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Nonmyeloablative Hematopoietic Stem Cell Transplant for X-Linked Hyper-Immunoglobulin M Syndrome With Cholangiopathy

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ABSTRACT. *Objective.* **X-linked hyper-immunoglobulin M (X-HIM) syndrome is a rare genetic immunodeficiency syndrome caused by mutations in the gene encoding CD40 ligand (CD40L, CD154). Allogeneic hematopoietic stem cell transplantation (HSCT) offers the prospect of immune reconstitution in X-HIM syndrome. Standard HSCT using high-dose chemoradiotherapy can be followed by serious hepatic problems, including veno-occlusive disease, graft-versus-host disease, and/or drug-induced hepatotoxicity. In patients whose liver function is compromised before HSCT, such as in X-HIM syndrome caused by cholangiopathy and hepatitis related to opportunistic infections, there is a higher likelihood of hepatotoxicity. We explored nonmyeloablative HSCT in 2 patients with X-HIM syndrome. Nonmyeloablative HSCT without liver transplant for X-HIM syndrome, to our knowledge, has not been described previously.**

Methods. **Two children with X-HIM syndrome and persistent infections had documented cholangiopathy on liver biopsy. Both children underwent nonmyeloablative HSCT from HLA-matched siblings with fludarabine, busulfan, and anti-thymocyte globulin as their preparative regimen. Graft-versus-host disease prophylaxis consisted of cyclosporine.**

Results. **Both children are >2 years after their HSCT. One remains a mixed chimera, and the other shows 100% donor chimerism. Both children are now free of infections and are no longer dependent on intravenous gammaglobulin. Both show response to immunizations. Both have had resolution of their cholangiopathy.**

Conclusions. **Nonmyeloablative HSCT from HLA-matched siblings can offer immune reconstitution without hepatotoxicity in patients with X-HIM syndrome and preexisting cholangiopathy. Even with stable mixed chimerism after allogeneic HSCT, patients may be able to enjoy a normal phenotype. Nonmyeloablative HSCT warrants additional study in X-HIM syndrome.** *Pediatrics* 2004;113:e122–e127. URL: http://www.pediatrics.org/cgi/content/full/113/2/e122; *stem cell transplant, nonmyeloablative, immunodeficiency, hyper-IgM, cholangiopathy.*

ABBREVIATIONS. X-HIM, X-linked hyper-immunoglobulin M; IVIG, intravenous immunoglobulin; G-CSF, granulocyte colony-stimulating factor; HSCT, hematopoietic stem cell transplantation; VNTR, variable-number tandem repeats; H&E, hematoxylin and eosin; CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; GVHD, graft-versus-host disease; CSA, cyclosporin A; PBSC, peripheral blood stem cells; MNC, mononuclear cell.

X-linked hyper-immunoglobulin M (X-HIM) syndrome is a rare genetic immunodeficiency syndrome caused by mutations in the gene encoding CD40 ligand (CD40L, CD154). Binding of CD40L expressed on activated T cells to CD40 on B cells is essential for isotype switching, germinal center formation, and upregulation of co-stimulatory and antigen-presenting functions.[1] Therefore, patients with X-HIM syndrome have profound deficiency of IgG, IgA, and IgE, and their lymph nodes lack germinal centers.[2] They have defective cell-mediated immunity, making them susceptible to opportunistic infections, and frequently develop neutropenia. Chronic cholangitis, a common complication of X-HIM syndrome, is usually associated with *Cryptosporidium parvum* infection and may lead to hepatic cirrhosis and hepatobiliary tumors[3,4] with a fatal outcome.

