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***Retrospective Study***

**Post-infantile giant cell hepatitis: A single center 25 years experiences**

Matta B *et al*. Post-infantile giant cell hepatitis

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**Abstract**

***BACKGROUND***

Giant cell hepatitis (GCH) in the adult population remains very poorly defined with only 100 case reports published in the literature over the last 3 decades.

***AIM***

To present our center’s experience in an attempt to learn about its predisposing factors, outcomes, and efficacy of proposed therapeutic interventions.

***METHODS***

A retrospective chart review was conducted through the electronic records of the University of Pittsburgh Medical Center. We queried 36726 liver biopsy reports from January 1, 1991 to December 6, 2016. Our search yielded 50 patients who were identified as carrying definite diagnosis of Post-infantile GCH (PIGCH) by pathology. The data recollected included demographic information, laboratory data (liver function tests, autoimmune markers) and transplant status. In order to better analyze patient characteristics and outcomes, subjects were separated into a non-transplant (native) liver group and a post-liver transplant (allograft) group.

***RESULTS***

The incidence of PIGCH was approximately 0.14% of all biopsies queried in the 25-year period. The mean age was 48 years, with 66% females. Liver function tests were classified as 38.2% cholestatic, 35.3% hepatocellular, 26.5% mixed. Autoimmune hepatitis was found to be the most prevalent predisposing factor leading to PIGCH constituting 32% of cases. Management consisted mainly of immunosuppression, viral targeted therapy, supportive care, and in six cases liver transplantations.

***CONCLUSION***

The diagnosis of PIGCH remains clinically challenging and requires a high index of suspicion as well as a thorough history, physical examination, serological workup and liver biopsy. Treatment of the underlying cause can result in clinical stability in a large number of cases.

**Key words:** Post-infantile giant cell hepatitis; Liver transplantation; Autoimmune hepatitis

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**Core tip:** Post-infantile giant cell Hepatitis is a rare disorder and very poorly defined in the literature. Our study aims to present our centered experience in an attempt to shed more light about its predisposing factors, outcomes and efficacy of proposed therapeutic interventions.

Matta B, Cabello R, Rabinovitz M, Minervini M, Malik S. Post-infantile giant cell hepatitis: A single center 25 years experiences. *World J Hepatol* 2019; In press

**INTRODUCTION**

Giant cell hepatitis (GCH) is a relatively common histologic finding in neonates. It is believed to occur secondary to insults to immature hepatocytes. In children, it typically presents with cholestasis, conjugated hyperbilirubinemia and variable degrees of inflammation[1]. Idiopathic GCH refers to these histologic findings with a structurally intact biliary system as opposed to conditions where biliary abnormalities are present, such as biliary atresia[1]. The most commonly proposed pathophysiological hypothesis to account for the presence of giant cells includes an ineffective cytoplasmic division in the setting of cellular fission (endomitosis) in contrast to cellular hepatocyte fusion secondary to hepatic injury[2].

As common as GCH is in children, it is exceedingly rare in adults. GCH in the adult population remains very poorly defined with only 100 case reports published in the literature over the last 3 decades[3]. In adults the entity is referred to as Post-infantile giant cell hepatitis (PIGCH), also known as syncytial or adult onset GCH. PIGCH represents a histologic diagnosis which has been associated with a myriad of medical conditions including infectious, hematologic, autoimmune disorders, and drug reactions (table 1)[3-13]. Pathological analysis is characterized by the presence of giant multinucleated syncytial hepatocytes**.** In particular, more than four to five nuclei in hepatocytes should be seen in a single lobule combined with other features of hepatitis such as lobular disarray, inflammation, Kupffer cell hypertrophy and spotty hepatocytes necrosis (Figure 1).

The clinical course of patients with giant cells on histology is widely variable, ranging from minimal symptoms without major clinical implications, to acute liver failure often times fatal despite standard clinical care. In the current study, we aim at presenting our center’s experience with this very rare disease entity in an attempt to shed more light about its predisposing factors, outcomes, and efficacy of proposed therapeutic interventions.

**MATERIALS AND METHODS**

After obtaining local institutional review board approval, we queried liver biopsy reports (36726) at the University of Pittsburgh Medical Center electronic records using the keywords “giant cell hepatitis” from January 1, 1991 to December 6, 2016. Our search yielded 127 individual patient records out of which, 45 were diagnosed prior to 18 years of age. The remaining 82 records were evaluated by 3 physicians (BM, SM, MM) after which 50 patients were identified as carrying a definite diagnosis of PIGCH based on liver biopsy. In order to better analyze patient characteristics and outcomes, subjects were separated into a non-transplant (native) liver group and a post-liver transplant (allograft) group.

