peanut-derived peptides. Although in this report we do not address questions about clinical sequelae, our results justify further investigation of the phenotype and role of $CD8^+$ T cells, often overlooked, in IgE-mediated food allergy.

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Combined liver and hematopoietic stem cell transplantation in patients with X-linked hyper-IgM syndrome

To the Editor:

X-linked hyper-IgM syndrome (XHIGM [or HIGM1]) is a combined immunodeficiency caused by mutations in the gene encoding CD40 ligand *(CD40LG)*, leading to an impairment of both cellular and humoral immunity.[1] Lack of CD40 ligand (CD40L) and hence of interaction between CD40L and CD40 results in defective T-cell function and costimulation, with ensuing impaired class-switch recombination and somatic hypermutation in B cells, hindering an effective secondary antibody response. Moreover, activation of natural killer cells, dendritic cells, and monocytes is impaired, which results in an impaired inflammatory response.[1] Around 40% of patients present with *Pneumocystis jirovecii* interstitial pneumonia, and recurrent respiratory tract infections are present in 80% of cases. Other pathogens include mainly bacteria; mycobacteria; fungi, such as *Histoplasma*, *Cryptococcus*, and *Candida* species; and viruses, especially cytomegalovirus (CMV).[1-3]

Gastrointestinal manifestations are described in 40% of patients and include diarrhea with failure to thrive, inflammatory bowel disease, and oral ulcers; neuroendocrine tumors of the gastrointestinal tract have been reported.[1,2,4,5] Liver involvement can manifest as an increase in levels of liver enzymes, infectious hepatitis, and sclerosing cholangitis. *Cryptosporidium* species infection has been reported in as many as half of the cases of sclerosing cholangitis, often leading to cirrhosis and liver failure.[1-5] Central nervous system disease can be present in up to 11% of patients at presentation in the form of central nervous system infections or neurodegenerative disease.[1-5] Hematologic abnormalities, such as neutropenia and anemia, are described in more than 60% and 15% to 20% of patients, respectively.[1,3-5]

Despite immunoglobulin substitution and antimicrobial prophylaxis, the overall prognosis is poor, with a median survival time from diagnosis of 25 years.[6] Both European and US registries report mortality of 10% to 20% before the age of 30 years in their patient cohorts.[1,3-6]

A recent retrospective observational study analyzed the survival rate of 176 patients with a diagnosis of XHIGM between 1964 and 2013 and compared outcomes for those patients treated with or without hematopoietic stem cell transplantation (HSCT).[6] Liver or biliary involvement at diagnosis represented the only significant predictor of mortality, and survival was not influenced by HSCT.[6] However, a survival benefit for patients undergoing transplantation was noted starting from 1987, suggesting improvements in transplantation practice over the last 4 decades. Also, patients treated with HSCT demonstrated improvement on scales of daily living (Lansky or Karnofsky) when compared with the group not undergoing transplantation.[6]

A recent retrospective study from the United Kingdom of 24 patients with XHIGM reported a crude mortality of 38% in patients with liver disease compared with 6% in patients without liver disease.[7] Mortality as high as 80% was reported for patients with XHIGM with liver disease treated with HSCT compared with 10% for those treated with HSCT without liver pathology.[6] Therefore it is generally recommended that patients with XHIGM patients receive HSCT upfront and before the onset of liver disease.[6,7]

Liver transplantation (LT) has been performed in small numbers of patients with XHIGM who have end-stage liver disease with or without concomitant HSCT. Mortality in patients with XHIGM only receiving LT is high. This is likely because the underlying immune defect is not corrected and could be aggravated further by the immunosuppression needed for LT, as previously reported.[6,8] Improved outcome is noted when both LT and HSCT are performed.[6,7]

The aim of this study was to systematically report and compile the data on published and unpublished patients with XHIGM who received LT with or without HSCT. Patients were included from the previous study by de la Morena et al,[6] as well as through

TABLE I. Transplantation characteristics of 13 patients with XHIGM who underwent LT with or without HSCT

