

Giant cell hepatitis and autoimmune hemolytic anemia after chickenpox

Suçiçeği sonrası otoimmün hemolitik anemi ve dev hücreli hepatit

Maşallah BARAN¹, Funda ÖZGENÇ¹, Ömer BERK¹, Demir GÖKÇE², Kaan KAVAKLI³, Funda YILMAZ⁴, Sait ŞEN⁴, Raşit Vural YAĞCI¹

Departments of, ¹Pediatric Gastroenterology, Hepatology and Nutrition, ³Pediatric Hematology, ⁴Pathology, Ege University School of Medicine, İzmir

Department of ²Pediatric's, Dr. Behcet Uz Children Health and Disease Hospital, İzmir

Autoimmune hemolytic anemia with giant cell hepatitis is a distinct entity in children. It is usually fatal with progressive liver disease. Immunosuppressive treatment with conventional drugs offers some response; however, it is usually only temporary. Alternative therapeutic options with monoclonals have been reported with promising remission of the disease. We report a case with autoimmune hemolytic anemia+giant cell hepatitis after varicella infection. She was resistant to standard immunosuppressive combinations, and rescue therapy with rituximab was used. Remission was not achieved with the drug and the child died with septic complication.

Key words: Giant cell hepatitis, autoimmune hemolytic anemia, rituximab

Otoimmün hemolitik anemi ile dev hücreli hepatit çocuklarda ayrı bir klinik tablodur. Bu hastalık genellikle ilerleyici karaciğer hastalığı ile ölümcül seyredir. Geleneksel ilaçlarla yapılan immünsüpresif tedaviye kısmi yanıt sağlar, bununla beraber bu yanıt genellikle geçicidir. Monoklonal antikorlar ile yapılan alternatif tedavi sonrası hastalığın remisyonu rapor edilmiştir. Biz suçiçeği enfeksiyonu sonrası otoimmün hemolitik anemi ve dev hücreli hepatit tanısı alan, standart immünsüpresif ve rituksimab tedavisine dirençli bir kız hastayı rapor ediyoruz. Bu çocuk hastada tedaviye rağmen remisyona sağlanamadı ve septik komplikasyondan hasta kaybedildi.

Anahtar kelimeler: Dev hücreli hepatit, otoimmün hemolitik anemi, rituksimab

INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is an acute, self-limited childhood disease with good response to treatment. However, on very rare occasions, it is accompanied by giant cell hepatitis (GCH), which is progressive and often fatal (1,2). Giant cell transformation of the liver is commonly seen during the neonatal and early infantile periods, and it is described in association with autoimmune disorders, drug reactions and viral infections (3,4). Coombs-positive hemolytic anemia supports the autoimmune pathogenesis of AIHA with GCH entity, and treatment with immunosuppressive drugs may offer beneficial effects and resolution of both diseases (5). Resistance to immunosuppressant treatment and treatment-associated complications such as infections are the problems frequently faced in the management of these patients, and liver transplantation is one of the options

that has to be considered in those patients unresponsive to immunosuppressants (6,7). We report an infant with GCH and AIHA who failed to respond to treatment and died after a trial of CD20 monoclonal antibody (rituximab).

CASE REPORT

A three-month-old infant was first admitted to a local hospital with vesicular skin lesions and loss of appetite. Her physical evaluation with a history of chickenpox-infected brothers at home guided the diagnosis of varicella infection. The mother could not clearly define her past vesicular infection or vaccination. Paleness and scleral jaundice were observed on the patient's second visit, and she was hospitalized with suspected infectious or post-infectious complications of the viral disease. Labora-

tory analyses revealed Coombs-positive hemolytic anemia and elevated liver enzymes. Antiviral therapy with acyclovir was started during the active disease with skin rash. She required red blood cell (RBC) transfusions and fresh frozen plasma (FFP) for emerging hemorrhagic diathesis. AIHA was diagnosed and intravenous immunoglobulin (IVIG) was used to suppress the autoimmune process. Soon after the skin lesions regressed, methylprednisolone was started (30 mg/kg); however, autoimmune hemolysis and RBC requirement persisted, and she was referred to our clinic for progressing hepatitis and hepatic synthetic failure.

