

CD40 Ligand Deficiency With Grade III Liver Fibrosis, Transplanted by a Treosulphan-based Conditioning Regimen

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Abstract

X-linked Hyper IgM is characterized by an absence of the CD40 ligand on activated T lymphocytes resulting in defects of both cellular and humoral immunity. Patients usually present with recurrent bacterial and opportunistic infections. Chronic liver disease is seen in about 75% of patients as a complication. Here, we report a 3.5-year-old boy with X-linked Hyper IgM referred to our clinic for bone marrow transplant. He was transplanted from an HLA-identical sibling donor using a new conditioning agent, treosulphan, together with cyclophosphamide. Since 6 months of age, he has had recurrent respiratory infections, and his XHIGM was diagnosed when he was 1.5 years old. The diagnosis was confirmed by sequence analysis of the CD40L gene. On physical examination, growth failure, bilateral fine crackles in both lungs, and hepatosplenomegaly were detected. The results of his liver function tests were abnormal, and a liver biopsy showed grade III fibrosis and compensated cirrhosis. After conditioning with treosulphan (12 g/m²/d × 3 d) and cyclophosphamide (50 mg/kg/d × 4 d), bone marrow from his HLA-identical sister was infused. CD40L expression on activated lymphocytes of the patient was 84% on day +21. His posttransplant period was uneventful. He is now at posttransplant 2 years, with full donor chimerism, and mild, chronic, graft-versus-host disease on his tongue. In conclusion, treosulphan is

a new agent for conditioning regimen with less toxicity in patients with severe liver disease.

Key words: Bone marrow transplantation, CD40 Ligand deficiency

Introduction

X-linked Hyper IgM (XHIGM), also known as *Hyper IgM syndrome type I (HIGM1)*, is a rare, primary immunodeficiency disease characterized by severe defects of both cellular and humoral immunity owing to impaired expression of the CD40 ligand on activated T lymphocytes.¹ Patients with XHIGM usually present within the first 2 years of life with severe and recurrent pyogenic bacterial infections. They are also prone to opportunistic microorganisms such as *Pneumocystis jiroveci*, *Histoplasma Capsulatum*, and *Cryptosporidium Parvum*.² *C parvum* causes persistent diarrhea and is associated with sclerosing cholangitis, and liver cancer.^{1, 3} Other complications include neutropenia, autoimmune diseases, and malignancies. In general, the prognosis of XHIGM is poor, and up to 50% of persons with the disease do not survive beyond the age of 30 years.

The only curative treatment currently available for HIGM1 is allogeneic hematopoietic stem cell transplant, ideally before the onset of life-threatening complications and organ damage.³ Here, we report a successful bone marrow transplant from an HLA-identical sibling donor using a new conditioning agent, treosulphan, together with cyclophosphamide, in a 3.5-year-old XHIGM child with liver cirrhosis.

Case Report

The patient was the third child of consanguineous parents with no family history of immunodeficiency.

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Since 6 months of age, he had recurrent upper and lower airway disease and oral aphthous lesions and was diagnosed with XHIGM when he was 1.5 years old. The diagnosis of XHIGM was confirmed by sequence analysis of CD40L gene showing a hemizygous deletion of a C nucleotide in exon 5, which results in a frameshift and a premature stop codon.

He was referred to our clinic when he was 3.5 years old for a bone marrow transplant. On physical examination, growth failure, bilateral fine crackles on both lungs, and a 9-cm hepatomegaly and 6-cm splenomegaly were detected. On tomographic evaluation of the thorax, an atelectatic segment was seen on the inferior lobe of left lung. Results of liver enzymes were abnormal, and ultrasonographic evaluation of liver suggested chronic liver disease together with hepatosplenomegaly. Liver biopsy revealed ductal proliferation, chronic cholestasis, increased fibrous tissue in the portal areas with porto-portal bridging, and it was named *grade 3 liver fibrosis* (Figure 1). The pathologic evaluation did not reveal sclerosing cholangitis. In addition, there was