Supportive management of X-HIM syndrome includes intravenous immunoglobulin (IVIG), antibiotic prophylaxis against opportunistic infections, and granulocyte colony-stimulating factor (G-CSF) for neutropenia.[5,6] The high cumulative morbidity and mortality of patients so treated in reported series[5,7] has prompted attempts at definitive treatment with hematopoietic stem cell transplantation (HSCT). HSCT can reconstitute immune function and correct neutropenia in X-HIM syndrome.[6,8–12] However, its potential to stabilize or even reverse established X-HIM syndrome–associated chronic hepatobiliary disease is unclear. Furthermore, standard myeloablative HSCT carries a high risk for liver toxicity in the presence of existing cholangiopathy.[3] One successful nonmyeloablative HSCT after a liver transplant in a patient with X-HIM syndrome and chronic liver disease was recently reported.[13] To our knowledge, successful nonmyeloablative HSCT without a liver transplant in patients with X-HIM syndrome and established hepatobiliary disease has not been reported. We describe 2 children who had X-HIM syndrome, cholangiopathy, and liver disease and under-

went nonmyeloablative HSCT from HLA-matched donor siblings.

METHODS

Permission to view the patients' medical records for this report was granted by Children's Memorial Hospital Institutional Review Board. Induction of CD40L expression was performed as described previously.[14] After CD40L is upregulated with phorbol myristate acetate and ionomycin, it is analyzed by flow cytometry. CD40L is expressed mostly on CD4$^+$ T cells. Because phorbol myristate acetate and ionomycin reduce CD4 expression on T cells, CD4 cannot be used as a positive selection marker. Therefore, a negative gating strategy is used and results are expressed as the percentage of CD40L$^+$ in vitro in activated CD3$^+$CD8$^-$ T cells.

Isolation of genomic DNA and RNA, synthesis of cDNA, polymerase chain reaction amplification and DNA sequencing were performed as described previously.[15] Donor chimerism after HSCT was assessed with variable-number tandem repeats (VNTR) and was always examined in the peripheral blood. At the end of 2001, the laboratory also started reporting lymphoid and myeloid chimerism.

For histologic evaluation, liver and bile duct tissue samples were fixed in 10% buffered formalin, and 5-μ-thick paraffin-embedded sections were reviewed. The sections were stained with hematoxylin and eosin (H&E) and Masson's trichrome. One biopsy sample from the bile duct was not fixed in formalin. This sample had been processed for electron microscopy studies by fixing in 2% glutaraldehyde and cutting 1-μ-thick epon-embedded sections, stained with toluidine blue.

RESULTS

Case 1

X-HIM syndrome was diagnosed in a 2-year-old boy with history of streptococcal gingivitis, otitis media, pneumonia, and characteristic laboratory abnormalities (Table 1). As previously reported,[15] the patient's T cells showed defective CD40L expression, and analysis of CD40L cDNA and genomic DNA demonstrated an 8 base pair deletion in intron 2 of the CD40L gene associated with aberrant RNA splicing of exon 3. The patient was treated with co-tri-moxazole and IVIG. He developed oral ulcers and chronic neutropenia requiring treatment with G-CSF. By age 6, he had elevated levels of liver function tests (Table 1). Ultrasound examination showed distended common bile duct (CBD) without filling defect, endoscopic retrograde cholangiopancreatography (ERCP) demonstrated distended CBD with incomplete filling of the intrahepatic ducts, and liver biopsy revealed preserved architecture with 1 portal area containing a focus of acute and chronic inflammation. There was no increase in fibrous tissue. Cryptosporidial oocysts were detected in bile fluid obtained at ERCP. Two years later, the patient developed increased CBD dilation and new dilation of the common hepatic duct and intrahepatic ducts. Repeat ERCP demonstrated largely dilated CBD with numerous filling defects that were relieved endoscopically. Repeat liver biopsy revealed advancing liver disease with increased fibrous tissue in the portal areas with portal-to-portal bridging. Portal areas had more chronic inflammation with focal interface hepatitis compared with the previous biopsy. Bile duct biopsy revealed severely damaged bile duct epithelium with intense adjacent chronic inflammation (Fig 1). There was no cryptosporidial infection. He was treated with ursodiol without notable improvement. Because of the high risk of progression to cirrhosis and liver failure, his poor general health, and the availability of an HLA-matched sibling donor (unaffected boy), HSCT was performed at 9 years of age. For reducing hepatotoxicity, the patient received nonmyeloablative conditioning (fludarabine 30 mg/m^2 per day for 6 days, busulfan 0.8 mg/kg/dose intravenously every 6 hours for 2 days, and equine anti-thymocyte globulin 40 mg/kg per day for 4 days). Graft-versus-host disease (GVHD) prophy-

