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COMBINATION OF STEROID WITH AZATHIOPRINE IN TREATMENT OF GIANT CELL AUTOIMMUNE HEPATITIS*

*Yasemen Eroğlu MD***, *Öznur Düzovalı MD****, *Salih Kavukçu MD*****
*Gülersu İrken MD******, *Benal Büyükgebiz MD*******

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Giant cell hepatitis is a rare disorder after the newborn period. Drugs, autoimmunity, and viruses (lately, paramyxovirus infection) have been implicated in its etiology. Without treatment, liver dysfunction is progressive and fatal. Immunosuppression with steroids and azathioprine has been demonstrated to sustain improvement in the disease. In this report, a one-year-old boy who has giant cell hepatitis with Coombs' positive hemolytic anemia and anti-smooth muscle antibodies is presented, and the course of the disease and the patient's response to treatment with steroid and azathioprine is reviewed. *Key words: giant cell hepatitis, autoimmune hemolytic anemia, steroid and azathioprine therapy.*

Although there is a frequent pattern of liver injury in neonates, giant cell hepatitis (GCH) is uncommon after infancy. Its association with drugs, viruses, and a autoimmunity has been reported previously[1-4]. Most recently, paramyxovirus infection has been implicated in its etiology[5]. Coombs' positive hemolytic anemia may occur concomitantly with GCH, though this is rare in young children[6,7]. GCH is known as a progressive and often fatal disease process. Since the liver disease was assumed to be immune-mediated, a combined immunosuppressive regimen with steroid and azathioprine has been introduced to patients, with sustained improvement in clinical, laboratory and pathological features[6,7].

This report presents a one-year-old boy who has GCH associated with Coombs' positive hemolytic anemia, and reviews the course of this disease under combination treatment of steroid and azathioprine.

Case Report

A one-year-old boy was referred to our clinic for jaundice, hepatosplenomegaly and elevated serum aminotransferases levels. One and a half months prior to his referral, he had upper respiratory tract infection and was treated with

* From the Department of Pediatrics, Dokuz Eylül University Faculty of Medicine, İzmir.
** Assistant Professor of Pediatrics, Dokuz Eylül University Faculty of Medicine.
*** Fellow in Pediatric Hematology, Dokuz Eylül University Faculty of Medicine.
**** Associate Professor of Pediatrics, Dokuz Eylül University Faculty of Medicine.
***** Professor of Pediatrics, Dokuz Eylül University Faculty of Medicine.

trimethoprim-sulfamethoxazole. Otherwise, he had no history of toxin or drug exposure. There was nothing notable in his or his family's past history.

On physical examination, jaundice and mucosal pallor were strikingly apparent. Liver and spleen were palpable without pain 15 cm below the respective costal margins, and were smooth on surface.

On admission, the patient's laboratory findings were as follows: hemoglobin 2.6 g/dl, hematocrit 9%, erythrocyte count 590,000/mm^3, and reticulocyte count 50%. A peripheral blood smear revealed normoblastemia, anisocytosis, polikilocytosis, microspherocytosis and polychromasia. Prothrombin time was 17 seconds (N: 12-15) and activated partial thromboplastin time was 47 seconds (N: 35-45).

Blood chemistry was as follows: total bilirubin 30.5 mg/dl (N: < 1), conjuguted bilirubin 19.6 mg/dl (N: < 0.2), alanine aminotransferase (ALT) 685 U/L (N: < 45), aspartate aminotransferase (AST) 1000 U/L (N: < 55), gamma-glutamyl transferase (GGT) 127 U/L (N. 5-32), alkaline phosphatase (AP) 295 U/L (N: 145-200), total protein 6.7 g/dl (N: 6.1-7.9), albumin 3.5 g/dl (N: 3.9-5), alpha-1-antitrypsin 120 mg/dl (N: 50-200), ceruloplasmin 32 mg/dl (N: 27-47), NH_3 183 µg/dl (N: 20-120), and serum iron 110 µg/dl (N: 50-120). Copper excretion in urine was 96 µg/day (N: < 40).

Direct Coombs' test was strongly positive (IgG+ complement). Glucose-6-phosphate dehydrogenase activity, hemoglobin electrophoresis, serum and urine amino acid chromatography were normal.