**RESULTS**

The incidence of PIGCH was approximately 0.14% of all biopsies queried in the 25-year period. The mean age of the studied patient sample was 48 years, with 66% females. Liver function tests were classified as follows: 38.2% cholestatic, 35.3% hepatocellular, 26.5% mixed; 73.5% of patients had bilirubin values exceeding 1.5 mg/dL at the time of diagnosis and 42% of patients had bilirubin values exceeding 5 mg/dL. Mean follow up of the entire cohort was over six years (79 mo; SD = 76.1). Patient demographics and liver function tests for patients are outlined in Table 2. Patients with GCH found in the native liver group were older, had higher aspartate aminotransferase, alanine aminotransferase and total bilirubin when compared to the allograft group.

Autoimmune hepatitis (AIH) was found to be the most prevalent predisposing factor leading to PIGCH constituting 32% of cases, while drugs accounted for 12%. Other etiological associations included viral infections (hepatitis A, B, C, CMV, EBV), systemic autoimmune conditions (but not enough to give a diagnosis of AIH) and hematologic conditions. In nearly 1/3rd of cases, no predisposing factor for PIGCH was found (idiopathic). In the post-transplant population, the most prevalent predisposing factor leading to PIGCH was AIH as well, accounting for 30% of cases.

Autoimmune markers related to liver disease were not uncommon: Anti-nuclear antibody (ANA) in 34%, elevated immunoglobulin G 22%, anti-smooth muscle antibody 10%, anti-mitochondrial -antibody 8%, and anti-liver kidney microsomal antibody in 2%.

Drugs which were identified as the possible culprit for GCH development consisted of microdantin, ranitidine, omeprazole, moxifloxacin, ranitidine, plaquenil, as well as chromium picolinate.

Notable pathological findings included diffuse necrosis in 24% of the patients, 56% exhibited features of inflammation and acute hepatitis, while 12% had overt cirrhosis. Of the 10 patients with GCH post liver transplant, 5 had concomitant features of acute cellular rejection.

Management of the PIGCH consisted mainly of immunosuppression, viral targeted therapy, supportive care, and in six cases liver transplantations. Management and outcomes are outlined in Table 4. Among the patients who were treated with immunosuppression, 8 patients (53%) had improvement in their liver function tests. Of the patients treated with ganciclovir, two patients (100%) had improvement in their liver function tests.

Among the native group, 5 patients (13%) required liver transplantation, one patient developed graft failure from post-transplant GCH and required a second transplant. Five (13%) patients died from liver related complications in the native liver group compared to 2 (20%) in the allograft group. Among these 7 patients, five died with “acute liver failure”. Patient #1 had received two liver transplants. The first transplant was for HCV cirrhosis and subsequently developed PIGCH in allograft despite achieving a sustained virologic response after anti-viral therapy. This patient eventually developed allograft cirrhosis attributed to PIGCH and required a second transplant for this reason. The patient died of a spontaneous intracranial hemorrhage. Patient #2 had developed cirrhosis attributed to PIGCH, and died of pneumonia and sepsis. The five remaining patients presented with acute liver failure. Patient #3 was urgently transplanted however developed infected necrotizing pancreatitis to which he succumbed. Patient #4 was found to develop a pneumothorax and died from hemothorax after placement of a thoracotomy tube. Patient #5 died after developing subcapsular hepatic bleeding following a liver biopsy. Patients # 6 and #7 developed a massive variceal bleed and lower gastrointestinal bleeding (exact cause unknown) respectively which led to their demise.

Of the 50 patients with GCH, 12 (6 native and 6 allograft) underwent a repeat liver biopsy of which, 66% still had evidence of GCH despite “treatment”. Half of these patients had undergone a liver transplantation (AIH, PSC/AIH overlap, HCV, GCH, alcoholic, and cryptogenic cirrhosis). These patients had persistent GCH on repeat biopsies despite immunosuppression. The patient with PSC/AIH overlap had improvement of GCH findings on subsequent biopsy. One subject had evidence of acute cellular, then chronic rejection on subsequent biopsies. Cirrhosis developed in a patient transplanted for alcoholic cirrhosis and GCH. Among the native liver group, 6 patients had recurrent GCH on biopsy. One had acute hepatitis B, while the rest did not have a specific predisposing factor.