Distended abdomen and liver palpable 6 cm below the costal margin at the mid-clavicular area were noted on examination, and laboratory evaluation revealed marked anemia (6.2 g/dl) with reticulocytosis (15%). Her initial alanine and aspartate aminotransferases, total bilirubin levels and international normalized ratio (INR) were 800 IU/L, 1200 IU/L, 59 mg/dl and 1.2, respectively. As there was ample evidence of hepatitis, diagnosis focused on the etiology. The viral serology was found negative, including hepatotropic viruses and human immunodeficiency virus (HIV); inborn errors of metabolism were ruled out by extensive metabolic work-up. Autoimmune antibodies (ANA, AMA, LKM, ASMA) were negative, and plasma alpha 1 antitrypsin levels were within normal limits. Portal vein Doppler ultrasonography (USG) showed hepatomegaly with normal parenchyma and normal blood flow. Liver biopsy illustrated multinuclear GCH, and the diagnosis of GCH with AIHA was established based on clinical, biochemical and histopathological findings.

The immune suppressive therapy was started with prednisolone 2 mg/kg and she was also supplemented with choleretic ursodeoxycholic acid (UDCA) and vitamins. Red cell consumption and elevation of liver enzymes persisted, so vincristine (1 mg/m², every week) and cyclosporin (CSA, 2 mg/kg/day) were added to the therapy (Figure 1). Evaluation after the second vincristine cycle documented pancytopenia. Drug toxicity-related bone marrow suppression was suspected, and it was successfully managed after cessation of vincristine. The CSA dosage was adjusted and sustained in normal therapeutic ranges according to blood levels (2-12 mg/kg/d); however, the patient experienced hypertension, which was treated with anti-hypertensive treatment. Cardiac and renal toxic side effects of CSA were also monitored by regular renal function tests and echocardiography. Adequate clinical and biochemical response could not be obtained with different immunosuppressive combinations and in time, she experienced side effects like bloodstream infections and obesity. Alternative immunosuppressive therapies were debated due to lack of response. Liver transplantation was not decided at first because recurrence of the disease in the transplanted liver is high, and AIHA persists unrelated to the liver disease. After the commitment of the local ethical committee and with written consent of the family, rituximab (375 mg/m², once a week) was started with a treatment plan of four weeks. Biological efficacy of rituximab was demonstrated by slope-down of pre- and post-treatment CD20 lymphocyte counts; however, only partial clinical and biochemical response could be assessed (Figure 1). She was being followed-up,