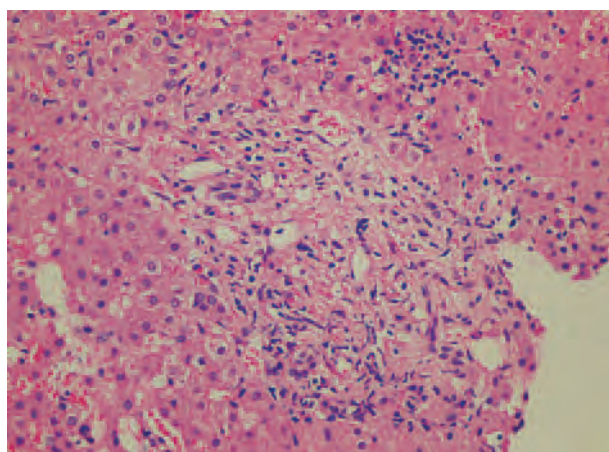


Figure 1. Ductal proliferation, chronic cholestasis, increased fibrous tissue in the portal areas with porto-portal bridging in the liver.

no evidence of cryptosporidial infection (cryptosporidium was negative in the stool repeatedly).

He was treated with ursodeoxycholic acid without notable improvement. After conditioning with treosulphan ($12 \text{ g/m}^2/\text{d} \times 3 \text{ d}$) and cyclophosphamide ($50 \text{ mg/kg/d} \times 4 \text{ d}$), bone marrow ($6.1 \times 10^6/\text{kg}$ CD34 + cells/kg) from his HLA-identical sister was infused. Owing to the high risk of progressive cirrhosis and liver failure, treosulphan was chosen as the conditioning agent instead of busulphan. Cyclosporine was given for graft-versus-host disease prophylaxis for 6 months after the transplant. Myeloid engraftment was achieved on day 13, and CD40L expression on activated lymphocytes was found to be 84% on day 21. No life-threatening infection or other transplant-related organ damage, including mucositis occurred. After the bone marrow transplant, a moderate increase in liver function test results (aspartate aminotransferase, $8 \text{ } \mu\text{kat/L}$ [473 U/L]; alanine aminotransferase, $7.82 \text{ } \mu\text{kat/L}$ [460 U/L]; total bilirubin, $25.6 \text{ } \mu\text{mol/L}$ [1.49 mg/dL]; D. bilirubin, $18.4 \text{ } \mu\text{mol/L}$ [1.07 mg/dL]; gamma glutamyl transferase, $1.61 \text{ } \mu\text{kat/L}$ [95 U/L]) with mild *cytomegalovirus* antigenemia (416 copies/ μL), but these resolved in a short time, and the patient was discharged on day 43.

During follow-up, a lesion on his tongue resembling chronic graft-versus-host disease developed and was treated with topical steroids for 6 months. Intravenous immunoglobulin replacement was stopped when immunoglobulin levels were found to be normal at 1 year. He is now 2 years posttransplant and in good clinical condition. The results of his liver enzyme levels and function tests are summarized in Table 1. His hepatosplenomegaly was continued, ultrasonographic evaluation revealed

Table 1. Levels of liver enzymes and liver function tests.

	Before HSCT	Day 0	+Day 10	+Day 20	+Day 27	+Day 35	+Day 42	+Month 6	+Month 12	+Month 15	+Month 18
AST ($\mu\text{kat/L}$)	0.76	0.73	1.02	2.82	9.38	4.47	2.34	2.0	0.74	1.02	0.85
ALT ($\mu\text{kat/L}$)	0.39	0.56	0.74	1.98	10.4	6.29	2.99	1.97	0.40	0.76	0.79
GGT ($\mu\text{kat/L}$)	0.57	0.85	2.51	1.51	1.7	1.88	2.0	1.10	0.40	0.35	0.44
ALP ($\mu\text{kat/L}$)	3.06	2.55	4.11	5.42	5.83	5.08	4.36	4.13	2.68	2.43	2.83
T. Bilirubin ($\mu\text{mol/L}$)	7.1	5.8	15.2	22.3	25.9	19.1	16.2	8.2	6.3	2.9	4.7
D. Bilirubin ($\mu\text{mol/L}$)	2.7	2.3	5.1	13.6	18.1	12.3	11.2	3.2	2.9	1.5	3.0
PT (sn)	10.9		15.3	14.5	12.7						12.3
PTT (sn)	35.5		43.7	45.3	44						34.7
INR	0.96		1.21	1.24	1.1						0.98

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time.

granularity and irregular liver borders suggesting parenchymal liver disease, but owing to his normal liver enzymes, liver rebiopsy was not performed. He requires no treatment with full donor chimerism other than mild chronic graft-versus-host disease on his tongue.

