

Diclofenac-Induced Post Infantile Giant Cell Hepatitis

Sidish S. Venkataraman, BSA, Vishnu Mohan, MD, Jeffrey A. Conyers, MD, Rukma R. Govindu, MD

Sidish S. Venkataraman, Vishnu Mohan, Rukma R. Govindu, Department of Internal Medicine, McGovern Medical School at UTHealth, Houston, TX, the United States

Jeffrey A. Conyers, Department of Pathology, McGovern Medical School at UTHealth, Houston, TX, the United States

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Correspondence to: Sidish S. Venkataraman, BSA, Department of Internal Medicine, McGovern Medical School at UTHealth, 6431 Fannin Street, Houston TX 77030, the United States.

Email: Sidish.S.Venkataraman@uth.tmc.edu

Telephone: +1-713-500-6714

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ABSTRACT

INTRODUCTION: Post-infantile Giant Cell Hepatitis (PIGCH) is a rare type of autoimmune hepatitis (AIH) characterized by an idiosyncratic response to liver injury from various causes in which liver cells respond to insult by rapid proliferation and without the appropriate cellular division, leading to the formation of the multi-nucleated giant cells. We encountered a case of Diclofenac induced PIGCH in a patient with untreated seropositive rheumatoid arthritis. To the best of our knowledge, this is first such case reported in the literature.

CASE PRESENTATION: A 48-year-old Hispanic woman with type II diabetes and rheumatoid arthritis, not on DMARDs presented with acute onset jaundice and right upper quadrant pain. She was taking 50mg of Diclofenac, 2 pills daily for the past 3 months and

unknown quantity of garlic tablets. Workup for hepatitis including infectious and toxic etiologies were ruled out. Serum IgG levels were elevated with increased globulin gap, and positive ANA titer of 640, anti-smooth muscle cell antibodies elevated at 41 units (moderate to strong positive > 30 units). Liver biopsy demonstrated submassive necrosis in the setting of post-infantile giant cell hepatitis. The differential diagnoses included idiopathic autoimmune hepatitis, viral or drug induced injury. Our diagnosis was drug induced autoimmune liver disease (DIALD), the etiology is likely due to Diclofenac given temporal relationship of drug intake and symptom onset, as well as a calculated Roussel Uclaf Causality Assessment Method (RUCAM) score of 6, signifying probable drug-induced liver disease. Patient was started on Prednisone and Azathioprine with complete resolution of clinical and laboratory findings within 5 months.

DISCUSSION: The outcome of PIGCH is unpredictable, usually adopts a fulminant course leading to cirrhosis within months, however, a more benign course has also been described. PIGCH is triggered by three primary etiologies: drugs, infection, and autoimmune liver injury. This case highlights that giant cell hepatitis is a multifactorial condition that can be precipitated by drug use in the setting of autoimmune phenotype. Garlic and garlic extracts, through their antioxidant activities, have been reported to provide protection against free radical damage in the body. The innocuous course of PIGCH in our patient could possibly be due to concurrent consumption of garlic tablets. Further research is needed in this area.

Key words: Diclofenac; Hepatitis; Giant Cell

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INTRODUCTION

Autoimmune hepatitis (AIH) is a disease in which the body's own immune system attacks the liver leading to inflammation and destruction of the liver parenchyma. Often times the symptoms of AIH are minor, however in 10-20% of patients, AIH can present like acute hepatitis with sudden onset (< 1 mo) jaundice, abdominal pain,

loss of appetite, and pale stools^[1]. Of those with acutely symptomatic AIH, a significant proportion is drug-induced, with medications, herbs, or cosmetics precipitating AIH^[2]. Postinfantile Giant Cell Hepatitis (PIGCH) is a rare type of AIH of unknown etiology that only occurs in 2-5 adults per 100,000 patients who underwent a liver biopsy^[3]. It is more often described in neonates, often in the first three months of life^[4]. The course of PIGCH is usually fulminant with a rapid progression to cirrhosis and death within months^[5]. However, a more benign course for PIGCH has also been described, with medical management resulting in the resolution of symptoms and a normal liver panel within 2-12 months of therapy^[2]. This case illustrates a benign course of Diclofenac-induced PIGCH in a patient with rheumatoid arthritis and type II diabetes mellitus. Full resolution of symptoms and return to baseline laboratory values were achieved within 5 months of starting treatment with Prednisone.

