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Giant Cell Hepatitis and Immune Thrombocytopenic Purpura: Reversal of Liver Failure With Rituximab Therapy

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Giant cell hepatitis (GCH) associated with autoimmune hemolytic anemia (AHA), GCH-AHA, can be difficult to treat, often requiring intense immunosuppression (1,2). Liver transplantation for GCH-AIH can be problematic due to recurrent disease. Some patients have achieved remission with rituximab when they have been resistant to conventional immunosuppression (3).

We describe the first reported case, to our knowledge, of GCH and immune thrombocytopenic purpura (ITP). The patient's liver disease was resistant to steroids but was successfully treated with rituximab. Additionally, the liver tissue stained intensely for membrane attack complex, lending new insight into a potential complement-mediated mechanism of action by which liver injury occurs.

The patient presented at 2 months of age with petechiae and a platelet count of 13,000/ μ L. He was born full term after an uncomplicated pregnancy, labor, and delivery. Newborn complete blood count, drawn for maternal positivity for group B streptococcus, revealed a platelet count of 315,000/ μ L. White blood cell count and hemoglobin were normal; reticulocyte count was slightly elevated at 3.8%. Direct Coombs was weakly positive with 1 + immunoglobulin G. Lactate dehydrogenase was 420 IU/L, aspartate aminotransferase (AST) was 64 IU/L, alanine amino-transferase (ALT) was 54 IU/L, and total bilirubin was 0.9 g/dL (Table 1). Maternal blood counts at the time of initial evaluation were normal. When platelet counts fell into single digits and did not recover after 2 weeks, he was treated with intravenous immunoglobulin for presumed ITP; however, platelets did not improve. Bone marrow evaluation revealed numerous megakaryocytes, normal trilineage hematopoiesis, normal cellularity, normal cytogenetics, and negative in situ hybridization screening for myelodysplastic syndrome. Corticosteroids were begun at 2 mg $\cdot$ kg⁻¹ $\cdot$ day⁻¹,

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and after 2 weeks of treatment, his platelet count improved supporting the diagnosis of immune-mediated platelet destruction. During the ensuing 2 months, his platelets normalized and corticosteroids were tapered to $<0.2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$, although at the lowest dose of his taper, his platelet count fell between 40 and 100,000/mL.

At this time (7 months of age), he became febrile and jaundiced. AST and ALT were 3329 and 3929 IU/mL, respectively; total and direct bilirubin were 5.9 and 4.0 mg/dL, respectively. White blood cell count was 20,200/ μL , hemoglobin was 11.1 g/dL, and platelet count was 99,000/ μL . Coagulation studies were normal. Liver biopsy revealed moderate to severe hepatitis with extensive giant cell transformation, along with focal septal bridging and sinusoidal fibrosis. Anti-smooth muscle antibody was positive at 1:20. Total immunoglobulin G was 707 mg/dL (normal 214–704).

He was presumptively diagnosed as having auto-immune hepatitis, and his corticosteroid dose was increased to $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$. Transaminases steadily declined, although during the subsequent taper, his liver disease worsened: AST 264 to 515, ALT 579 to 1050, and total/direct bilirubin 1.9/1.2 to 2.3/1.7. Intravenous corticosteroids were reinstituted, but liver biochemistries continued to worsen. He developed systemic hypertension, requiring treatment with enalapril, and had linear growth failure, attributed to long-term corticosteroid use. He had coagulopathy with a peak international normalized ratio of 2.1.

He was referred for evaluation for liver transplantation. Before transplant, the decision was made to use rituximab (anti-CD20 antibody), on the presumption that the pathophysiology of his disease was akin to GCH-AHA. He received 4 weekly doses of 375 mg/m^2 , which were well tolerated. Liver biochemistries improved after the first dose. Corticosteroids were tapered, and enalapril was weaned. Azathioprine was started with normal red blood cell thiopurine methyltransferase levels.