Patient no.	Age	Age at diagnosis of liver disease	SC	*Cryptosporidium* species infection	Order of transplantation	Time elapsed between HSCT/LT	Year of and age at LT	IS	Year of and age at HSCT	Type of HSCT	Conditioning	GvHD	Rx	Complications	Donor chimerism at last FU	Survival after LT	Outcome
P1	27 y	9.5 y	Yes	Yes	LT - HSCT	2 mo	2009, 17 y	CS Tacro MMF	2009, 17 y	MUD	NM Flu ATG	No	—	HSC graft failure, relapse of cryptosporidiosis and sclerosing cholangitis after LT	Lost	8 y	A/W
					HSCT - LT	7 wk	2010, 19 y	CS Tacro MMF Basilix	2010, 19 y	MUD	RIC Flu Treo ATG	Acute, gut	CS	—	Full		
P2	25 y	10 y	Yes	Yes	HSCT - LT	2 y	2009, 16 y	CS Tacro	2007, 14 y	Matched cord from sibling	RIC Flu Mel Alem	No	—	—	NA	9 y	A/W
P3	13 y	7 y	No	Yes	HSCT - LT	3 y	2015, 10 y	CS Tacro	2012, 7 y	Mismatched MUD	RIC Flu Treo Alem	Acute, gut and liver (grade IV)	CS Inflix ATG ECP	Catheter-related sepsis, *Klebsiella* species UTI, adenovirus infection after HSCT	Mixed	2 y	A/W
P4	18 y	5 y	Yes	Yes	HSCT - LT	1 y	2008, 8 y	CS Tacro MMF	2007, 7 y	MUD	M Bu Cy ATG	Acute and chronic; skin, gut, and liver (grade III)	CS Tacro MMF Etanercept	HHV-6 infection, hypertension after HSCT Transient renal and hepatic insufficiency after LT	Full	10 y	A/W
P5	11 y	3 y	Yes	Yes	LT - HSCT	4 wk	2015, 8 y	Tacro CSA Basilix	2015, 8 y	MUD	RIC Flu Treo Thio	Acute, skin and liver (grade II)	CS MMF	Mild/moderate acute LT rejection, CMV reactivation, bilateral optic neuritis	Full	3 y	A/W
P6	23 y	18 y	Yes	Yes	LT - HSCT	4 wk	2016, 21 y	CS Tacro	2016, 21 y	Matched sibling	RIC Flu Mel	No	—	—	Full	2 y	Alive, relapse of *Cryptosporidium* species infection (asymptomatic)
P7	38 y	5 y	Yes	No	LT - HSCT	5 wk	1998, 18 y	CS Tacro	1998, 18 y	MUD	RIC Flu Mel ATG	Acute, skin and gut (mild)	CS	—	NA	20 y	A/W
P8	38 y*	33 y	Yes	No	LT	—	1995, 38 y	NA	—	—	—	—	—	NA	—	Deceased soon after LT	Cause of death: LT-related complications
P9	16 y*	11 y	Yes	Yes	HSCT - LT	2 mo	1999, 16 y	Tacro	1999, 16 y	Mismatched MUD	M Cy Alem TBI	Acute, skin	NA	HSC graft failure and liver failure after HSCT Pulmonary hemorrhage and renal failure after emergency LT	Lost	Deceased soon after LT	Cause of death: disseminated cryptosporidiosis and HLH
P10	12 y*	7 y	Yes	Yes	LT - HSCT	2 mo	2005, 12 y	NA	2005, 12 y	Mismatched MUD	RIC Flu Mel Thio ATG	Acute, gut and liver (grade II)	—	Pleuric effusion, renal failure, relapse of cryptosporidiosis and sclerosing cholangitis after LT	Full	Deceased 4 mo after LT	Cause of death: relapse of *Cryptosporidium* species infection and sclerosing cholangitis, renal failure
P11	13 y*	6 y	Yes	Yes	LT	—	1993, 10 y	CS CSA	—	—	—	—	—	—	—	Deceased 3 y after LT	Cause of death: relapse of *Cryptosporidium* species infection and sclerosing cholangitis
P12	15 y*	13 y	Yes	Yes	LT	—	2016, 14 y	Tacro	—	—	—	—	—	Hepatic artery stenosis, relapse of cryptosporidiosis, chronic rejection	—	Deceased 1 y after LT	Cause of death: relapse of *Cryptosporidium* species infection, fulminant liver failure