HOSPITAL COURSE

A 48 year old Hispanic woman from El Salvador with a past medical history of type II diabetes (HbA1c = 7.4) and rheumatoid arthritis, (not on any disease modifying anti-rheumatic drugs), presented to the hospital with progressively worsening yellow discoloration of the skin and eyes as well as worsening epigastric and right upper quadrant pain for the past 4 weeks. There was no history of fever, prodrome, GI bleeding, exposure to toxins, recent travel, prior GI issues, or alcohol consumption. The patient endorsed a 1 month history of nausea and mild itchiness. Abdominal exam revealed no abdominal distension or ascites. Her home medications included Metformin 500mg twice per day, glucosamines, garlic tablets (unknown quantity), and Diclofenac 50mg (purchased over-the-counter in El Salvador) all of which were taken daily. She said she has been compliant with all her medications for the past 3 months but stopped taking the Diclofenac and Metformin upon symptom onset, a little less than one month prior to presentation in the emergency department. Upon arrival, her vitals were normal. However, she was strikingly jaundiced without any evidence of encephalopathy. Her abdomen was non-tender and there was no palpable organomegaly. Further there were no neurological abnormalities. Liver function tests were ordered and showed: alanine transaminase (ALT) - 368 [Normal: 7-56]; aspartate aminotransferase (AST)-679 [Normal: 10-40]; alkaline phosphatase (Alk P) - 446 [Normal: 44-147]; total bilirubin (Tbili) - 26.6 mg/dL [Normal: 0.1-1.2 mg/dL]; and direct bilirubin (Dbili)-21.1 [Normal: 0-0.3 mg/dL]. Lipase was 253 U/L [Normal: 73-393 U/L]. Prothrombin time was elevated (22.5 seconds) as was partial thromboplastin time (41.2 seconds). Additionally, anti-nuclear antibody (ANA) titer was elevated at 640 (Figures 1 and 2), rheumatoid arthritis factor (RA factor) was > 6000 IU/mL [Normal: 0-15 IU/mL] and serum IgG level was 3080 mg/dL [Normal: 700-1600 mg/dL]. Of particular importance, anti-smooth muscle cell antibodies were elevated at 41 units (moderate to strong positive > 30 units), strongly suggestive of autoimmune hepatitis. However, ds-DNA, anti-mitochondrial antibodies, and anti-smith antibodies were all negative. Abdominal ultrasound showed a contracted gallbladder with trace pericholecystic fluid and a mildly nodular contour of the liver. No stones or biliary dilatation were identified. CT abdomen corroborated these findings showing an edematous gallbladder with no intra or extrahepatic biliary dilatation, ampullary mass, or stones. Workup for a viral source of acute hepatitis including Hepatitis A, B, and C as well as Epstein-Barr virus, and Cytomegalovirus were negative. Serological workup for A1AT deficiency, Wilson's disease, hemochromatosis, and granulomatosis with polyangiitis were also negative suggesting a possible autoimmune or drug-induced hepatitis.

There was no evidence of intra or extrahepatic biliary dilatation or obstruction on MRCP. A diagnostic transjugular liver biopsy was then performed, (percutaneous was avoided due to elevated PT and PTT). Biopsy (Figure 3) revealed extensive submassive necrosis with loss of liver parenchyma, scattered multinucleated hepatocytes consistent with post-infantile giant cell hepatitis (PIGCH), portal inflammation with preserved bile ducts, and lack of significant fibrosis. The patient was strongly encouraged to avoid any herbal remedies or medications acquired without a prescription. She was then started on 60mg/day methylprednisone, 50mg azathioprine, and 900mg/day ursodiol. After 4 days of this medication regimen, the patient was discharged with prednisone 40mg/day and azathioprine 50mg/day and instructed to follow-up with gastroenterology in 1 week. At follow-up in gastroenterology clinic, the patient was switched from 40mg/day to 20mg/day of prednisone. She was maintained on 20mg/day prednisone, 300mg/day Ursodiol, and 50mg/day azathioprine. After 5 months of taking this medication regimen outpatient, repeat liver function tests showed ALT- 24; AST-19; Alk P-171; Tbili-0.5; DBili-0.2 (Figures 1 and 2).