During the next few months, liver biochemistries improved dramatically, although transaminases did not normalize. Bilirubin, coagulation studies, comprehensive metabolic panel, and complete blood cell count remained within normal limits. He was started on $1.25 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ of azathioprine, and a subsequent 6-thioguanine level was 38 $\text{pmol}/8 \times 10^8$ RBCs. In light of difficulties attaining therapeutic levels of 6-thioguanine in young children, mycophenolate was used (initial dose $40 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) (4). At 15 months of age, his steroid dose is $0.4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$. He is no longer receiving enalapril. His height, although still below the third percentile, has steadily improved.

Liver tissue underwent immunohistochemical staining with the terminal complement cascade neoantigen, anti-human C5b-9 complex, which is formed in the assembly of the membrane attack complex during complement-mediated cell injury (5). The hepatocytes had intensely positive staining with appropriately negative control stains. This suggests a complement-mediated mechanism of hepatocyte injury in this patient with GCH (Fig. 1).

DISCUSSION

GCH-AHA is a rare and serious disorder that may lead to liver failure and can recur after liver transplantation. Rituximab has been successfully used as a means of avoiding the need

for liver transplantation. In the present case, a different but presumably similar immune-mediated process occurred. ITP, as opposed to AHA, was followed by the development of GCH. Many patients with ITP respond to corticosteroid and intravenous immunoglobulin therapy; those with refractory disease require escalated immunosuppression including rituximab (6).

In the present case, hepatocytes stained intensely with the terminal complement cascade neoantigen, indicating the formation of membrane attack complex, which leads to cell lysis. This pattern of staining has been observed in neonatal alloimmune liver disease, often referred to as neonatal hemochromatosis, and is not observed in normal liver or GCH due to metabolic disease (5). Minimal staining may be observed in severe acute viral hepatitis (7). Complement-mediated cell destruction has been detected in a variety of infectious and immune-mediated etiologies of liver disease. Although complement may be activated by alternative pathways, an antibody-mediated mechanism is highly likely in this patient.

This patient's liver disease was refractory to corticosteroid treatment. In addition, he developed significant corticosteroid-related adverse effects, including growth retardation and systemic hypertension. Given the natural history of recurrence of liver disease posttransplant in patients with GCH-AHA, we presumed a similar risk in this patient. Because rituximab has been successfully used in both ITP and GCH, independently its use was reasonable in an effort to reduce corticosteroid exposure and avoid liver transplantation. Rituximab, a CD20 monoclonal antibody, is thought to work predominantly by removing B cells, which are the only cells known to express CD20 and are the source of autoantibody production (8). Rituximab may also improve the function of abnormal T regulatory cells. Although there are potential adverse effects, namely, increased risk of infection, most patients tolerate rituximab well, and its use is being investigated in a number of autoimmune disorders.

Thrombocytopenia has been reported in a patient with both GCH and AHA (2). This patient appears to be the first who initially present with ITP and then develop GCH. Given the overlap of hepatic involvement with autoimmune hematologic disorders, infants with ITP should have their liver function monitored. Therapeutic approaches used in the treatment of GCH and AHA may be applicable to GCH in the setting of ITP.

References

1. Raj S, Stephen T, Debski RF. Giant cell hepatitis with autoimmune hemolytic anemia: a case report and review of pediatric literature. *Clin Pediatr (Phila)*. 2011; 50:357–9. [PubMed: 21436150]
2. Maggiore G, Sciveres M, Fabre M, et al. Giant cell hepatitis with autoimmune hemolytic anemia in early childhood: long-term outcome in 16 children. *J Pediatr*. 2011; 159:127–132. e1. [PubMed: 21349541]
3. Miloh T, Manwani D, Morotti R, et al. Giant cell hepatitis and auto-immune hemolytic anemia successfully treated with rituximab. *J Pediatr Gastroenterol Nutr*. 2007; 44:634–6. [PubMed: 17460499]
4. Rumbo C, Shneider BL, Emre SH. Utility of azathioprine metabolite measurements in post-transplant recurrent autoimmune and immune-mediated hepatitis. *Pediatr Transplant*. 2004; 8:571–5. [PubMed: 15598326]
5. Pan X, Kelly S, Melin-Aldana H, et al. Novel mechanism of fetal hepatocyte injury in congenital alloimmune hepatitis involves the terminal complement cascade. *Hepatology*. 2010; 51:2061–8. [PubMed: 20512994]

