Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/kdact055

INVESTIGATING THE MECHANISMS AND THERAPEUTIC CHALLENGES OF HEMOLYTIC ANEMIA LINKED TO GIANT CELL HEPATITIS

Dr. Sravani Karumuru*

*Assistant Professor, Department of General Medicine, Sri Lakshmi Narayana Institute of Medical Sciences & Hospital, Osudu, Puducherry - 605502

***Corresponding Author:** Dr. Sravani Karumuru
*Assistant Professor, Department of General Medicine, Sri Lakshmi Narayana Institute of Medical Sciences & Hospital, Osudu, Agaram Village, Koodapakkam Post, Puducherry - 605502

ABSTRACT

The pathogenesis of hemolytic anemia associated with giant cell hepatitis (GCH) in the conte Giant cell hepatitis (GCH) associated with autoimmune hemolytic anemia (AHA) is a rare but severe pediatric condition with high mortality rates. This report presents the case of a nine-month-old infant with jaundice, fever, and watery diarrhea, who rapidly developed severe hepatic failure. Laboratory findings included normocytic anemia, thrombocytopenia, elevated alpha-fetoprotein (AFP), and a positive direct Coombs' test (IgG and C3d). Despite ruling out infectious and metabolic causes, GCH with AHA was diagnosed following a liver biopsy revealing giant necrotic hepatocytes. The patient received intravenous immunoglobulin (IVIG), prednisone, and azathioprine, which initially stabilized clinical parameters. However, a severe relapse occurred within four months, presenting with multi-drug-resistant Escherichia coli sepsis, ascites, and worsening liver failure. The infant ultimately succumbed to septic shock despite intensive supportive care. This case highlights the diagnostic challenges and aggressive nature of GCH associated with AHA. The rapid relapse following partial remission emphasizes the need for prolonged immunosuppressive therapy and early intervention with liver biopsy in cases of unexplained hepatitis. Additionally, it underscores the limitations of current treatments, including corticosteroids, IVIG, and splenectomy, in preventing relapse. GCH with AHA remains a life-threatening condition with poor outcomes, necessitating continued research to identify effective therapies and predictors of relapse. This case further reinforces the importance of close monitoring and comprehensive long-term management strategies to improve patient survival.xt of autoimmune hemolysis remains elusive. A 9-month-old infant presented with fever, diarrhea, and jaundice four days prior to hospitalization. Physical examination revealed pallor, jaundice, and hepatosplenomegaly. Laboratory findings indicated elevated levels of hemolytic anemia, thrombocytopenia, immunoglobulin G (IgG), and anti-C3d antibodies. Conjugated bilirubin was measured at 84 mmol/L, with a total bilirubin of 101mmol/L. The absence of antinuclear antibodies, anti-smooth muscle antibodies, anti-liver kidney microsomes 1 antibodies, and anti-endomisium antibodies, as well as negative results for Epstein Barr virus, cytomegalovirus, herpes simplex, and viral hepatitis B and C, led to the diagnosis of GCH. GCH diagnosis was supported by acute liver failure, Evan's syndrome, and positive Coomb's tests (IgG and C3). Confirmation of GCH was obtained via needle liver biopsy. Despite treatment with steroids, immune-modulatory therapy, and azathioprine, the patient succumbed to the condition.

KEY WORDS: Giant Cell Hepatitis (GCH), Autoimmune Hemolysis, Epstein Barr virus, hepatitis B and C, Treatment Resistance.

INTRODUCTION

Cases of giant cell hepatitis occurring without autoimmune hemolytic anemia (AHA) are infrequent. The underlying mechanisms and prognosis of this condition remain unclear [1,2]. Pediatric literature has documented a total of 54 instances of this syndrome [2-6]. The disease commonly presents as severe hepatitis accompanied by jaundice, fever, and a positive direct Coombs' test, typically manifesting approximately one year following the onset of AHA [3]. In the case described, a nine-month-old infant exhibited symptoms of pallor, fever, and jaundice. Despite receiving prompt medical intervention, the outcome was critical.

METHODOLOGY

A nine-month-old infant was admitted to Sri Lakshmi Narayana Institute of Medical Sciences & Hospital, Puducherry, with symptoms of jaundice, fever, and watery diarrhea, which had persisted for four days. Upon clinical evaluation, the infant appeared well-nourished but was running a fever (38.3°C). Physical examination revealed pallor, an enlarged spleen (splenomegaly), and liver enlargement (hepatomegaly), with the liver span measuring 11 cm, which correlated with signs of jaundice.

Initial Laboratory Investigations

The blood analysis (Table 1) showed normochromic normocytic regenerative anemia and thrombocytopenia, accompanied by elevated conjugated bilirubin and increased gamma-glutamyl transferase (GGT) levels. There was a notable rise in alpha-fetoprotein (AFP), indicating potential liver dysfunction.