DISCUSSION

Post-infantile giant cell hepatitis (PIGCH) is a rare variant of autoimmune hepatitis (AIH) that occurs in 0.1%-0.25% of all hepatic diseases^[6,7]. Only about 100 cases of PIGCH have been reported so far^[1]. The etiology of PIGCH is varied and is thought to occur in the setting of 4 different etiologies: (1) Autoimmune diseases; (2) Viral Causes; (3) Drugs; and (4) Miscellaneous, with autoimmune liver disease (systemic lupus erythematosus, rheumatoid arthritis, etc.) being the most common cause (40%) followed by viruses (paramyxovirus, hepatitis, Epstein-Barr virus, *human papillomavirus*)

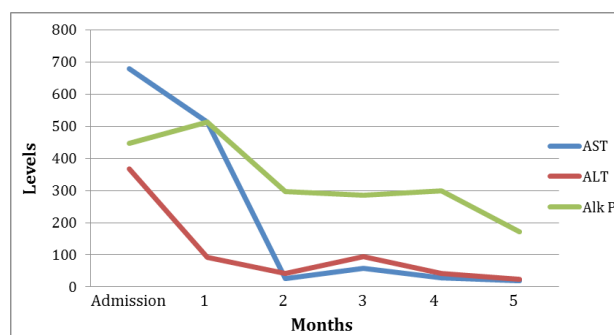


Figure 1 Shows the patient's AST (aspartate aminotransferase), ALT (alanine transaminase), and Alk P (alkaline phosphatase) levels in response to treatment with Prednisone, Ursodiol, and Azathioprine over 5 months.

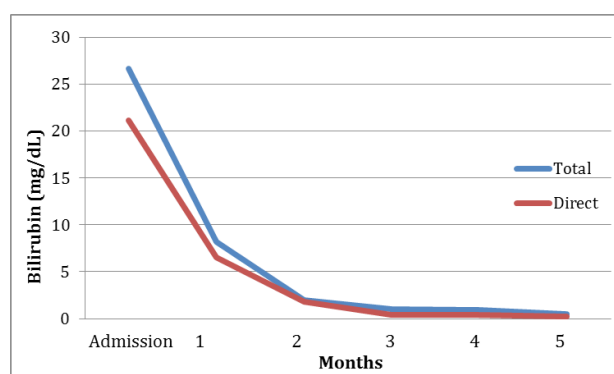


Figure 2 Shows the patient's total and direct bilirubin levels in response to treatment with Prednisone, Ursodiol, and Azathioprine over 5 months.

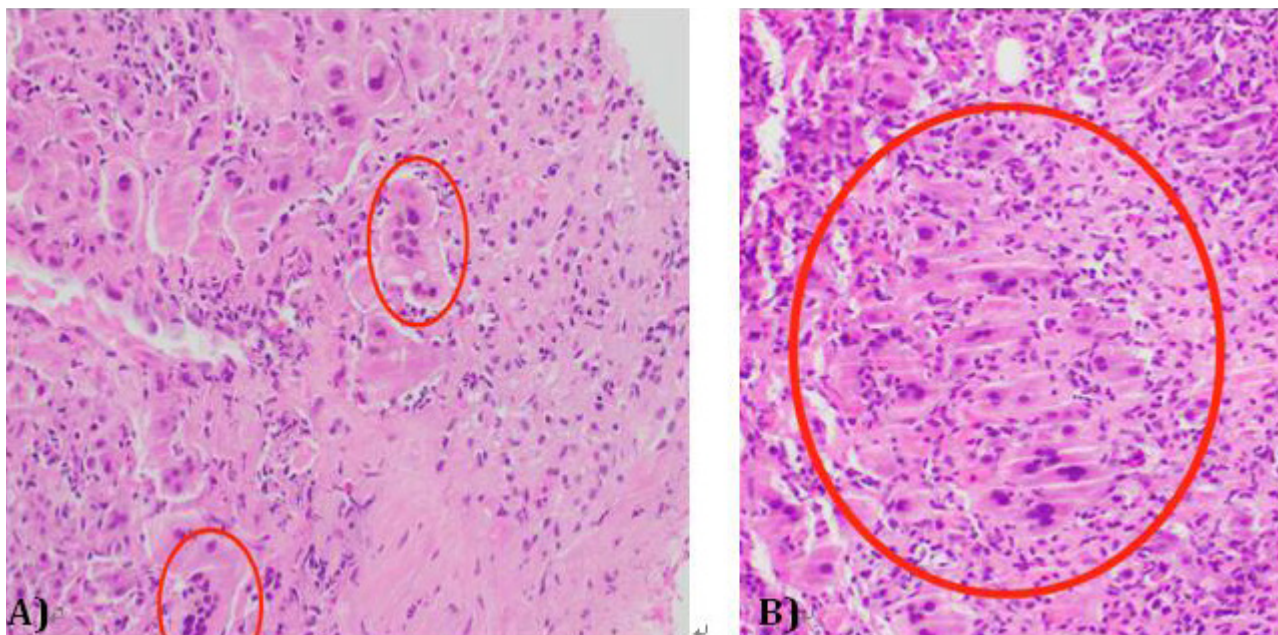


Figure 3 Microscopic view of the liver biopsy. A: Liver biopsy shows panlobular hepatitis scattered multinuclear hepatocytes, areas of necrosis, occasional acidophil bodies, and a mixed inflammatory infiltrate consisting of lymphocytes, plasma cells, and neutrophils (H&E, 100X). B: The multinucleated hepatocytes are appreciated better on higher power imaging (H&E, 200X).