TABLE 1. Laboratory Values for the 2 Cases, Before and After HSCT

	Diagnosis	2–3 Years Before	Pre-HSCT	1 Year After	2 Years After	Reference Ranges (Units) for Age
Case 1						
IgA	<6.67			<6.67	<6.67	45–236 mg/dL
IgE	<2.0			<2.0	<2.0	6.1–58.5 IU/mL
IgM	199			211	100	52–242 mg/dL
IgG	46			615*	466	608–1572 mg/dL
Tetanus antibody	0				0.01†/0.13‡	>0.1 IU/mL
Total bilirubin	NA	0.3	0.8	0.7	0.9	0.2–1.0 mg/dL
ALT	NA	96	62	44	47	2–30 IU/L
Alkaline phosphatase	NA	640	545	577	403	55–274 IU/L
γ-glutamyltransferase	NA	283	NA	NA	175	8–55 IU/L
Case 2						
IgA	<6.67			100	110	25–154 mg/dL
IgE	<2.0			24.1	51.9	6.1–58.5 IU/mL
IgM	24			132	130	48–207 mg/dL
IgG	108			576	587	463–1236 mg/dL
Tetanus antibody	0.34§			>0.1†	1.14	>0.1 IU/mL
Total bilirubin	NA	NA	0.6	NA	0.6	0.2–1.0 mg/dL
ALT	NA	96	158	64	25	2–30 IU/L
Alkaline phosphatase	NA	NA	462	NA	NA	55–274 IU/L
γ-glutamyltransferase	NA	279	276	169	77	8–55 IU/L