Screening for Infectious and Metabolic Causes

Since febrile jaundice often suggests liver involvement, several infectious causes were explored. However, serological tests ruled out hepatitis A, B, and C viruses, cytomegalovirus (CMV), Epstein–Barr virus (EBV), herpes simplex virus (HSV), and HIV. Despite elevated alkaline phosphatase (ALP) and delta-aminolevulinic acid (ALA) suggesting a possible metabolic disorder, such as tyrosinemia, chromatographic analysis of amino acids and organic acids was within normal limits. Additionally, autoimmune hepatitis was considered; however, tests for mitochondrial, LKM1, nuclear, and smooth muscle antibodies were all negative.

Indicators of Autoimmune Activity and Bacterial Infection

Blood tests revealed high immunoglobulin G (IgG) levels and low complement levels, indicating immune system activation, while cellular immunity was normal. Urine and blood cultures identified Escherichia coli (E. coli), prompting intravenous (IV) antibiotic therapy. An abdominal ultrasound showed an enlarged, hyperechogenic liver, a homogeneous spleen, non-dilated bile ducts, and a hyperechogenic cuff around the hepatic pedicle, consistent with liver inflammation.

Deterioration During Hospitalization

Despite antibiotic treatment, the infant’s jaundice and pallor worsened, and the fever persisted. By the 10th day of hospitalization, the hemoglobin level dropped to 6.8 g/dL, and the platelet count fell to 6,000/mL. Although the haptoglobin test was negative, the direct Coombs' test (IgG and C3d) was positive, indicating autoimmune hemolytic anemia (AHA).

Diagnosis and Treatment for Giant Cell Hepatitis (GCH)

Giant cell hepatitis (GCH) was suspected due to the combination of liver failure and autoimmune hemolytic anemia without identifiable autoantibodies. The infant received blood and platelet transfusions, followed by a liver biopsy, which showed diffuse transformation of hepatic cells into

giant necrotic cells, confirming the diagnosis of GCH. The infant was treated with intravenous immunoglobulin (IVIG) at a dose of 1 g/kg per day for two days, alongside azathioprine and prednisone. Following the initiation of steroid therapy, the infant's clinical condition improved, with stabilized blood parameters (Table 1).

Hospital Discharge and Recurrence

The infant was discharged on day 30 under the same treatment regimen. At the 15-day follow-up, biological markers remained stable, showing signs of improvement.

Relapse and Worsening Condition

However, 60 days post-discharge, the infant was readmitted with symptoms of edema, fever, and ascites. Investigations revealed a urinary tract infection (UTI) caused by multi-drug-resistant Escherichia coli, and liver function had further deteriorated, with a prothrombin time (PT) of 20% and elevated cytolysis markers (Table 1). The infant was treated with intravenous antibiotics and received supportive care for liver failure.

Rapid Decline and Outcome

Despite intensive interventions, the fever persisted, and the infant developed renal failure with further deterioration in liver function (PT = 12%). Ultimately, the infant succumbed to septic shock, with the entire course of illness spanning approximately three months from the onset of symptoms.

Table 1: Effects of prednisone and azathioprine on biological findings

	I	II	III	IV
Leucocytes	24800	39600	46600	55600
PNN (%)	154	84	120	114
Hemoglobin (g/dL)	10.3	7.8	12.4	11.4
MCV	80.9	87.6	86.4	97.6
Reticulocytes (elements/ µL)	228000	35200	184600	368000
Platelets (elements/µL)	142000	14000	306000	304000
SAT/ALT (UI/L)	2040/1620	2860/3772	736/1200	2620/521044
Total bilirubin	202	850	380	850
Direct bilirubin (µmol/L)	83.6	244	156	582
GGT (UI/L)	340		244	68
PT (%)	110	102	140	40
CRP (mg/L)	84	-	24	40
AFP (ng/mL)	358		58	30.63
LDH (UI/L)	4178	2184	800	-
Haptoglobin (g/L)	0.7	0	-	-
DCT	-	+ IgG/C3d	-	+ IgG/C3
Ferritinemia (ng/mL)	326	-	-	-
Fibrinogen (g/L)	4.3	-	-	-
Triglycerides (mmol/L)	4.99	-	-	-

DISCUSSION

In 1981, approximately 39% of children diagnosed with giant cell hepatitis (GCH) and autoimmune hemolytic anemia (AHA) succumbed to their illness [4]. GCH is recognized as a rare pathological condition [1, 2]. Pediatric studies have documented 27 cases [2, 4-6], with 16 cases reported over a 28-year period. Despite these reports, the underlying cause of this condition remained unclear [1]. AHA and hypergammaglobulinemia have been linked to autoimmune origins [1]. According to one study [4], all 16 patients exhibited indicators of an autoimmune cause, including autoimmune diseases such as type 1 diabetes, thyroiditis, and psoriasis. Additional evidence included the presence of