Except for an immunoglobulin G antibody to hepatitis A, serologic tests for toxoplasmosis, rubella, cytomegalovirus, human immunodeficiency virus, and hepatitis A, B and C viruses were all negative.

C-reactive protein, rheumatoid factor, antinuclear antibody, antimitochondrial antibody, double-stranded DNA antibody, and anti-liver and kidney microsomal antibody were not detected. Serum C3 was 284 mg/dl (N: 80-150) and C4 was 27 mg/dl (N: 20-50). Test for anti-smooth muscle antibody was positive.

Abdominal ultrasonography was normal except for diffuse hepatosplenomegaly. Splenic vein diameter was 5.2 mm. There was no abnormality in the extrahepatic biliary system. Erythroid hyperplasia was prominent in bone marrow examination.

Prednisolone therapy (2 mg/kg/day) was initiated. Multiple transfusions were required due to severe hemolytic disease. Despite conventional steroid therapy, multiple hemolytic relapses were observed. On the 34^{th} day of admission, high dose methyl prednisolone (MP) was introduced. It was started at a dose of 30 mg/kg/day intravenously for the first three days, reduced to 20 mg/kg for five days, 10 mg/kg for one week and 5 finally to mg/kg/day. With this regimen, hemolysis was kept partially under control, and slight improvements in serum aminotransferases levels were observed. On several occasions, ofter tapering the steroid dosage, a relapse of hemolysis and hepatic disease followed, and the MP dose had to be increased again until remission was achieved.

In the second month of MP therapy, the patient had an encephalopathic episode with seizures. Arterial hypertension was detected (150/110 mmHg). Infectious and metabolic investigations, cerebrospinal fluid study and cerebral computed tomography were all negative. Steroid dose adjustments were made. The patient responded well to antihypertensive and anticonvulsant medication. No recurrence was observed during the rest of disease.

Because of the dependence on high dose MP, azathioprine (2 mg/kg/day) was added to the therapy on the 160th day of admission. Hemolysis could be controlled effectively with this combination and the patient's elevated transaminase levels showed improvement. During the full course of therapy, the direct Coombs' test was negative for only a very brief period. The hemolytic parameters and serum transaminase levels of the patient during the course of disease are shown in Figures 1 to 3.