**DISCUSSION**

With only 100 cases reported in the adult literature, PIGCH remains poorly understood. The prevalence of this disease has been reported at 0.1% to 0.25%[3], which is consistent with the incidence in our cohort (0.14%). Given the rarity of this entity, outcomes and management are largely based on anecdotal evidence. There is no approved therapies and no consensus on management strategies[13].

The histological finding of giant cells in adults seems to be a manifestation of hepatic stress as opposed to a primary hepatic injury[3,10]. The diagnosis is made based on the presence of multinucleated giant cells usually evident in zones 1 and 3 of the Rappaport acinus. More than four to five nuclei in hepatocytes should be seen in a single lobule combined with other features of hepatitis such as lobular disarray, acinar inflammation, Kupffer cell hypertrophy and spotty hepatocytes necrosis.Other common features may include non-suppurative cholangitis, ductopenia, and different stages of periportal fibrosis leading to cirrhosis[6,14]. Similar histological findings were observed among our patient cohort: the majority had notable inflammation on pathology, while about a quarter of them exhibited evidence of hepatic necrosis (28% spotty necrosis, 48% bridging/confluent necrosis, 19% sub-massive necrosis and 5% massive necrosis), with 12% demonstrating overt cirrhosis which is comparable to previous reported rates in the literature of about 13%[3].

Out of the six liver transplant recipients for PICGH; two died with recurrent disease with the first one in the early post-transplant period and the second passing away 11 years later. Two patients required two more liver transplants each for recurrent decompensated cirrhosis despite being on standard immunosuppression. One patient developed cirrhosis with features of chronic rejection which was thought to be related to recurrent hepatitis C, and another was related to CMV hepatitis.

Scant data exists on PIGCH in the post-transplant setting with prior observations indicating the need for re-transplantation in the majority of recipients due to recurrent disease. Pappo *et al*[15] examined the clinical and pathologic course of seven patient who developed GCH after liver transplantation. Five of these patients had GCH as their native liver disease. Two patients died; two patients required re-transplantation because of recurrent GCH; and one patient with recurrent GCH was still alive 6 years after transplantation. Similarly, in our study, 10 patients developed GCH after liver transplantation. Two patients had GCH as their native liver disease. One patient died due to sepsis related to second liver transplantation. Two patients developed recurrent GCH on allograft; one of those patients had their immunosuppression increased and had survived at 2 years and the other one required re-transplantation. Two patients developed *de novo* GCH that required increase in immunosuppression; one patient eventually needed liver transplantation and the other one improved with medical management. One patient developed *de novo* GCH and also found to have CMV hepatitis and was treated with ganciclovir. The remaining four patients were lost to follow up.

Management strategies to treat recurrence mainly consist of increasing immunosuppression and in rare cases the institution of ribavirin with variable success[16,17].

Our results were consistent with prior reports indicating a potential autoimmune link to the findings of PIGCH. We concluded that an autoimmune type hepatitis was seen in 1/3rd of our patients; 34% of the patients had a positive ANA, 22% had an elevated IgG, while 12 patients would fulfill at least a probable diagnosis of AIH based on the AIH scoring system[18] (table 3).

The majority of our patients were female (66%), which is somewhat different to previous reports with approximately equal numbers between genders[3]. Idiopathic PIGCH was present in 30% of our cohort which is much higher than prior published studies. A higher incidence of ‘idiopathic’ PIGCH in our cohort compared to the published literature is likely a manifestation of publication bias, *i.e.*, cases of PICGH were there is no clear link may be less apt to be reported[3]. Drug induced liver injury was the culprit in 12% of cases with all of the reported drugs being novel associations with PIGCH (table 3).

Viral causes amongst our cohort seem to have been less frequent than previously reported. Outcomes of those with a viral cause was variable, although the cases where CMV infection was felt to be the culprit did respond well to ganciclovir, similar to cases reported in the literature[7,19].

The majority of deaths were in the group labeled “idiopathic PIGCH”, while only two out of sixteen patients with autoimmune like features died. Notably, all of the idiopathic patients were managed supportively while most the autoimmune cases were managed with immunosuppression. One patient who died had chronic HCV in addition to AIH. HCV therapy (standard of therapy at the time was interferon-based treatment) was not offered given the patient’s decompensated state. PIGCH has been described in both acute and chronically infected HCV patients (or Co-infected with HIV) with a relatively good prognosis after treatment with interferon and ribavirin, or immunosuppressive therapy when autoimmune features are present[19-22]. No studies have been published to date using the highly potent direct acting antivirals which might potentially prove to have even better outcomes with higher rates of viral eradication[23].