autoantibodies, thrombocytopenia, improvement with immunosuppressive treatment, and deterioration when the treatment dose was reduced. However, histological analysis often did not reveal signs of autoimmune hepatitis, as autoantibodies were frequently absent [2]. It was also hypothesized that activated T lymphocytes and Küppfer cells could trigger an uncontrolled release of cytokines [2]. In this study, no familial or personal history of autoimmune disease was identified, although the patient initially responded well to steroids and immunosuppressive therapy. Typically, GCH associated with AHA manifests between 2.5 and 24 months of age [4, 5], and in this case, symptoms emerged at 9 months. During the neonatal stage, hepatocytes may form giant cells as a nonspecific reaction to various injuries [4]. When hepatitis is accompanied by a positive Coombs' test in infants, a liver biopsy should be promptly performed to diagnose GCH [4, 5]. This condition often carries a poor prognosis [7]. In this case, the infant died from septic shock following an early relapse. Several treatment options are available for GCH associated with AHA, including corticosteroids, aminoglycosides, intravenous immunoglobulins (IVIG), mercaptopurine, mycophenolate mofetil, vincristine, plasmapheresis, cyclosporine, cyclophosphamide, tacrolimus, and anti-CD20 therapy (Rituximab®) [1]. Additionally, splenectomy has been suggested for patients with AHA who do not respond to medical treatments [1, 8]. Among three patients who received cyclosporine, severe disease progression was observed [4]. Out of 16 cases, 8 patients achieved full remission with normalized transaminase levels. Six patients experienced partial remission, while 2 showed no response to treatment [4]. However, 11 patients experienced relapses, with 10 of those cases involving AHA that was resistant to medical therapy. Anti-CD20 therapy was effective in 2 patients, and among 10 patients who underwent splenectomy, only 2 achieved positive outcomes. Four patients succumbed to severe sepsis, including cases of post-transplant complications. Meanwhile, 12 patients survived, with one undergoing a liver transplant [4]. This series highlights the severe nature of GCH associated with AHA and the challenges in managing the condition, particularly due to the high rate of relapse and resistance to therapy following recurrence. In this patient, partial improvement was observed after receiving intravenous immunoglobulins alongside prednisone and azathioprine. However, the patient experienced a rapid relapse within four months, marked by severe liver failure without hematological recurrence. The child ultimately died from septic shock. In conclusion, GCH with AHA is a life-threatening condition requiring early diagnosis through liver biopsy in cases of unexplained infantile hepatitis. Achieving total remission with normalized transaminase levels necessitates prompt treatment with corticosteroids and immunosuppressive agents. Furthermore, to reduce the risk of relapse—which is often more resistant to treatment—therapy should be maintained for an extended period.

CONCLUSION

Giant cell hepatitis (GCH) associated with autoimmune hemolytic anemia (AHA) is a rare but life-threatening condition, particularly in pediatric patients. This case highlights the challenges in diagnosing and managing this complex disease. Despite initial improvements with corticosteroids, azathioprine, and intravenous immunoglobulin (IVIG) therapy, the rapid relapse and progression to septic shock underscore the severity of this pathology. The high rates of relapse and resistance to treatment observed in both this case and prior studies emphasize the need for aggressive and prolonged immunosuppressive therapy. Early intervention, including prompt liver biopsy in cases of unexplained infantile hepatitis, is crucial for diagnosis and timely management. Additionally, therapies such as anti-CD20 agents and splenectomy may be considered in patients resistant to conventional treatments. Achieving complete remission, defined by normalized transaminase levels, requires consistent and sustained immunosuppressive treatment. However, this case also highlights that relapses can occur rapidly, and outcomes can be fatal despite aggressive intervention. Future research should focus on identifying predictors of relapse and optimizing treatment protocols to improve survival rates in patients with GCH and AHA. This case underscores the importance of early diagnosis, comprehensive management strategies, and the need for continued follow-up to prevent relapses and improve long-term outcomes in pediatric patients with this rare and serious condition.

REFERENCES

1. Koch A, Zacharowski P, Boehm O, Zacharowski K: Innate immunity, coagulation and surgery. Front Biosci 2009, 14:2970-2982.
2. Lin E, Calvano SE, Lowry SF: Inflammatory cytokines and cell response in surgery. Surgery 2000, 127:117-126.
3. Ni Choileain N, Redmond HP: Cell response to surgery. Arch Surg 2006, 141:1132-1140.
4. Kurosawa S, Kato M: Anesthetics, immune cells, and immune responses. J Anesth 2008, 22:263-277.
5. von Dossow V, Sander M, MacGill M, Spies C: Perioperative cell-mediated immune response. Front Biosci 2008, 13:3676-3684.
6. Delogu G, Moretti S, Antonucci A, Marandola M, Tellan G, Sale P, Carnevali R, Famularo G: Apoptogenic effect of fentanyl on freshly isolated peripheral blood lymphocytes. J Trauma 2004, 57:75-81.
7. Oppenheim JJ, Yang D: Alarmins: chemotactic activators of immune responses. Curr Opin Immunol 2005, 17:359-365.
8. Klune JR, Dhupar R, Cardinal J, Billiar TR, Tsung A: HMGB1: endogenous danger signaling. Mol Med 2008, 14:476-484.