ALT indicates alanine transaminase.
* Patient receiving IVIG treatment.
† Before reimmunization.
‡ One month after reimmunization.
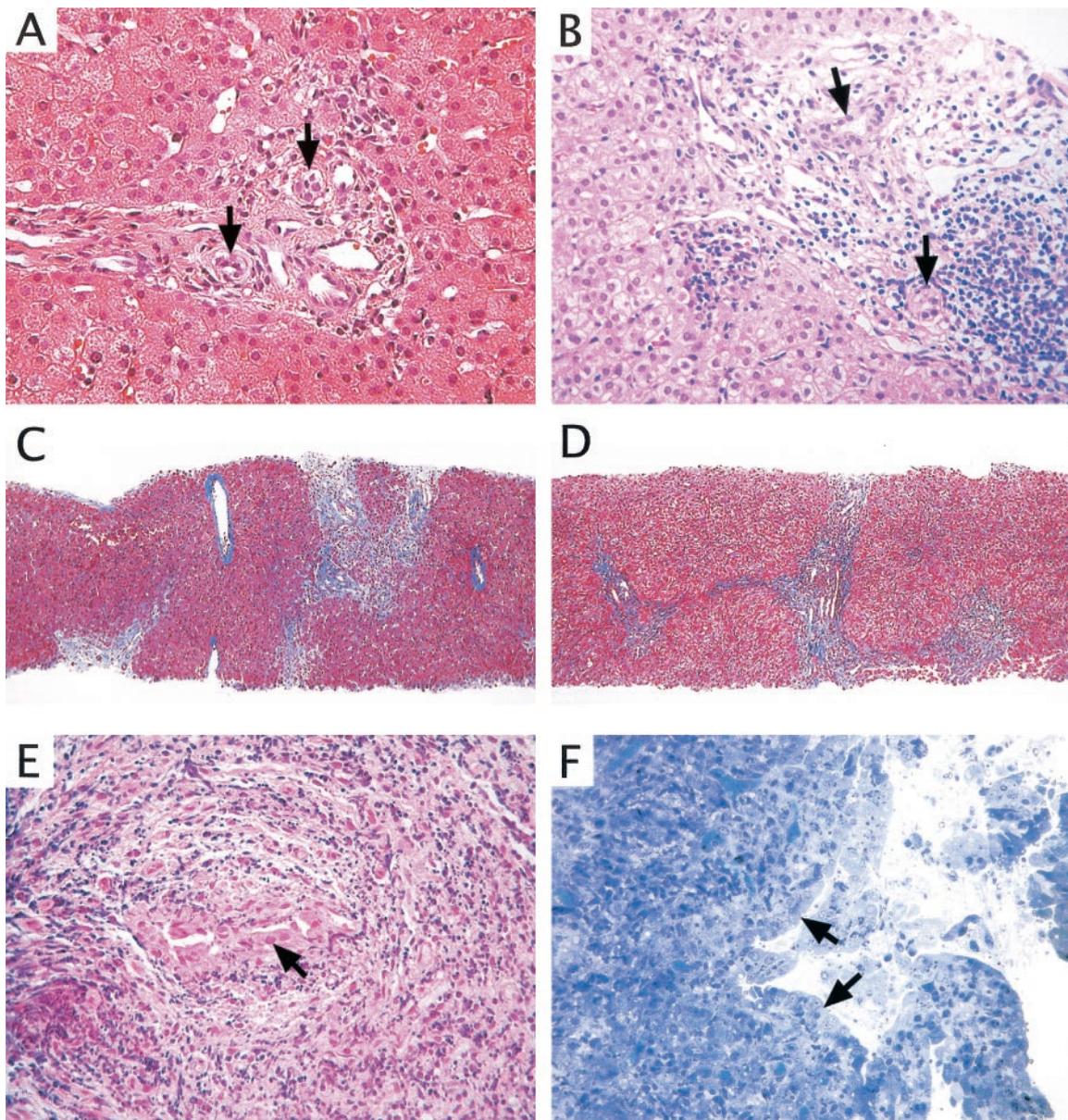§ At age 4 months-presumed maternal titer.

Fig 1. Histologic features of the liver in both patients. Sections A, C, and E correspond to case 2, and B, D, and F correspond to case 1. A, Mildly expanded portal tract caused by fibrosis; there is minimal chronic inflammation. The arrows indicate 2 mildly damaged bile ducts, which have epithelial cell swelling and vacuolation. (H&E stain; original magnification, ×10). B, Expanded portal tract caused by fibrosis and inflammation. The upper arrow indicates a dilated, distorted bile duct. The lower arrow shows a bile duct with mild damage similar to the bile ducts in A (H&E stain; original magnification, ×10). C and D, The blue-staining wide areas correspond to portal fibrosis, with formation of portal-to-portal bridges (trichrome stain; original magnification, ×4). E, Damaged bile duct (arrow) with intense surrounding inflammation (H&E; original magnification, ×20). F, Damaged bile duct with intense inflammation. The arrows indicate the epithelial lining cells of the bile duct (plastic embedded tissue, toluidine blue stain; original magnification, ×20).

laxis was cyclosporin A (CSA) at 6 mg/kg per day orally. The patient received peripheral blood stem cells (PBSC) (6.1×10^8 mononuclear cell [MNC]/kg, 6.7×10^6 CD34$^+$/kg) from his sibling. He never developed GVHD. By day 100, his absolute neutrophil count normalized and his donor chimerism (by VNTR) remained in the 40% to 50% range. Flow cytometric analysis showed robust expression of CD40L in 30% to 40% of in vitro activated helper T cells (Fig 2). Donor chimerism did not improve after CSA discontinuation, which occurred completely 6 months after HSCT. Therefore, 10 months after HSCT, he received a PBSC boost from the same donor (6.1×10^8 MNC/kg) without conditioning.