The presentations and outcomes of our patients coincide with previously reported observations in the literature of being highly variable. Some patients only manifested in mild elevations in liver function tests while others developed acute liver failure resulting in death or the need for liver transplantation (table 2). Most patients responded well to immunosuppressive therapy which consisted of mainly intravenous hydrocortisone, prednisone, azathioprine, and tacrolimus, especially with the presence of autoimmune features. One case (previously published) with PIGCH secondary to AIH complicating ulcerative colitis responded to prednisone with improved liver functions despite worsening ulcerative colitis with the patient ultimately requiring a colectomy[12]. Several cases of PIGCH associated with CLL have been reported with largely favorable outcomes after being managed with intravenous immunoglobulins (in the events where immunoglobulins are low), rituximab, or steroids[8,13]. This is similar to our patient with CLL who was managed successfully with prednisone but ultimately developed cirrhosis[24].

Our study has several limitations; it is based on retrospective chart review and is mainly descriptive. That being said, it includes the largest number of unique cases of PIGCH from a single institution included in a single manuscript.

The exact etiology of PIGCH and mechanism of injury remains unknown, and the histological findings are likely related to an idiosyncratic or cytopathic response to various hepatocyte stimuli. Our series suggests an autoimmune cause as the most common association. The diagnosis of PIGCH remains clinically challenging and requires a high index of suspicion as well as a thorough history, physical examination, and a thorough serological workup which should include viral, hematologic, and autoimmune causes. Ultimately a liver biopsy is required as PICGH remains a purely histomorphorpholical diagnosis. Treatment of the underlying cause (especially if it is autoimmune or viral) can result in clinical stability in a large number of cases. Treatment and monitoring should be done in close association with specialty centers including those capable of liver transplantation.

**ARTICLE HIGHLIGHTS**

***Research background***

Giant cell hepatitis (GCH) in the adult population remains very poorly defined with only 100 case reports published in the literature over the last 3 decades. Pathological analysis is characterized by the presence of giant multinucleated syncytial hepatocytes**.** The clinical course of patients with giant cells on histology is widely variable, ranging from minimal symptoms without major clinical implications, to acute liver failure often times fatal despite standard clinical care.

***Research objectives***

Our primary objective is to present our center’s experience in an attempt to learn about GCH predisposing factors, outcomes, and efficacy of proposed therapeutic interventions.

***Research methods***

A retrospective chart review was conducted through the electronic records of the University of Pittsburgh Medical Center. We queried 36726 liver biopsy reports from January 1, 1991 to December 6, 2016. Our search yielded 50 patients who were identified as carrying definite diagnosis of post-infantile giant cell hepatitis (PIGCH) by pathology. The data recollected included demographic information, laboratory data (liver function tests, autoimmune markers) and transplant status. In order to better analyze patient characteristics and outcomes, subjects were separated into a non-transplant (native) liver group and a post-liver transplant (allograft) group.

***Research results***

The incidence of PIGCH was approximately 0.14% of all biopsies queried in the 25-year period. The mean age was 48 years, with 66% females. Liver function tests were classified as 38.2% cholestatic, 35.3% hepatocellular, 26.5% mixed. Autoimmune hepatitis was found to be the most prevalent predisposing factor leading to PIGCH constituting 32% of cases. Management consisted mainly of immunosuppression, viral targeted therapy, supportive care, and in six cases liver transplantations.

***Research conclusions***

The diagnosis of PIGCH remains clinically challenging and requires a high index of suspicion as well as a thorough history, physical examination, serological workup and liver biopsy. Treatment of the underlying cause can result in clinical stability in a large number of cases.

***Research perspectives***

This study reports our center’s experience with PIGCH and the importance of thorough history, physical examination, serologic work up and liver biopsy in its diagnosis. Further research should aim at recognizing risk factors for progression from PIGCH to liver failure and further evaluation of therapeutic interventions (immunosuppression *vs* viral targeted therapy *vs* liver transplantation).