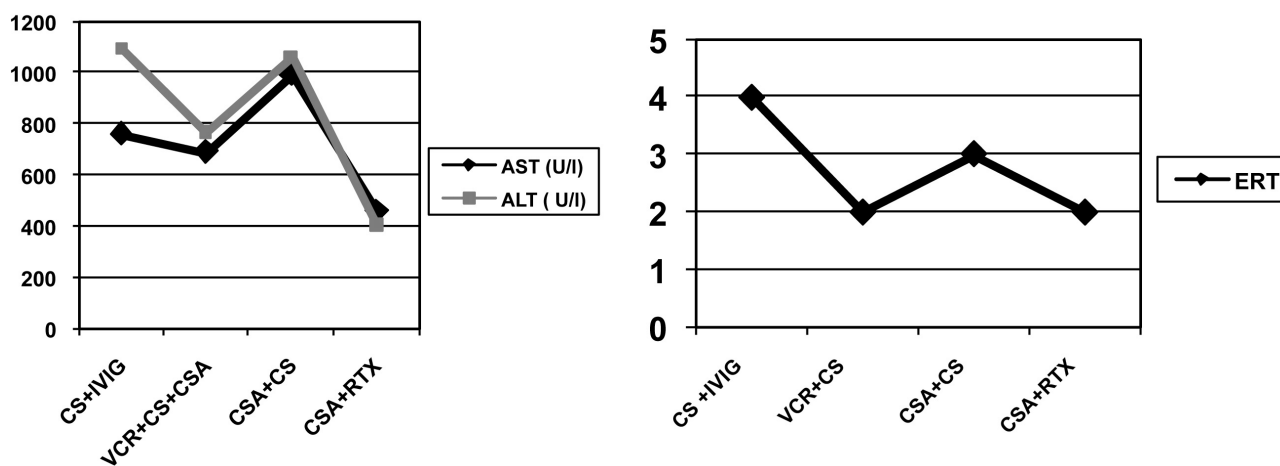


Figure 1. Course of hepatic tests and transfusion requirement vs. treatment over time (CS: Corticosteroid, IVIG: Intravenous immunoglobulin, CSA: Cyclosporin A, RTX: Rituximab).

transfused and medicated during outpatient visits when she presented with fever, anuria and dehydration. Bacterial sepsis was demonstrated with accompanying acute renal failure (urea: 153 mg/dl, creatinine: 5.4 mg/dl) with high cyclosporin level (CSA, 593 mcg/dl). Peritoneal dialysis was attempted with large spectrum antibiotics in the intensive care setting. The child died due to septic shock and adult-type respiratory distress syndrome (ARDS) on the 10th day of follow-up. Submassive necrosis and fibrosis were demonstrated in the autopsy liver specimen (Figure 2a, 2b). Autopsy specimen from the kidney revealed interstitial focal microcalcification and cellular vacuolization in the tubular epithelium, which was attributed to exogenous toxic insult, especially CSA (Figure 2c).

DISCUSSION

The combination of AIHA with GCH is a rare distinct entity with poor prognosis. GCH is commonly described in infants and is associated with autoimmune disorders, drug reactions and viral infections (3,4). Although the exact cause of the condition is unknown, HIV, hepatitis C and E and herpes virus are reported to be related with the presumed autoimmune process (3-9). For the current patient, drug reactions and autoimmune diseases were ruled out and post-infectious autoimmune reaction secondary to chickenpox was suspected. Association of varicella infection with AIHA is well established; however, there is only one patient with accompanying hepatitis in the literature (10,11). Moreover, histological confirmation highlighted the nature of the hepatitis in our patient. Although chickenpox is a benign childhood disease, the readers' attention is drawn once more to the rare but serious complications of the infection.

Autoimmune hemolytic anemia (AIHA) is claimed to be a self-limiting illness, unless it presents with early onset or GCH accompanies the clinical picture (12). The pathogenesis of AIHA mainly relies on destruction of RBCs by IgG or IgM type auto antibodies, and GCH is also suspected to arise from immune dysfunction and unrestrained release of cytokines (7). Treatment modalities target effectors of the immune system for both disease processes. Early institution of steroids has been shown to have a beneficial effect on both liver function and hemolytic anemia; however, acute varicella infections defined by eruptions prohibited early and prompt immunosuppressant use in our patient. IVIG was

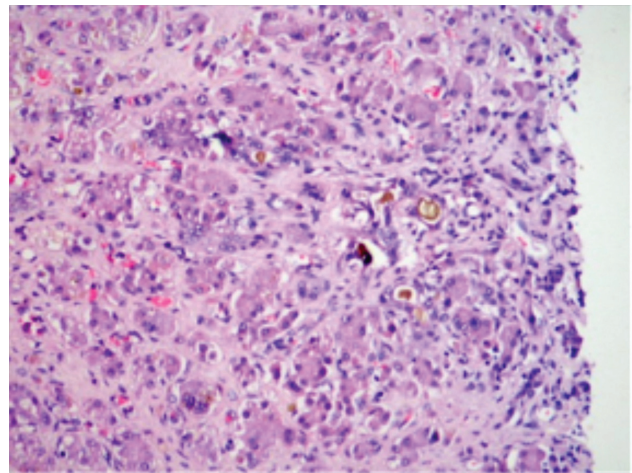


Figure 2a. Autopsy specimen of the liver. Hepatocytes had been lost and replaced by fibrosis. Hepatocyte rosettes and cholestasis were established (HE X400).

