(1):1471-1472. doi:10.1053/j.gastro.2006.07.013, PMID:16944469.

Nguyen TD, Stanek S, Rossi S. S2463 Giant Cell Hepatitis and Autoimmune Hepatitis in a Patient With HIV. American Journal of Gastroenterology 2011;106:1495-1496. doi:10.1038/ajg.2011.140, PMID:21440946.

Roy J, Jain R, Schreiber M. S2503 A Towering Case of Giant Cell Hepatitis. American Journal of Gastroenterology 2011;106:3132-3132. doi:10.1038/ajg.2011.98, PMID:21982286.

Ahmed K, Zucker SD. Giant cell hepatitis in a teenage woman. Clin Gastroenterol Hepatol 2008;6(5):A26-A26.e21. doi:10.1016/j.cgh.2007.10.025, PMID:18346669.

Stoffel MP, Steffen HM, Dries V, Dienes HP, Baldamus CA. Acute exacerbation of overlapping autoimmune liver disease with development of giant cell hepatitis after 14 years' disease duration. J Intern Med 1998;244(4):355-360. doi:10.1046/j.1365-2796.1998.01268.x, PMID:979500.

Acharya S, Mahapatra RS. Giant cell hepatitis associated with systemic lupus erythematosus. J Clin Pathol 1996;49(2):183-184. doi:10.1136/jcp.49.2.183, PMID:8778494.

Dohmen K, Ohtsuka S, Nakamura H, Arase K, Yokogawa Y, Asayama R, et al. Postinfantile giant cell hepatitis with Features of Acute Severe Autoimmune Hepatitis Probably Triggered by Picornavirus in a Patient with Connective Tissue Disease. Mediterr J Rheumatol 2019;30(4):224-230. doi:10.14155/17202915.

Gupta E, Yacoub M, Higgins M, Al-Katib AM. Syncytial giant cell hepatitis due to autoimmune hepatitis type II (LKM1+) presenting as right upper lobe living-related liver transplantation. J Clin Exp Hepatol 2011;1(2):136. doi:10.1016/j.jceh.2011.06.014.30973-0883(11)60144-8, PMID:25755336.

Bhati C, Rastogi A, Srin S. Postinfantile giant cell hepatitis: an etiological and prognostic perspective. Hepat Res Treat 2013;2013:612090. doi:10.1155/2013/612090. PMID:23555054.
Jiao J. et al: Post-infantile giant cell hepatitis

Pereosinophilia. Gastroenterology 1991;101(5):1417–1419. doi:10.1016/0016-5085(91)90096-4, PMID:1936812.

[68] Zenda T, Araki I, Sasaki M. Asymptomatic giant cell hepatitis: a subtype of post-infantile giant cell hepatitis. J Clin Gastroenterol 2009;12(4):367–371. doi:10.1097/MCG.0b013e32832b9b9f, PMID:2084190.

[69] Hussmans Y, Galant C, Nicholas ML, Lamy M, Geubel AP. Failure of ribavirin or immunosuppressive therapy to alter the course of post-infantile giant cell hepatitis. J Hepatol 1995;22(3):382. doi:10.1016/0168-8278(95)90298-3, PMID:7608496.

[70] Matta B, Cabello R, Rabonovitz M, Minervini M, Malik S. Post-infantile giant cell hepatitis: a single center’s experience over 25 years. World Journal of Hepatology 2019;11(12):7555–7560. doi:10.4254/wjh.v11.i12.7555.

[71] Leroy H, Han M, Woottum M, Bouchet J, Xie M, et al. Virus-Mediated Cell-Cell Fusion. Int J Mol Sci 2020;21(24):9644. doi:10.3390/ijms21249644, PMID:33348900.

[72] Randhawa PS, Jenkins FJ, Nalesnik MA, Williams PA, Ries A, et al. Herpesvirus 6 variant A infection after heart transplantation with giant cell transformation in bile ductular and gastroduodenal epithelium. Am J Surg Pathol 1997;21(7):847–853. doi:10.1097/00000478-199707000-00014, PMID:9236842.