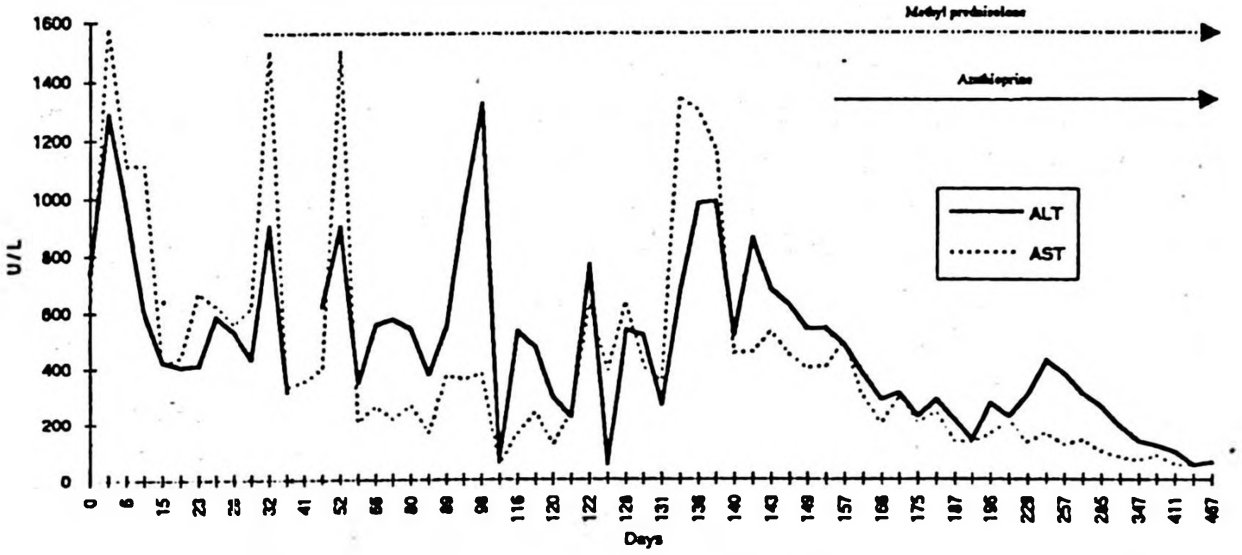
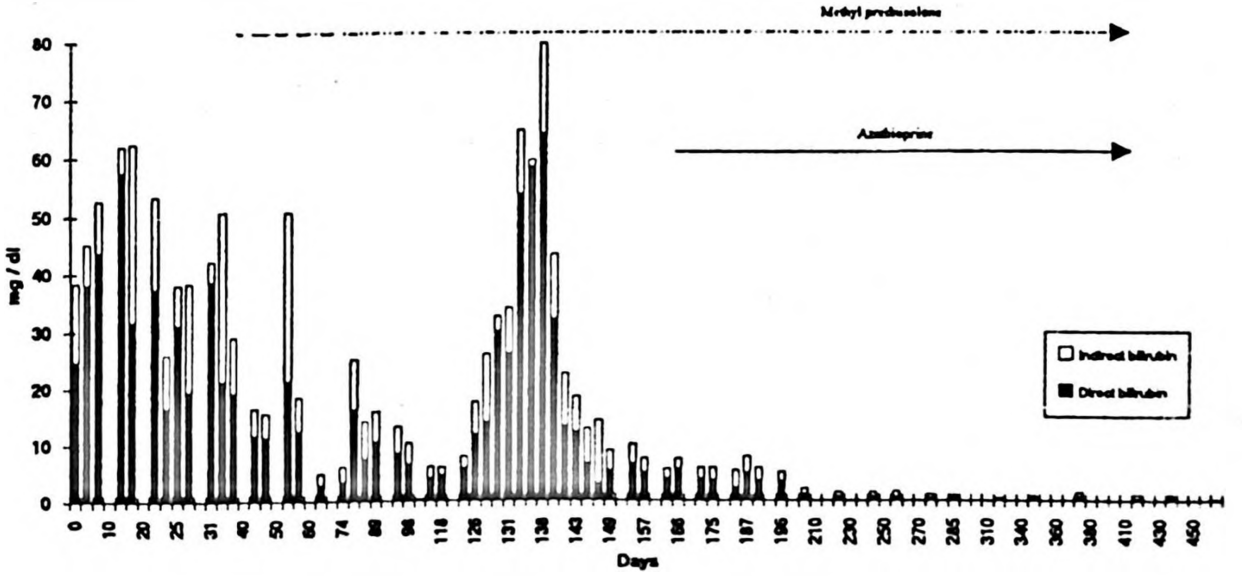
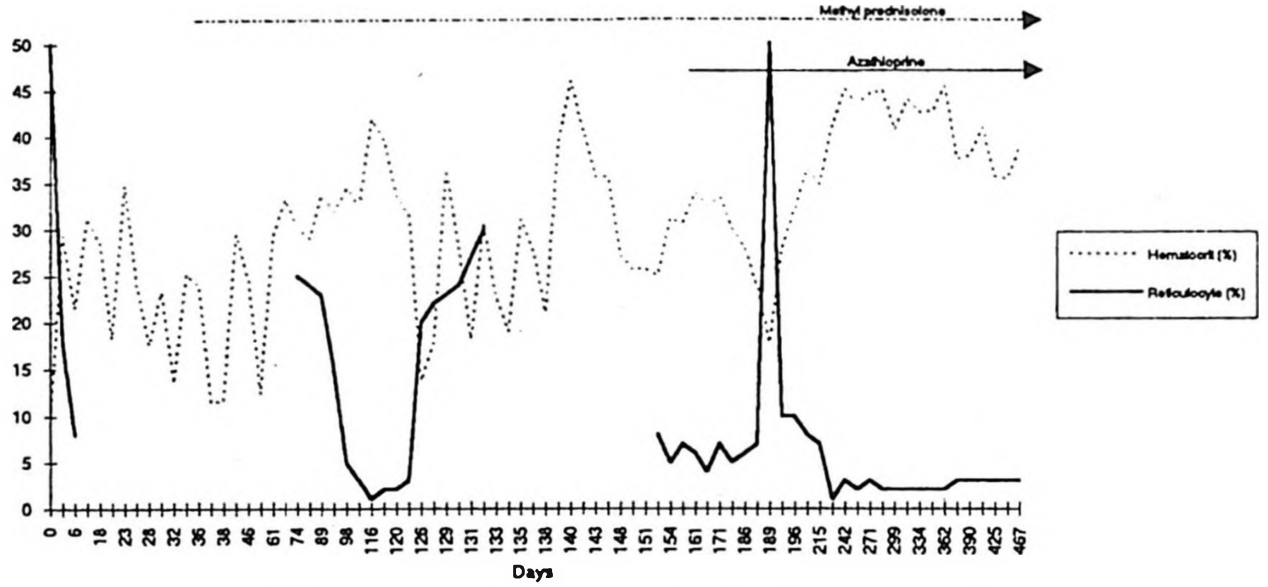