More than 2 years after HSCT, he remains with mixed chimerism (VNTR 25%–40%, CD40L 30%–60%). Lymphoid and myeloid donor chimerisms were obtained between 1.5 and 3 years after HSCT, and they ranged between 25% and 30% and 35% and 45%, respectively. After discontinuing IVIG therapy, serum IgM normalized, IgG is below the normal range but ~10-fold above the level at diagnosis, and IgA is undetectable; the patient mounted a protective antibody response to immunization with tetanus toxoid (Table 1). Clinically, the patient is thriving with no major infections. There is evidence of liver recovery based on liver function tests (Table 1) and abdominal ultrasound showing no intrahepatic or CBD
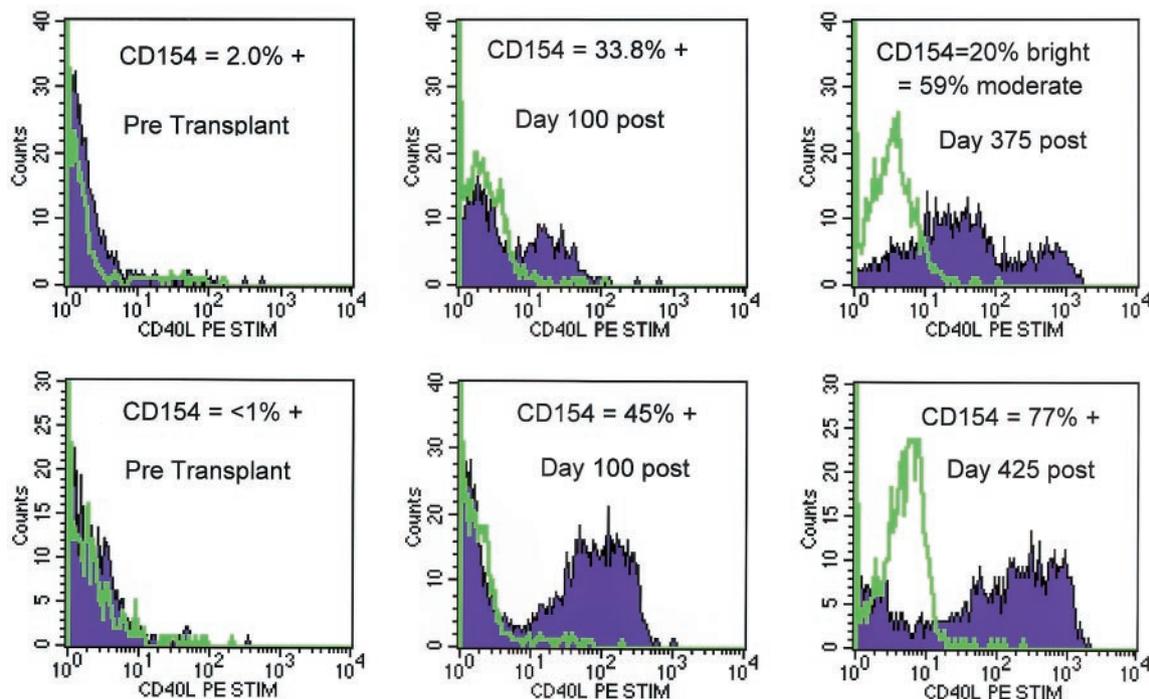
Fig 2. CD40L (CD154) protein expression on peripheral blood T cells (CD3$^+$CD8$^-$) of the 2 patients. CD40L expression on in vitro–activated T cells was detected by phycoerythrin-conjugated anti-CD40L monoclonal antibody (mAb; clone TRAP-1, BD Pharmingen, San Diego, CA). Fluorescence histograms shown are for case 1 before transplantation, 100 days after HSCT, and 375 days after HSCT (top) and for case 2 before transplantation, 100 days after HSCT, and 425 days after HSCT. All studies were gated on CD3$^+$CD8$^-$ cells (ie, >90% CD4$^+$ T cells) either unstimulated or stimulated with optimal concentrations of phorbol ester and calcium ionophore (the fluorescent green lines indicate CD40L expression on resting, unstimulated CD4$^+$ T cells). The dark purple histograms represent CD40L (anti-CD40L-PE) expression on CD4$^+$ T cells after 4 hours of in vitro stimulation at 37°C (as per "Methods").