6. Bredlau AL, Semple JW, Segel GB. Management of immune thrombocytopenic purpura in children: potential role of novel agents. *Paediatr Drugs*. 2011; 13:213–23. [PubMed: 21692546]
7. Whittington PF, Pan X, Kelly S, et al. Gestational alloimmune liver disease in cases of fetal death. *J Pediatr*. 2011; 159:612–6. [PubMed: 21592512]
8. Weiner GJ. Rituximab: mechanism of action. *Semin Hematol*. 2010; 47:115–23. [PubMed: 20350658]

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FIGURE 1.

Liver biopsy with immunohistochemical staining for C5b-9 complex. The image demonstrates numerous multinucleate giant cells with various degrees of positive staining for C5b-9 (warm brown color). All of the hepatocytes in the specimen showed some degree of positive staining. The insert shows the same field with isotype control primary antibody; with this treatment, no positive staining was seen in the entire specimen. Both images were photographed at an initial magnification of $\times 400$.

TABLE 1

Clinical course

Age, mo	Wt (z score)	Ht (z score)	Platelet count, cells/mm ³	Alb	T/D bili, mg/dL	ALT, IU/L	INR	Treatment
2	0.8	-0.8	4000	3.9	0.9/ND	54	ND	IVIG red 2 mg/kg
4	-0.2	-1.2	109,000	ND	ND	ND	ND	Pred 1.5 mg/kg
5	-0.6	-1.5	314,000	ND	ND	ND	ND	Pred 0.4 mg/kg
6	-1.0	-1.7	100,000	ND	ND	ND	ND	Pred 0.2 mg/kg
7	-1.5	-2.1	99,000	3.1	5.9/4.0	3929	1.0	Pred 2 mg/kg
8	-1.5	-3.1	137,000	2.0	4.8/3.0	1598	2.2	Rituximab 135 mg/dose #1, Pred 2 mg · kg ⁻¹ · day ⁻¹
8	ND	ND	102,000	2.3	6.6/4.1	1041	2.0	Rituximab 135 mg/dose #2, Pred 2 mg · kg ⁻¹ · day ⁻¹
9	-1.5	-3.4	181,000	2.4	7.7/5.0	961	2.1	Rituximab 135 mg/dose #3, Pred 2 mg · kg ⁻¹ · day ⁻¹
9	ND	ND	217,000	2.4	7.2/4.1	856	2.1	Rituximab 135 mg/dose #4, Pred 2 mg · kg ⁻¹ · day ⁻¹
10	-1.9	-3.9	375,000	3.5	1.7/1.2	127	1.1	Azathioprine 10 mg/day, Pred 1.5 mg · kg ⁻¹ · day ⁻¹
11	-2.1	-3.9	421,000	3.7	0.9/0.6	82	1.0	Azathioprine 15 mg/day, Pred 0.7 mg · kg ⁻¹ · day ⁻¹
12	ND	ND	428,000	3.7	0.3/0.1	121	0.9	Azathioprine 15 mg/day, Pred 0.7 mg · kg ⁻¹ · day ⁻¹
13	ND	ND	393,000	3.6	0.3/0.1	110	0.9	Mycophenylate 40 mg · kg ⁻¹ · day ⁻¹ , Pred 0.5 mg · kg ⁻¹ · day ⁻¹
15	-1.5	-2.8	388,000	ND	0.3/ND	105	0.9	Mycophenylate 40 mg · kg ⁻¹ · day ⁻¹ , Pred 0.4 mg · kg ⁻¹ · day ⁻¹

Alb = albumin; ALT = alanine aminotransferase; Ht = height; INR = international normalized ratio; IVIG = intravenous immunoglobulin; ND = not done; Pred = prednisone; T/D bili = total/direct bilirubin; Wt = weight.