and drug-induced liver injury (DILI)^[1]. This case is unique in that it details an account of likely DILI-induced post-infantile giant cell hepatitis (PIGCH) caused by Diclofenac. While it is possible that this patient’s liver injury was due to a virus or autoimmune phenomenon, anti-smooth muscle cell antibodies were elevated at 41 units (moderate to strong positive > 30 units), strongly suggestive of autoimmune hepatitis. Further, viral panel was negative as were ds-DNA (SLE), anti-mitochondrial (primary biliary cirrhosis), and anti-smith antibodies (autoimmune hepatitis). ANA titer (640) was positive. However, the patient had coexisting rheumatoid arthritis, which likely explains the high titers.

Liver damage in the setting of RA is thought to be due to three main causes: (1) a hepatic manifestation of RA; (2) a medication used to treat RA (which can often be hepatotoxic); or (3) autoimmune hepatitis, since patients with one autoimmune phenomenon are more likely to have another^[8]. To the first point: liver injury is not generally recognized as a significant extra-articular feature of RA^[8]. Further, of the patients with RA that did have liver involvement, histology primarily showed mild chronic inflammatory infiltrate of the portal tract^[9], whereas liver biopsy in this patient showed a more diffuse, panlobular hepatitis with multinucleated hepatocytes. To the second point: the only drug that the patient was taking known to cause liver injury was Diclofenac. It should be noted that the patient was not taking any disease-modifying antirheumatic drugs such as Methotrexate that are known to be associated with liver injury^[10]. To the third point: distinguishing between whether or not this is a drug-induced cause of PIGCH or a separate autoimmune disease process can be difficult. The Roussel Uclaf Causality Assessment Method (RUCAM) assessment is a score designed to indicate the likelihood of whether or not the damage is due to a drug-induced process. This patient’s RUCAM score was 6 (Table 1) indicating that a drug-induced cause was probable^[11]. Further, the time from drug withdrawal until reaction onset was less than 30 days, and anti-smith antibodies, associated with autoimmune hepatitis, were negative, both more consistent with a drug-induced rather than an autoimmune process. Together, these observations support Diclofenac usage as the underlying etiology for this patient’s PIGCH.

Table 1 indicates the patient’s Roussel Uclaf Causality Assessment Method^[12]. Under “assessment” are the variables that go into calculating the score. Under “response” are the replies based on the patient’s history. Under “score” is the number of points the patient received for each assessment. A score of 6 indicates that the patient’s liver damage due to an acute drug reaction is probable.

Roussel Uclaf Causality Assessment Method (RUCAM)		
Assessment	Response	Score
Time from Drug Intake Until Reaction Onset	> 90 days	1
Time from Drug Withdrawal Until Reaction Onset	≤ 30 days	1
Alcohol or Pregnancy Risk Factor	Absent	0
Age Risk Factor	< 55	0
Course of the Reaction	≥ 50% improvement 180 days	2
Concomitant Therapy	Time to onset compatible but with unknown drug reaction	
Exclusion of Non-Drug Causes	Rule Out	2
Previous Information on Hepatotoxicity	Reaction published but unlabeled	1
Response to Re-Administration	Not available	0
	Total	6 points

The exact mechanism by which drug-induced liver injury (DILI) leads to PIGCH remains to be understood, however, the formation of giant cells is thought to be an idiosyncratic reaction in response to tissue injury^[12]. When DILI occurs, destruction of liver parenchyma leads to the exposure of liver proteins inducing an autoimmune phenomenon. In genetically susceptible individuals, the liver cells attempt to recover from injury by rapidly proliferating without appropriate cellular division leading to multinucleated, giant cells^[1]. Many of these patients also tend to exhibit other autoimmune characteristics or have other autoimmune conditions (as in rheumatoid arthritis for this patient). This is possibly because inflammatory states (rheumatoid arthritis, etc.) delay the elimination of drug metabolites via reduction of biliary excretion^[13].