(Continued)

TABLE I. *(Continued)*

Patient no.	Age	Age at diagnosis of liver disease	SC	*Cryptosporidium* species infection	Order of transplantation	Time elapsed between HSCT/LT	Year of and age at LT	IS	Year of and age at HSCT	Type of HSCT	Conditioning	GvHD	Rx	Complications	Donor chimerism at last FU	Survival after LT	Outcome
P13	25 y*	NA	Yes	Yes	LT	—	2008, 24 y	CS Tacro MMF	—	—	—	—	—	Hemorrhagic shock during biopsy, *Enterococcus* species bacteremia, CMV reactivation, pericarditis, relapse of cryptosporidiosis	—	Deceased 1 y after LT	Cause of death: relapse of *Cryptosporidium* species infection, sepsis

Alem, Alemtuzumab; *A/W*, alive and well; *Basilix*, basiliximab; *Bu*, busulfan; *CS*, corticosteroids; *CSA*, cyclosporine; *Cy*, cyclophosphamide; *ECP*, extracorporeal photopheresis; *Flu*, fludarabine; *FU*, follow-up; *HHV-6*, human herpesvirus 6; *HLH*, hemophagocytic lymphohistiocytosis; *Inflix*, infliximab; *M*, myeloablative; *Mel*, melphalan; *NA*, not available; *NM*, nonmyeloablative; *RIC*, reduced-intensity conditioning; *Rx*, therapy; *SC*, sclerosing cholangitis; *Tacro*, tacrolimus; *TBI*, total-body irradiation; *Thio*, thiotepa; *Treo*, treosulfan; *UTI*, urinary tract infection.
*Deceased.

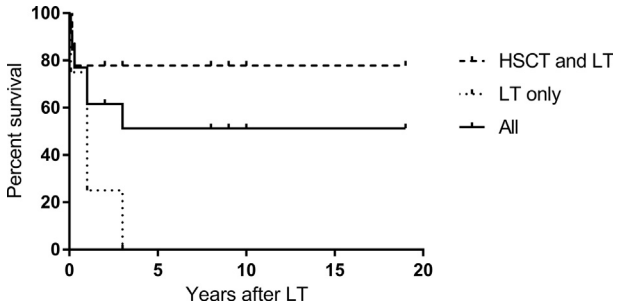

FIG 1. Kaplan-Meier curve of survival for 13 patients with XHIGM undergoing LT with or without associated HSCT.

contacting corresponding authors of previously reported cases (the relevant bibliographic references can be found in this article's Online Repository at www.jacionline.org). Additionally, a query was sent to the Primary Immune Deficiency Treatment Consortium, the Inborn Errors Working Party of the European Group for Blood and Marrow Transplantation, and the Stem Cell Transplant for primary Immune Deficiencies in Europe registry. For review of the questionnaire used, please see this article's online repository at www.jacionline.org.

We report the clinical manifestations, clinical course, and outcome of 13 patients with XHIGM from 3 continents and 8 countries who underwent LT for sclerosing cholangitis. Five of these patients (P1, P4, P5, P7, and P11) were previously reported as cases in the literature (the relevant bibliographic references can be found in this article's online repository at www.jacionline.org), 3 patients (P1, P2, and P8) were included from the previous study, and 1 patient (P7) was included in the study by Azzu et al.[7] LT and HSCT characteristics are summarized in Table I. Except for 1 patient (P8, who received a diagnosis in adulthood after onset of sclerosing cholangitis), all patients received diagnoses of XHIGM in infancy or childhood, with a median age at diagnosis of 3.5 years (range, 5 months to 36 years).

Additional clinical and genetic data are summarized in Table E1 in this article's online repository at www.jacionline.org. A genetic diagnosis of XHIGM was confirmed in 10 of the 13 patients; in 3 patients diagnosis was based on clinical and immunologic criteria (hyper-IgM and absent CD40L expression). Of the 9 reported mutations, 1 is a missense in the promoter region of *CD40L*, 1 is a splice-site missense mutation downstream of exon 1, 1 is a nonsense mutation in exon 5, 5 are frameshift mutations (1 in exon 1, 1 in exon 2, and 3 in exon 5), and 1 is a partial deletion of the *CD40L* gene. Familial cases were found in 5 patients.