Fig. 1: Serum transaminase levels during follow-up.



Fg. 2: Serum bilirubin levels during follow-up



Fg. 3: Reticulocyte counts and hematocrit values during follow-up.

The addition of azathioprine to the treatment made it possible first to taper and then to terminate MP therapy in the 16th month of admission, without any exacerbation in the hemolytic and hepatic disease. Currently, at two and one-half years, the subject is doing quite well on 1 mg/kg/day azathioprine. He had only mild hepatosplenomegaly. His latest hemoglobin was 12.4 g/dl, Htc 35%, reticulocyte 3.6%, AST 54 U/L, ALT 33 U/L, AP 439 U/L, GGT 65 U/L, prothrombin time was 14.6 seconds and the direct Coombs' test was positive.

During the course of his illness, the patient had two percutaneous liver biopsies. The first biopsy was performed after two weeks of steroid therapy. The sections showed good cores of liver tissue with an apparently preserved, yet slightly distorted achitecture. The parenchyma demonstrated clarification of the cytoplasm of the hepatocytes, with a few multinucleated giant hepatocytes (Fig. 4). Overall,

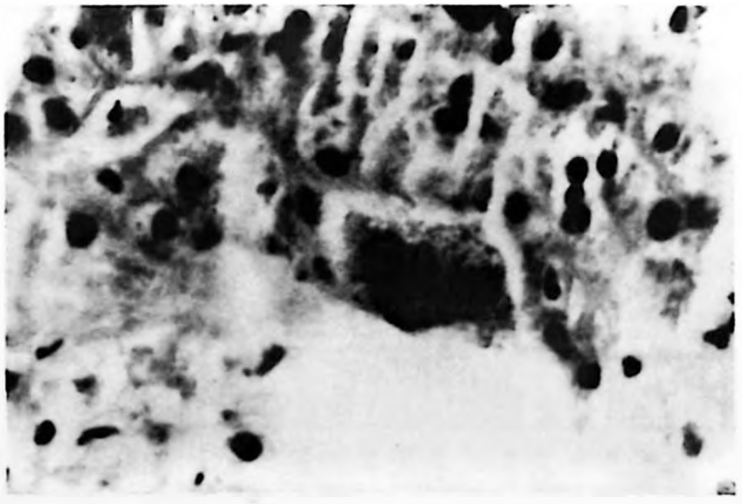


Fig. 4: Multinucleated giant hepatocyte in liver biopsy.

the inflammation was very mild. Iron-pigmented macrophages were present and there was mild to moderate cholestasis with canalicular bile plugs. A second biopsy was taken four and a half months later, while the patient was on MP and azathioprine therapy. The findings were basically similar, but multinucleated giant hepatocytes were more obvious than before and there was a grade I parenchymal siderosis and a more marked and diffuse reticuloendothelial iron load. Though inflammation was, overall, again minimal, the degree of fibrosis appeared to have progressed; the shape of the specimen suggested early parenchymal nodule formation. Liver tissue in both specimens showed GCH, with evidence of focal and bridging parenchymal necrosis.

