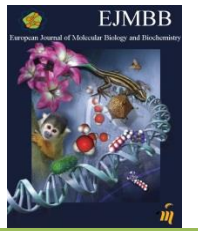
e - ISSN - 2348-2206
Print ISSN - 2348-2192

European Journal of Molecular Biology and Biochemistry

Research article

Journal homepage: www.mcmed.us/journal/ejmbb



EXPLORING THE PATHOGENESIS AND TREATMENT CHALLENGES OF HEMOLYTIC ANEMIA ASSOCIATED WITH GIANT CELL HEPATITIS

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Article Info

Received 03/10/2019
Revised 16/10/2019
Accepted 24/10/2019

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

ABSTRACT

The pathogenesis of hemolytic anemia associated with giant cell hepatitis (GCH) in the context 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.

INTRODUCTION

In particular, persons with giant cell hepatitis without autoimmune hemolytic anemia (AHA) were rare. The pathogenesis and outcome of this disease are unknown [1,2]. A total of 54 cases of this syndrome have been reported in pediatric journals [2-6]. Typically, a sever hepatitis with jaundice, fever, and direct Coombs' test positive occurs about a year after the onset of AHA [3]. In this case, an infant of nine months presented with pallor, fever, and jaundice, and despite early treatment, the outcome was severe.

METHODOLOGY

The 9-month-old infant had jaundice, fever, and watery diarrhea for the past four days. The physical examination of the infant revealed that the infant was eutrophic and febrile (38.3 °C). An enlarged spleen, pallor, and hepatomegaly (liver span of 11 cm) were evident signs of jaundice.

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A bicytopenia (Table 1) was not demonstrated, including nor- mochromic normocytic regenerative anemia and thrombocytopenia, as well as elevated conjugated bilirubin levels and gamma glutamyl transpeptidase levels. The level of beta fetoprotein (AFP) was also very high in this case. The association between febrile jaundice and liver injury led to the suspicion of infectious causes. This study found no antibodies to the hepatitis A, B, and C viruses, the cytomegalovirus, the Epstein Barr virus, the herpes simplex virus, or HIV. A high level of ALP and delta-aminolevulinic acid suggested a metabolic cause, particularly tyrosinemia; however, amino and organic acids chromatographies were normal. A possible autoimmune hepatitis was also considered, but no antibodies against mitochondria, LKM1, nuclei, or smooth muscle were detected. A blood test showed high immunoglobulin G (IgG) levels and low complement levels. Immunity was normal at the cellular level.

Both urine and blood cultures detected *Escherichia Coli* (*E. Coli*). Intravenous antibiotics were

administered to treat this infection. In an abdominal ultrasonography, the liver was hyperechogenic and enlarged, the spleen was homogenous, the biliary ducts were nondilated, and a hyperechogenic cuff was found surrounding the hepatic pedicle. Jaundice and pallor worsened as the fever persisted. Hemoglobin was 6.8 g/dL on day 10 of hospitalization, while platelets were 6000 elements/mL. The haptoglobin test was negative, and the direct Coombs' test (IgG and C3d) was positive. Study considered GCH due to the fact that hepatic insufficiency was associated with AHA in an infant without autoantibodies. Following blood and platelet transfusions and stabilization of the patient, a liver biopsy was performed. Hepatic cells were diffusely transformed into giant necrotic cells. After receiving an intravenous immunoglobulin course of 1 g/kg per day for 2 days, the patient received azathioprine and prednisone.

Following the start of steroid therapy, the patient's clinical and biological status improved (Table 1). Under the same treatment, the infant was discharged from the hospital on day 30. A 15-day follow-up showed stable biological data. After 60 days, he was hospitalized again for edema, fever, and ascites. There was an infection of the urinary tract caused by multi-resistant E. coli, as well as an insufficiency of the liver (prothrombin time (PT) = 20%) and aggravation of cytolysis (Table 1). Antibiotics were administered intravenously to the patient. Symptomatic measures were taken to treat liver insufficiency. However, the fever persisted, renal failure developed, and liver function deteriorated (PT = 12%). Septic shock caused the baby's death. The follow-up period had lasted three months since 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

Approximately 39% of children with GCH and AHA died as a result of their illness in 1981[4]. It is a rare pathological entity [1, 2]. Pediatric reviews have reported 27 cases [2, 4-6]. During a 28-year period, they described 16 children. This entity's pathogenesis was unknown [1]. AHA and hypergammaglobulinemia have been associated with autoimmune origin [1]. A study [4] found that the 16 patients had an autoimmune origin as evidenced by autoimmune conditions such as type 1 diabetes, thyroiditis, and psoriasis, autoantibodies, thrombocytopenia, improvement with immunosuppressive therapy, and decline with tapering doses. In addition, histologically, there was no evidence of autoimmune hepatitis, as autoantibodies were often absent[2]. There was also a possibility that activated T lymphocytes and Küppfer cells may release cytokines non-controllably [2]. No family or personal history of autoimmune disease was found in the present study; however, steroids and immunosuppressive therapy were initially successful. In most cases, GCH associated with AHA appears between the ages of 2.5 and 24 months [4,5]. In our patient, symptoms appeared at 9 months of age. During the neonatal period, hepatocytes can transform into giant cells as a nonspecific reaction to various aggressions [4]. An infant with hepatitis and a positive Coombs' test should undergo liver biopsy promptly to confirm the diagnosis of GCH [4, 5]. A poor prognosis was often associated with this pathology [7]. Our patient died of septic shock after an early relapse. Among the possible treatments, steroids, aminoglycosides,

intravenous immunoglobulins, mercaptopurine, mycophenolate mofetil, vincristine, plasmapheresis, cyclosporine, cyclophosphamide, tacrolimus, and anti-CD20 (Rituximab®) are possible treatments [1]. For patients with AHA resistant to medical treatment, splenectomy has also been recommended [1, 8]. The three remaining cases had severe presentations due to cyclosporine association [4]. Eight cases with a normalized transaminase level achieved total remission out of 16. Six of the sixteen cases had partial remissions, while the other two had absent remissions [4]. There was a relapse in 11 patients, 10 of whom had AHAs that were resistant to medication. In 2 patients, anti-CD20 therapy was successful, 5/10 patients underwent splenectomy, but only 2 had successful outcomes. Four patients died from severe sepsis and post-transplantation in this series. Twelve other patients are still living, and one has undergone liver transplantation [4]. It is evident that the present series illustrates the severity of this pathology and the difficulty of treating it by illustrating the high rate of relapse and resistance to therapy after relapse. After starting treatment with immunoglobulins intravenously, added prednisone and azathioprine with partial improvement (improving but not normalizing transaminases). It relapsed rapidly (in less than four months) with severe hepatic insufficiency, but not with recurrent hematological disorders. Septic shock was the cause of death for our patient. As a result, GCH associated with AHA is a serious medical condition. If an infant develops hepatitis of unknown origin, a liver biopsy should be performed to confirm the diagnosis. Obtaining total remission with normal transaminases requires early treatment with corticotherapy and immunosuppressive drugs. To prevent relapses that are more resistant to therapy, it is imperative to maintain treatment for as long as possible.

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