Six patients had recurrent respiratory tract infections, and 4 patients had chronic lung disease, but only 2 presented with confirmed *P jirovecii* pneumonia. One patient had pulmonary *Mycobacterium avium* infection and aspergillosis. One patient had tuberculosis of the shoulder and knee and septic arthritis of the hip, and another patient had an episode of cryptococcal meningitis. Seven patients manifested neutropenia, and 1 had pancytopenia caused by hypersplenism. Eight patients had gastrointestinal manifestations, such as chronic diarrhea, and 6 patients had failure to thrive. In all but 1 patient (P3), liver disease was diagnosed as sclerosing cholangitis, and *Cryptosporidium* species infection was reported in 11 cases. P3 manifested liver disease after HSCT; his liver histology was compatible with chronic graft-versus-host disease (GvHD), but he also had *Cryptosporidium* species infection since before HSCT (microscopically identified) that did not respond to antimicrobial treatment.

All patients were receiving immunoglobulin substitution treatment at the time of LT; *P jirovecii* pneumonia prophylaxis with trimethoprim-sulfamethoxazole was used in 11 of 13 patients. Azithromycin, nitazoxanide, and paromomycin were used alone or in combination as prophylaxis or treatment of *Cryptosporidium* species infection in 7 patients. Two patients were receiving ursodeoxycholic acid for sclerosing cholangitis.

A total of 14 LTs and 10 HSCTs were performed in 13 patients (P1 received 2 LTs and 2 HSCTs, Table I). The median age at LT was 14 years (range, 8-38 years). The average time gap between XHIGM diagnosis and onset of liver disease in this cohort was 4.5 years (range, 0.1-17.5 years). Nine patients underwent LT and HSCT. Four patients received LT alone. Among those patients treated with both LT and HSCT, in 5 patients the LT followed HSCT by an average of 15 months (range, 1.6 months to 3 years), whereas in 4 patients LT preceded HSCT by an average of 1 month (range, 1-2 months). All patients received liver allografts from deceased unrelated donors. Living related donor LT was not used for patients in whom a family member was the HSCT donor. One LT was performed as emergency transplantation in the context of liver failure after HSCT (P9). In the patients for whom information is available, standard ABO matching was used for the LT.

Immunosuppression regimens for LT consisted of standard therapies according to the center performing the LT. These included tacrolimus for 11 patients (P1-P7, P9, P12, and P13), which was combined with steroids in 8 patients. Two patients (P5 and P11) received cyclosporine, and mycophenolate mofetil (MMF) was added to dual calcineurin inhibitor and steroids in 3 patients (P1, P4, and P13). Basiliximab was added as induction in 2 patients (P1 and P5).

Nine patients received 10 HSCTs. In 5 patients the HSCT preceded the LT. Donor characteristics included 5 patients treated with matched unrelated donors (MUDs; 3 bone marrow and 2 unknown), 3 patients had mismatched unrelated donors (mMUDs; bone marrow), and 2 patients had matched sibling donors (bone marrow). Conditioning was myeloablative in 2 cases and reduced intensity in 7 cases. The conditioning regimen used in the patients who received HSCT first was not limited due to liver dysfunction in any of the cases.

Of 10 HSCTs performed, 5 resulted in full donor chimerism, 1 in mixed chimerism (64% on granulocytes and 80% on lymphocytes), and 2 in HSC graft failure (P1 and P9). Both patients who lost donor chimerism manifested a recurrence of cryptosporidiosis and liver failure. P1 showed loss of chimerism 6 months after an MUD HSCT with nonmyeloablative conditioning, followed by relapse of *Cryptosporidium* species infection, sclerosing cholangitis, and cirrhosis of the previously transplanted liver (LT was performed 2 months before HSCT). He was rescued by a second HSCT from a different unrelated donor after reduced-intensity conditioning, closely followed by a second LT, both of which were successful. P9 had early loss of donor chimerism after an mMUD HSCT with myeloablative conditioning. He experienced acute liver failure and died from disseminated *Cryptosporidium* species infection and hemophagocytic lymphohistiocytosis after emergency LT. It is possible that the graft failure in P1 was facilitated by the presence of allogeneic T cells from the recently transplanted liver.