Currently, there is a paucity of research regarding the exact clinical picture that corresponds to drug-related PIGCH. In a case review

by Johnson *et al*, 9 cases of post-infantile giant cell hepatitis were described^[6]. Patients presented after having anywhere from 4 days – 2 months of symptoms ranging from jaundice, vomiting, pale stools, and pruritus to general malaise and neurological symptoms such as tingling and encephalopathy. Most cases of Diclofenac-induced liver injury exhibited a predominately hepatocellular pattern of damage (significant increases in alanine transaminase (ALT) and aspartate aminotransferase (AST) levels). However, this is likely affected by the timing of presentation with many patients initially exhibiting a hepatocellular pattern early in the disease course followed by a more mixed pattern (markedly elevated alkaline phosphatase (Alk P) as well as ALT and AST), as in this patient^[14-17].

In addition to the varied clinical presentation, the prognosis of PIGCH is unpredictable. Shetty *et al* summarized 5 drugs and 1 herbal medicine currently associated with PIGCH and their respective prognoses: Methotrexate (mild hepatitis), Chlorpromazine (mild hepatitis), Clometacine (acute liver failure), Amoxicillin + Clavulanate (chronic hepatitis with acute decompensation), Doxycycline (acute liver failure), and ISABGOL also known as Psyllium husk (mild hepatitis), a herbal remedy used for treating constipation^[12]. Three out of the six drugs resulted in clinical improvement within 2-6 months either spontaneously or with the use of prednisone, while the other three led to liver failure. This variation in the prognosis of PIGCH has been corroborated by other studies, which also noted the significant variation in prognosis from clinically asymptomatic with a mild increase in liver transaminases to fulminant liver failure^[3-5]. In each of these 6 cases, there was no significant difference in ALT or AST levels or antibody titers between these patients that could have been useful in predicting outcomes. Further, even with liver transplantation some patients have had recurrence of PIGCH within 2 months-2 years suggesting a transmissible element as the potential etiology.

It should also be noted that our patient's more benign presentation of PIGCH could be related to daily consumption of garlic tablets, which might have had a therapeutic effect, helping to prevent PIGCH from progressing to fulminant liver failure. While NSAIDs are metabolized by the liver and excreted in the urine, the method by which NSAIDs (other than Aspirin) cause hepatotoxicity is thought to be through an idiosyncratic reaction rather than direct hepatotoxicity^[18]. In susceptible patients, this reaction to NSAIDs can cause asymptomatic increases in serum transaminases and in rare occasions, symptomatic liver damage. Garlic, is known to have hepatoprotective effects as a consequence of its anti-inflammatory properties. Studies have shown that garlic decreases levels pro-inflammatory cytokines such as NF- κ B, COX-1, COX-2, and LTB^[19]. Additionally, studies have shown decreased rates of liver injury in animal models treated with isoniazid and rifampin^[20]. Further, a compound extracted from garlic, PMK-S005, was shown to decrease NSAID-induced gastric damage in animal models^[21]. It is therefore, possible that garlic attenuated the liver damage induced by Diclofenac in this patient.

This case illustrates that giant cell hepatitis is a multifactorial condition that can be precipitated by drug use in the setting of an autoimmune phenotype. Moreover, it emphasizes the importance of obtaining a thorough history of prescribed or non-prescribed, herbal, and alternative medications, which are commonly used in the US especially among the immigrant population. Further research is needed to predict the prognosis of PIGCH based on the drug involved, the clinical course, and laboratory findings as well as to determine the best treatment strategy for patients with drug-induced PIGCH. Lastly, the hepatoprotective effects of garlic need to be further investigated.

CONCLUSION

This case report discusses an incidence of PIGCH, likely caused by drug-induced liver injury (DILI) secondary to Diclofenac use. The diagnosis was confirmed by biopsy (Figure 3), and the patient has been treated with Prednisone and Azathioprine resulting in significant clinical and laboratory improvement (Figures 1 and 2). There are few reported cases of PIGCH and this is the only case, to our knowledge, of PIGCH possibly secondary to Diclofenac use. The presentation of PIGCH is highly variable from mild jaundice to encephalopathy and the prognosis is unpredictable ranging from spontaneous resolution to fulminant liver failure. In this report, Diclofenac induced PIGCH resulted in an innocuous course possibly due to concurrent consumption of daily garlic tablets. Going forward, patients need to be made aware of the potentially toxic effects associated with NSAID use and physicians should be vigilant about the ability for NSAIDs to induce autoimmune hepatitis even months after discontinuation of the drug. Further, care must be taken by providers to ask about non-prescription medications in the setting of liver injury.

Author Contribution

SSV wrote and critically revised the manuscript. VM critically revised the manuscript. JAC provided and annotated the histopathology and critically revised the manuscript. RRG conceived study design and wrote and critically revised the manuscript.

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