Discussion

This one-year-old boy had severe and recurrent hemolytic anemia and hepatitis. Extensive investigation for virologic, metabolic and autoimmune causes was made. At first sight, a diagnosis of autoimmune hepatitis could have been considered because of the positive Coombs' test and the presence of anti-smooth muscle antibodies, a finding which was later confirmed. Type I autoimmune hepatitis is usually encountered in young women and associated with the antinuclear antibody and anti-smooth muscle antibody[8]. Type II is more common in children and associated with the anti-liver and kidney microsomal antibody. The very young age of our patient and seronegativity for the antinuclear antibody were not consistent with type I autoimmune hepatitis, while the seronegativity for the anti-liver and kidney microsomal antibody was inconsistent with the type II disease. In autoimmune hepatitis, the histological evaluation of liver tissue is essential, although a specific pathognomonic feature has not been identified. Moderate to severe periportal or periseptal piecemeal necrosis with a predominantly lymphoplasmocytic infiltrate (with or without portal-portal or central-portal bridging necrosis) and lobular hepatitis are more commonly found in autoimmune hepatitis[9, 10]. In our patient, the liver biopsy revealed giant cell hepatitis with focal and bridging necrosis. The minimal inflammatory reaction in both liver specimens was considered to be related to the steroid therapy. A lymphoplasmocytic infiltrate typical for autoimmune hepatitis was not identified. The liver histology together with the positive Combs' test and anti-smooth muscle antibodies in our patient led to the diagnosis of giant cell autoimmune hepatitis (GCAH).

GCH is a morphologic variant of a nonspecific expression of hepatocellular injury characterized by multinucleated giant hepatocytes. Drugs[1], sickle cell disease[11], hypoparathyroidism[12], hepatitis B virus[2], human immunodeficiency virus[3] and paramyxovirus infection[5] have been reported to be associated with the disease beyond the neonatal period. Autoimmune etiology has been implicated in 40% of the cases with giant cell hepatitis[4, 13]. In this subgroup

of the disease, elevated globulin levels, antinuclear antibodies, antimitochondrial antibodies, anti-smooth muscle antibodies, a positive direct Coombs' test, and circulating lupus anticoagulant have been noted[13, 14]. Our patient had both a positive Coombs' and seropositivity for the anti-smooth muscle antibody, indicating the autoimmune nature of GCH.

Steroid drugs have been used in the past with particular success in the treatment of GCAH. At present, a combination of steroid with azathioprine is the common treatment[7]. Usually, response to therapy is rapid and prolonged, though unresponsive fatal relapses have occurred when the drugs are tapered[6, 7, 13, 14]. During the clinical management, our patient's recurrent and severe hemolytic disease was more troublesome than his liver disease. There was no response to conventional steroid therapy, nor was the high dose MP treatment successful. With the addition of azathioprine, remission first in the hemolytic and then in the hepatic disease was achieved and sustained, so that weaning from the high dose steroid regimen was possible. The second liver biopsy of our patient, taken shortly after azathioprine had been started, demonstrated that histological findings were basically the same, but the degree of fibrosis had, in part, progressed. This might have been due to the partial therapeutic effect of high dose MP. Since a third biopsy had not been taken at the writing of this report, the complete effect of azathioprine on liver histology is not known.

Brichard et al.[7] described a progressive fatal encephalopathy with seizures in one of their patients, with no deterioration in the hematologic and hepatic diseases. The etiology remained unknown in spite of extensive investigations, including a brain biopsy. The encephalopathy was not an indication of brain involvement of an autoimmune multi-system process. During the high dose MP therapy, we observed a brief encephalopathic state with seizures in our patient. Hypertension, as the primary cause of encephalopathy, was probably steroid-induced. The patient responded well to medication. The neurological symptoms in these patients need further confirmation and should be carefully followed in other cases.

In conclusion, GCH is a descriptive pathologic diagnosis. After recognition, evidence should be searched for indication of viral and autoimmune disease. Idiopathic cases need to be looked at also for as-yet-unrecognized causes, since new etiologies and associated conditions are likely. Patients with autoimmune hemolytic anemia should also be examined for signs of liver disease. If present, a liver biopsy should follow, with investigation for other autoimmune markers. Since GCAH is a progressive and fatal hepatic disease, therapy with immunosuppressive drugs, preferably a combination of azathioprine and steroids, should be started as soon as possible.

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