[73] Yunis E, Agostini R. Syncytiat giant-cell hepatitis. N Engl J Med 1992;327(2):130–133. doi:10.1056/NEJM199207093270218, PMID:1603130.

[74] Koff RS. Acute and chronic giant cell hepatitis: a parvovirus infection? Gastroenterology 1991;110(3):863–864. doi:10.1016/0016-5085(91)90553-w, PMID:1860651.

[75] Spichinin HP, Gudat F, Schmidt M, Pirovino M, Altorfer J, Bianchi L. Microtubular aggregates in human chronic non-A, non-B hepatitis with bridging hepatocytic giant cells. Liver 1982;2(4):355–360. doi:10.1111/j.1600-0676.1982.tb00834.x, PMID:6820105.

[76] Yunis EJ, Agostini RM Jr, Gilew KH. Fine structural observations of the liver in alpha-1-antitrypsin deficiency. Am J Pathol 1976;82(2):265–286. PMID:56137.

[77] Simpson DG, Walker JH. Hypersensitivity to Para-Aminosalicylic Acid. American Journal of Medicine 1960;29(2):297–306. doi:10.1016/0002-9343(60)90026-7.

[78] Coe RO, Bull FE. Cirrhosis Associated with Methotrexate Treatment of Psoriasis. JAMA 1968;206(7):1515–1520. doi:10.1001/jama.206.7.1515, PMID:5695945.

[79] Milivanic SK, Maccarthy JD. Hepatitis in Association with Prolonged 6-Mercaptopurine Therapy. Blood 1959;14(1):80–90. doi:10.1182/blood.1959.14.1.80, PMID:1749-6632.1959.005708.x.

[80] Berk PD, Martin JF, Young RS, Creech J, Selikoff IJ, Falk H, et al. Vinyl Chloride-Associated Liver Disease. Ann Intern Med 1976;84(6):717–731. doi:10.7326/0002-9343-84-6-717, PMID:945708.

[81] Smetana HF. The histopathology of drug-induced liver disease. Annals of the New York Academy of Sciences 1963;110(3):821–846. doi:10.1111/j.1749-6632.1963.tb05786.x.

[82] von Gizycki C, Granda EG, Chandler TM. S2572 Giant Enigma: A Case Report of Post-infantile Giant Cell Hepatitis Presenting With Seizures. Am J Gastroenterol 2021;116:S1083–S1084. doi:10.14309/01.ajg.0000.783820.41108.4f.

[83] Nair S, Baisden B, Boitnott J, Klein A, Thuluvath PJ. Recurrent, progressive giant cell hepatitis in two consecutive liver allografts in a middle-aged woman. J Clin Gastroenterol 2001;32(5):454–456. doi:10.1097/00004836-200105000-00024, PMID:11319236.

[84] Hassoun Z, N’Guyen B, Cote J, Marleau D, Willems B, Roy A, et al. A case of giant cell hepatitis recurring after liver transplantation and treated with ribavirin. Can J Gastroenterol 2000;14(8):729–731. doi:10.1155/2000/807681, PMID:1185540.

[85] Pappo O, Yunis E, Jordan JA, Jaffe B, Mates R, Fung J, et al. Recurrent and de novo giant cell hepatitis after orthotopic liver transplantation. Am J Surg Pathol 1994;18(8):804–813. doi:10.1097/00000478-199408000-00007, PMID:8037295.

[86] Shah JA, Steinbrecher UP, Erb SR, Tha SP, Yoshida EM. Recurrent giant cell hepatitis in an 18 year old liver transplant patient. Ann Hepatol 2008;7(3):257. PMID:18723895.

[87] Elbach D, Hogan B, Sarpong N, Winter D, Struck NS, Adu-Sarkodie Y, et al. Viral metagenomics revealed novel betatorquevirus species in pediatric inpatients with encephalitis/meningoencephalitis from Ghana. Sci Rep 2019;9(1):2360. doi:10.1038/s41598-019-38975-z, PMID:30787417.