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Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C, C

Grade D (Fair): 0

Grade E (Poor): 0

**Table 1 Reported causes of post-infantile giant cell hepatitis**

|  |  |
| --- | --- |
| Infectious | Hepatitis A, B, C  Epstein-barr virus (EBV)  Cytomegalovirus (CMV)  Paramyxo-like virus  Human immunodeficiency virus (HIV)  Herpesvirus 6A  Human papillomavirus (HPV) |
| Autoimmune | Autoimmune hepatitis (AIH)  Ulcerative colitis (UC)  Primary sclerosing cholangitis (PSC)  Primary biliary cholangitis (PBC)  Systemic lupus erythematosus (SLE)  Rheumatoid arthritis (RA)  Polyarteritis Nodosa (PAN) |
| Drugs | Methotrexate  6 Mercaptopurine  Amytriptyline  P-aminosalicylic acid  Vinyl Chloride  Chropromazine  Methotrexate |
| Hematologic | Chronic lymphocytic leukemia (CLL)  Lymphoma  Sickle cell disease (SCC)  Hypereosinophilia  Autoimmune hemolytic anemia |
| Endocrine | Hypoparathyroidism |
| Infiltrative | Sarcoidosis |
| Post-Transplant | - |
| Idiopathic | - |

**Table 2 Patient characteristics and liver function tests**

|  |  |  |
| --- | --- | --- |
|  | **GCH on native liver**  **(*n* = 40)** | **GCH on allograft**  **(*n* = 10)** |
| Mean age (yr) | 50.4 | 43.4 |
| Gender |  |  |
| Male (%) | 14 (35%) | 4 (40%) |
| Female (%) | 26 (65%) | 6 (60%) |
| AST | 433 ± 486 | 175 ± 158 |
| ALT | 488 ± 537 | 232 ± 206 |
| Alkaline phosphatase | 197 ± 151 | 296 ± 197 |
| GGT | 287 ± 582 | 246 ± 182 |
| Bilirubin | 10.9 ± 10.4 | 3.1 ± 3.8 |

GCH: Giant cell hepatitis; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: γ-glutamyl transpeptidase.

**Table 3 Predisposing factors, *n* (%)**

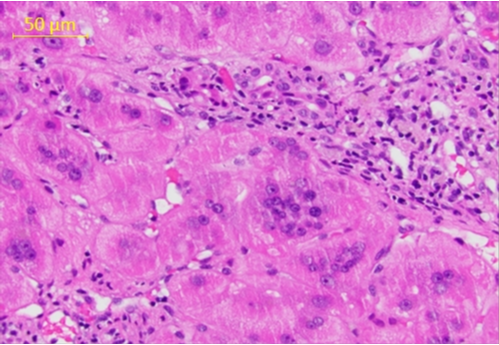
|  |  |  |
| --- | --- | --- |
| **Predisposing factors** | **GCH on native liver** | **GCH on allograft** |
| AIH | 13 (32) | 3 (30) |
| Drug induced | 6 (15) | 0 |
| No factor identified | 12 (30) | 3 (30) |
| UC | 2 (5) | 3 (30) |
| PSC | 3 (7) | 1 (10) |
| HCV | 2 (5) | 1 (10) |
| CMV | 1 (2) | 1 (10) |
| SLE | 2 (5) | 0 |
| Lymphoma | 2 (5) | 0 |
| HAV | 1 (2) | 0 |
| HBV | 1 (2) | 0 |
| EBV | 1 (2) | 0 |
| Sjogren | 1 (2) | 0 |
| Autoimmune hemolytic anemia | 1 (2) | 0 |
| CLL | 1 (2) | 0 |
| Peripheral eosinophilia | 1 (2) | 0 |
| SCC | 1 (2) | 0 |
| Celiac disease | 1 (2) | 0 |

GCH: Giant cell hepatitis; AIH: Autoimmune hepatitis; UC: Ulcerative colitis; PSC: Primary sclerosing cholangitis; HCV: Hepatitis C virus; CMV: Cytomegalovirus; SLE: Systemic lupus erythematosus; HAV: Hepatitis A virus; HBV: Hepatitis B virus; EBV: Epstein-Barr virus; CLL: Chronic lymphocytic leukemia; SCC: Sickle cell disease.

**Table 4 Management and outcomes, *n* (%)**

|  |  |  |
| --- | --- | --- |
|  | **GCH on native liver**  **(*n* = 40)** | **GCH on allograft**  **(*n* = 10)** |
| Management |  |  |
| Immunosuppression | 11 (28) | 4 (40) |
| Supportive care | 10 (25) | 0 (0) |
| Liver transplantation | 5 (13) | 1 (10) |
| Ganciclovir | 1 (3) | 1 (10) |
| Unknown | 13 (33) | 4 (40) |
| Outcomes |  |  |
| Survived | 25 (63) | 4 (40) |
| Died | 5 (13) | 2 (20) |
| Unknown | 10 (25) | 4 (40) |

GCH: Giant cell hepatitis.



**Figure 1 Liver biopsy of patient 44 years old female with autoimmune hepatitis (HE stain 40 ×).** Biopsy revealed chronic hepatitis with prominent giant multinucleated hepatocytes.