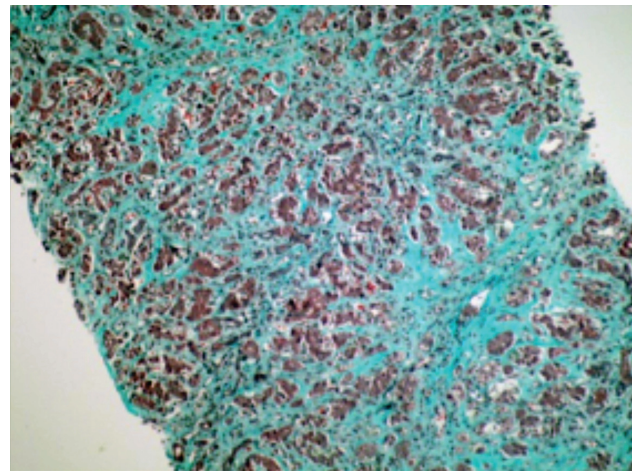


Figure 2b. Autopsy specimen of the liver. The striking fibrosis and submassive hepatocellular loss are prominent (Masson's trichrome X100).

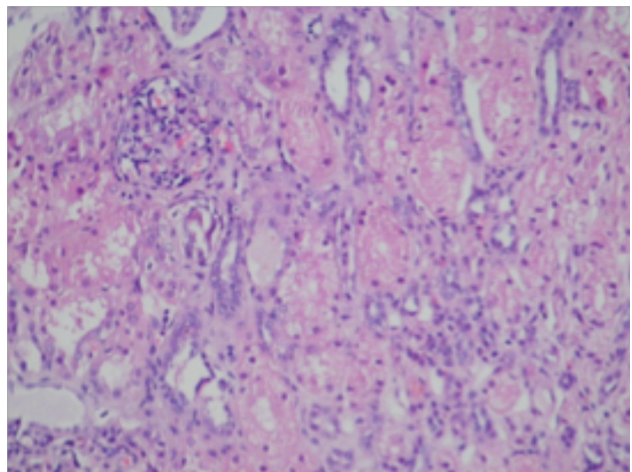


Figure 2c. Autopsy specimen of the kidney. Interstitial focal microcalcification and cellular vacuolization in the tubular epithelium are shown (HE X100).

preferred, and after the skin lesions regressed, immunosuppressives were started in the second month from the initial presentation of hemolysis and hepatitis. The patient received conventional immunosuppressive drug combinations due to lack of adequate response. Since the clinical progression of a refractory GCH is aggressive and fatal, the child was considered eligible for innovative therapies. Liver transplantation was not taken into consideration, because disease recurrence has occurred in most of the transplanted cases (6,7,13).

Rituximab is an anti-CD 20 monoclonal antibody; it inhibits B cell proliferation and antibody production. It has been successfully used for AIHA (14). Gorelik et al. (2) first used rituximab for refractory AIHA with GCH and documented resolution of hemolysis and hepatitis. Soon after Gorelik's experience, Miloh et al. (14) also tried rituximab as a rescue therapy for decompensated liver disease. The monoclonal was well tolerated without any major side effects in both cases. Transfusion requirement was decreased and suppression of liver enzyme levels was achieved with rituximab in our patient; however, from the aspect of response evaluation, remission was not achieved. The patient was faced with long-term threats of immunosup-

pressants and died due to septic complication. Postmortem evaluation of the liver verified the clinical non-response. Although rituximab is reported to be effective as a rescue therapy for liver disease, non-response in our patient may be attributable to the delayed use of the drug (14). It is well known that early and prompt use of steroids is associated with a better response in cases with OIHA+GCH, and it may also be the same for alternative therapies with monoclonals.