Seven patients experienced GvHD. Two of those who received HSCT after LT manifested grade II acute liver GvHD (P5 and P10). We can speculate that the occurrence of GvHD in the transplanted liver was more likely to happen because of the HLA mismatch between the liver donor and the HSC donor, although 2 patients treated with HSCT before LT manifested acute GvHD on the native liver (P3 and P4).

Six of 13 patients died, 4 of whom received LT alone without HSCT (4/4), 1 in whom LT preceded HSCT (1/4), and 1 in whom LT occurred after HSCT (1/5, Fig 1). In patients who received HSCT, survival was better if HSCT was performed in more recent years, probably because of improved transplantation practices (see Fig E1 in this article's Online Repository at www.jacionline.org). In 5 of the 6 patients who died, *Cryptosporidium* species infection was present before LT/HSCT, and a persistence/relapse of cryptosporidiosis with or without liver disease was considered the cause of death. The sixth patient died of early LT-related complications. Only 1 patient (P6) who received LT followed by HSCT had a relapse of *Cryptosporidium* species infection without signs of liver disease 2 years after LT. Except in 1 case, in which HSC engraftment failed (P9), *Cryptosporidium* species was not identified after LT in those patients who had received successful HSCT before LT.

This case series describes the current published data available on LT in patients with XHIGM. Liver involvement in patients with XHIGM is commonly described as sclerosing cholangitis, which is reported in 6% to 20% of patients and is frequently associated with *Cryptosporidium* species infection.[3,5-7] Sclerosing cholangitis is responsible for one third of the cases of cirrhosis and liver failure in patients with XHIGM, although it represents only 4% of cases of LT in the general population. It has also been reported in association with liver carcinoma and cholangiocarcinoma.[1,3]

The mortality noted herein (6/13 [46%] patients) is in line with previously published data showing how liver disease represents a significant negative predictor of survival for patients with XHIGM, who otherwise have better survival if not affected by hepatic dysfunction.[6,7,9] Moreover, the survival rate of pediatric LT recipients has increased over the last few decades and is set now between 70% and 80% at 20 years after transplantation,[E7] whereas in our cohort overall crude survival was noted to be less than 55%, with an average follow-up of 6.8 years. However, survival is improved in those patients with XHIGM who underwent both LT and HSCT, regardless of the order of transplantation (80% survival with an average follow-up of 6 years, Fig 1). GvHD in the transplanted livers after allogeneic HSCT was found in 2 of 9 patients but was never the reason for liver graft failure or death. Also, only 1 patient experienced HSC graft failure when HSCT was performed after LT, possibly influenced by the presence of allogeneic T cells in the liver graft. The need for LT also in patients who underwent HSCT before the onset of liver failure can be explained by the irreversibility of an already established biliary disease, mostly diagnosed many years before HSCT was performed. Moreover, in 2 cases the occurrence of liver GvHD after HSCT likely worsened the course of disease in the already compromised liver. Relapse of *Cryptosporidium* species and liver disease was associated with fatal outcome in all patients undergoing LT who did not receive an HSCT, highlighting the role of this pathogen in this primary immunodeficiency (PID).[7]

HSCT represents the only currently available definitive treatment of XHIGM. When performed at an early age, before major complications, such as liver disease, HSCT can improve a patient's quality of life as long as appropriate immunologic reconstitution is achieved and there is absence of long-term HSCT-related complications, such as GvHD.[6] This report highlights the importance of HSCT when patients with XHIGM require an LT for survival.[6] Despite the underlying immunodeficiency, patients with XHIGM who received both LT and HSCT tolerated the associated immunosuppressive regimens commensurate to the organ transplanted, suggesting that such dual therapies are feasible and associated with potential success in these patients. Transplant-related CMV status of donor liver allografts was not addressed in this study because of limited information. Given the risk associated with CMV for patients with XHIGM, procurement of CMV-negative liver allografts should be carefully considered.