dilation but a heterogeneous echotexture consistent with previous fibrosis.

Case 2

X-HIM syndrome was diagnosed in a 4-month-old boy with a history of recurrent otitis media and a maternal uncle with X-HIM syndrome. CD40L expression was characteristic of X-HIM syndrome, and sequence analysis of cDNA and genomic DNA showed a 5-bp deletion within the sequence encoding exon 5 of the gene encoding CD40L. Despite treatment with IVIG and pneumocystis carinii pneumonia prophylaxis, he had recurrent otitis media and sinusitis. He developed oral ulcers and chronic neutropenia requiring G-CSF therapy. At 3 years of age, abdominal ultrasound revealed intra- and extra-hepatic bile duct dilation without filling defects and a normal gallbladder. Cryptosporidial oocysts were detected in stool specimens, for which he received a prolonged course of azithromycin. By 4 years of age, he had chronically elevated levels of liver function tests (Table 1). At 5 years of age, ultrasound of the abdomen showed ongoing intrahepatic bile duct dilation with resolution of the CBD dilation. ERCP revealed multiple areas of narrowing within the intrahepatic ducts and a prominent CBD. Liver biopsy demonstrated portal areas with increased fibrous tissue, scant chronic inflammation, and evidence of bile duct epithelial injury, consisting of the formation of cytoplasmic vacuoles and nuclear pleomorphism. Bile duct biopsy revealed intense chronic inflammation, predominantly lymphocytic, surrounding the

duct (Fig 1). No organisms were observed. He was treated with ursodiol without improvement. Because his disease course suggested a poor long-term prognosis and the availability of an HLA-matched sibling donor (sister, noncarrier of X-HIM), an HSCT was performed at 5 years of age. The sister's PBSC (7.5 × 10^8 MNC/kg, 7.3 × 10^6 CD34$^+$/kg) were infused after identical conditioning as for case 1. He had no GVHD, and by day 180, he was off CSA and IVIG was discontinued. His donor chimerism by VNTR was 70% at day 100, 66% at day 180, 86% at 1 year, and 100% at 14 months and every time since then. Lymphoid and myeloid chimerisms, which were checked from 14 months on, also remain at 100%. By 2 years after HSCT, absolute neutrophil count and serum immunoglobulin levels were normal, antibody responses to tetanus toxoid were protective (Table 1), and he has 100% donor chimerism by VNTR. CD40L expression is normal (Fig 2). Also at 2 years after HSCT, his peripheral blood MNC proliferation assay is consistent with normal in response to phytohemagglutinin, concanavalin A, and pokeweed mitogen. He remains healthy, with no serious infections or clinical evidence of liver dysfunction. Ultrasound examination shows unremarkable liver with no bile duct dilation.

CONCLUSIONS

Allogeneic HSCT offers the prospect of immune reconstitution in X-HIM syndrome. Standard HSCT using high-dose chemoradiotherapy can be followed by serious hepatic problems, including veno-occlu-

sive disease, GVHD, and/or drug-induced hepato-toxicity. In patients whose liver function is compromised before HSCT, such as in X-HIM syndrome caused by cholangiopathy and hepatitis related to opportunistic infections,[3] there is a higher likelihood of hepatotoxicity.[16] Given this concern, nonmyeloablative HSCT[17] is an attractive option for patients with X-HIM syndrome and established hepatobiliary disease.