Discussion

Bone marrow transplant had been performed for patients with XHIGM in 1995 for the first time.⁴ In 2004, it had been concluded that hematopoietic stem cell transplant was curative for XHIGM if it was performed before significant infection and organ damage.⁵ Overall, 75% of patients with XHIGM develop liver complications, which are the main cause of death; also, they make successful bone marrow transplant more difficult.⁶

Khawaja and associates reported that 4 of 8 patients died after bone marrow transplant because of severe liver disease.⁸ In 2000, Hadzic and associates reported an XHIGM patient with end-stage chronic liver disease on whom was performed a deceased donor orthotopic liver transplant 34 days before bone marrow transplant from a matched unrelated donor. The authors suggest that the combination of the liver transplant and nonmyeloablative bone marrow transplant is a promising treatment approach for patients with end-stage liver disease.⁸ In 2004, according to European survey from 8 countries regarding 38 patients with CD40L deficiency treated with hematopoietic stem cell transplant, cure was obtained in 58% of the patients, 72% of those without hepatic disease.⁹

The combination of busulphan and cyclophosphamide and/or total body irradiation, fludarabine, and thiotepa were the most convenient conditioning regimens for XHIGM.^{5, 6-10} In a previous report, 2 patients with cholangiopathy were given fludarabine, busulfan, and antithymocyte globulin as nonmyeloablative preparative regimen. Both patients were reported alive with a mixed chimera in one.¹¹

Despite the effectiveness of busulphan-containing conditioning regimen, liver toxicity (eg, veno-occlusive disease and acute hepatocyte damage) occurs in up to 40% of hematopoietic stem cell transplant recipients.¹² Treosulphan is a water soluble, immunosuppressive and myeloablative alkylating agent that promises a favorable toxicity

profile compared with busulphan. Formerly, treosulphan/cyclophosphamide combination for the preparative regimen in allogeneic hematopoietic stem cell transplant was used in 18 patients with hematologic malignancies.¹³ Beelen and associates reported that this combination was an effective, comparatively well-tolerated, myeloablative conditioning regimen, even in the patients with an increased risk for regimen-related toxic complications.¹³ In pediatric population with various malignancies, Cutting and associates proposed that treosulphan/cyclophosphamide causes less toxicity than busulphan when it was used in similar combination. No veno-occlusive disease of the liver was detected in those patients combined with a low incidence of mucositis.¹⁴ Similar findings with treosulphan-containing regimens were reported in children with nonmalignant diseases like primary immunodeficiencies such as hemophagocytic lymphohistiocytosis, severe combined immunodeficiency disease, Wiskott-Aldrich syndrome, chronic granulomatous disease, leukocyte adhesion deficiency, Shwachman-Diamond syndrome, and thalassemia major.^{15, 16} However, this is the first report that treosulphan has been used in a XHIGM patient with severe liver disease. Treosulphan/cyclophosphamide has been well tolerated by the patient. Neither mucositis nor any other complications related to the conditioning regimen occurred (including organ dysfunction other than myelosuppression).

As the liver disease accompanying to XHIGM is a factor affecting the outcome of stem cell transplant, physicians should be careful in performing even liver biopsy before hematopoietic stem cell transplant to make an objective assessment related to high-risk-causing liver disease. Treosulphan seems to be a promising, less-toxic agent, especially in patients with chronic liver disease. In conclusion, treosulphan, used as a conditioning regimen in XHIGM with liver disease, might increase the success rate of transplants in high-risk patients.

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