In summary, GCH with AIHA is a rare and distinct entity during infancy. It usually has a fatal outcome with progressive liver disease. Immunosuppressive treatment with conventional drugs offers some response; however, it is usually only temporary. Alternative therapeutic options with monoclonals have been reported with promising remission of the disease. We report a case with post-varicella AIHA+GCH who was resistant to standard immunosuppressive combinations, and response could also not be achieved with rituximab. We conclude that alternative treatments with monoclonals must be taken into consideration in the management of these patients; timing of these therapies may also have an impact on remission induction.

REFERENCES

- Bernard O, Hadchouel M, Scotto J, et al. Severe giant cell hepatitis with autoimmune hemolytic anemia in early childhood. *J Pediatr* 1981; 99: 704-11.
- Gorelik M, Debski R, Frangoul H. Autoimmune hemolytic anemia with giant cell hepatitis: case report and review of the literature. *J Pediatr Hematol Oncol* 2004; 26: 837-9.
- Moreno A, Moreno A, Pérez-Elías MJ, et al. Syncytial giant cell hepatitis in human immunodeficiency virus-infected patients with chronic hepatitis C: 2 cases and review of the literature. *Hum Pathol* 2006; 37: 1344-9.
- Devaney K, Goodman ZD, Ishak KG. Postinfantile giant-cell transformation in hepatitis. *Hepatology* 1992; 16: 327-33.
- Vajro P, Migliaro F, Ruggeri C, et al. Life saving cyclophosphamide treatment in a girl with giant cell hepatitis and autoimmune haemolytic anaemia: case report and up-to-date on therapeutical options. *Dig Liver Dis* 2006; 38: 846-50.
- Akyildiz M, Karasu Z, Arıkan C, et al. Successful liver transplantation for giant cell hepatitis and Coombs-positive hemolytic anemia: a case report. *Pediatr Transplant* 2005; 9: 630-3.
- Melendez HV, Rela M, Baker AJ, et al. Liver transplant for giant cell hepatitis with autoimmune haemolytic anaemia. *Arch Dis Child* 1997; 77: 249-51.
- Harmanci O, Onal IK, Ersoy O, et al. Postinfantile giant cell hepatitis due to hepatitis E virus along with the presence of autoantibodies. *Dig Dis Sci* 2007; 52: 3521-3.
- Domati-Saad R, Dawson DB, Margraf LR, et al. Cytomegalovirus and human herpesvirus 6, but not human papillomavirus, are present in neonatal giant cell hepatitis and extrahepatic biliary atresia. *Pediatr Dev Pathol* 2000; 3: 367-73.
- Terada K, Tanaka H, Mori R, et al. Hemolytic anemia associated with cold agglutinin during chickenpox and a review of the literature. *J Pediatr Hematol Oncol* 1998; 20: 149-51.
- Apak H, Karaman S, Doğan Y, et al. Varicella-induced hemolytic anemia with hepatitis. *Ann Hematol* 2006; 85: 64-5.
- Gehrs BC, Friedberg RC. Autoimmune hemolytic anemia. *Am J Hematol* 2002; 69: 258-71.
- Pappo O, Yunis E, Jordan JA, et al. Recurrent and de novo giant cell hepatitis after orthotopic liver transplantation. *Am J Surg Pathol* 1994; 18: 804-13.
- Miloh T, Manwani D, Morotti R, et al. Giant cell hepatitis and autoimmune hemolytic anemia successfully treated with rituximab. *J Pediatr Gastroenterol Nutr* 2007; 44: 634-6.