The improvement in our patients' hepatobiliary disease is of particular interest. Hadzic et al[13] reported a patient who had X-HIM syndrome and end-stage chronic liver disease and was treated successfully with liver transplantation followed by HSCT. However, stabilization or improvement of liver dysfunction in X-HIM syndrome after HSCT alone has not been previously reported. The pathophysiology of cholangiopathy in X-HIM syndrome is incompletely understood, but *C parvum* infection has been implicated in its cause[3] and was documented in both of our patients. On the basis of host immune responses to *C parvum* in murine models and in in vitro cell culture systems, both humoral and cell-mediated immunity seem to be involved in the resistance to infection and clearance of cryptosporidiosis. The key components for resolution of cryptosporidiosis in studies with murine models seem to be CD4$^+$ T cells and interferon-γ.[18] There is also evidence that CD40-CD40L interactions between T cells and biliary epithelial cells infected with *C parvum* may be important in triggering apoptosis of infected cells and thereby promoting clearance of infection.[19] This immune defense would be restored in X-HIM patients after successful HSCT. Therefore, the favorable hepatic outcome that we observed in our patients after HSCT may reflect reconstitution of host defense with clearance of an underlying infectious process. This outcome contrasts with that reported by Khawaja et al[20] in 3 patients with X-HIM syndrome and cholangitis, 2 of whom developed fatal liver failure and the third succumbed to sepsis and multiorgan failure soon after HSCT with standard cytoreductive conditioning. Factors that may have contributed to this striking difference in outcome include the reduced-intensity preparative regimen, that both of our patients had HLA-matched sibling donors, and the younger age and less advanced hepatic disease of our patients compared with those reported by Khawaja et al.

Nonmyeloablative HSCT frequently results in stable mixed hematopoietic chimerism.[17] The degree of donor chimerism required to correct fully the immunodeficiency in X-HIM syndrome is unknown. As a result of random X-chromosome inactivation, female carriers of X-HIM mutations have mosaic T-cell populations, usually with approximately equal numbers of T-cells expressing normal and mutant CD40L alleles. Such individuals usually have no immune compromise, but reported have been 2 female carriers of X-HIM mutations who had immunologic abnormalities associated with skewed X-chromosome inactivation and a low proportion (5%–12%) of T cells expressing CD40L; 1 of these carriers had mild

immunodeficiency, decreased IgG, and partial antibody deficiency, and the other had asymptomatic IgA deficiency.[21,22] Patient 1 achieved stable mixed chimerism with an estimated 40% to 50% donor T cells that expressed normal levels of CD40L. It is unclear why this degree of chimerism has not resulted in normal serum IgG levels or reconstitution of IgA synthesis. Nevertheless, a degree of functional immune reconstitution did occur, as indicated by the clinical improvement after HSCT and the normal serologic response to immunization.

Allogeneic HSCT remains a procedure with high risk, especially in the context of patients with immunodeficiency syndromes and infection. The risks and benefits of HSCT to patients with X-HIM syndrome must be weighed to decide whether to proceed. Although some patients with X-HIM syndrome may have a benign course with conservative management, in patients with a more complicated history, HSCT seems to be a reasonable option. Ideally, one would want to perform HSCT in patients who are well enough to tolerate the procedure but without HSCT would have a high likelihood of having severe problems in the future. Unfortunately, this timing is difficult, but our experience suggests that patients with early signs of liver dysfunction, hepatic fibrosis, or chronic cholangitis should be considered for HSCT when a matched sibling donor is available. Finally, we believe that for mitigating the high incidence of hepatic and other complications related to the preparatory regimen, a nonmyeloablative HSCT is an excellent way to promote immune reconstitution in patients with X-HIM syndrome, even if it results in partial donor chimerism.

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