Although there is an important time lapse between the first and last patient to receive an LT (1993 and 2016), we do not believe this contributed significantly to the outcome. Instead, *Cryptosporidium parvum* remains a major factor influencing outcomes, perhaps because of the limited effective therapeutic options for these patients. Solid-organ transplantation for patients with PIDs can be difficult. The limited availability of organs precludes candidates in whom there is high concern for allograft failure. In the case of patients with PIDs, concern for infectious

complications and potential GvHD induced by T lymphocytes present in the allograft are real considerations. However, the data reported herein emphasize the potential cure of combined LT and HSCT in those patients with XHIGM in need for LT.

Therefore we argue that the diagnosis of XHIGM should not be an *a priori* reason to exclude patients with XHIGM from LT, as long as HSCT is included in the treatment strategy. Our recommendation for these patients is to perform HSCT before LT. Our case series demonstrates the fundamental importance of immune reconstitution to control infection and allow a successful LT, as shown by the 100% rate of *Cryptosporidium* species recurrence in patients who received only LT or who experienced HSC graft failure. In case of fulminant liver failure and urgent LT, we recommend planning an HSCT as soon as possible after the LT, preferably after healing of the surgical wounds. As for conditioning and support therapy, we suggest a preference for reduced-intensity regimens, to avoid cyclophosphamide if possible, and to implement fluid restriction and ursodeoxycholic acid therapy during conditioning to reduce the risk of veno-occlusive disease.

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CASE REPORTS

P1

Patient P1 presented in 1991 at the age of 5 months with *P jirovecii* pneumonia requiring prolonged mechanical ventilation. A diagnosis of XHIGM was made, and he was started on substitutive immunoglobulins and trimethoprim-sulfamethoxazole prophylaxis. A mutation was later identified in the promotor region of the *CD40LG* gene (c.123A>C to c.-192A>C adapted to the current reference genome).[E1]

At the age of 9 years, the patient had sclerosing cholangitis, with documented *Cryptosporidium* species infection not responding to nitazoxanide treatment, gradually evolving into liver cirrhosis. At the age of 17 years, he underwent a deceased-donor orthotopic LT, followed 3 months afterward by an MUD HSCT from peripheral stem cells after a nonmyeloablative conditioning regimen with fludarabine and antithymocyte globulin (ATG). Immunosuppressive treatment with tacrolimus, MMF and steroids was used during LT.

In the first few months after transplantation, he experienced loss of HSCT engraftment and a relapse of *Cryptosporidium* species infection and sclerosing cholangitis despite antiparasitic prophylaxis with nitazoxanide. A second peripheral stem cell HSCT from a different MUD and a second LT were subsequently performed 14 months after the first HSCT. He received reduced-intensity conditioning with fludarabine, treosulfan, and ATG, and engraftment was successful. The immediate post-HSCT course was complicated by hepatic failure, renal failure, and pneumonia with *Candida* species and *C parvum* growth on sputum culture. Fifty days after the HSCT, he underwent a second deceased-donor orthotopic LT, with an immunosuppressive regimen consisting of basiliximab, tacrolimus, MMF, and steroids. He then experienced acute intestinal GvHD that responded well to steroid treatment.

At 26 years of age, he is now 7 years after the second HSCT and LT; has a donor chimerism of 100%; has a good quality of life with a score of 90, as measured by using Karnofsky scales; and has recently stopped immunoglobulin substitutive therapy.

P2

Patient P2 was given a diagnosis of XHIGM in 2000 at 7 years of age based on absent CD40L expression on peripheral lymphocytes. He presented with respiratory tract infections, chronic diarrhea, and failure to thrive, and at the age of 10 years, he had sclerosing cholangitis associated with *Cryptosporidium* species infection. He was treated with substitutive immunoglobulin and trimethoprim-sulfamethoxazole prophylaxis, and at the age of 14 years, he received a matched sibling HSCT from bone marrow after reduced-intensity conditioning with fludarabine, melphalan, and Campath. The course of transplantation was uncomplicated. Two years after HSCT, he underwent a deceased-donor orthotopic LT without major complications. He is now 24 years of age and has a good quality of life, scoring 90 on the Karnofsky scale.

P3

Patient P3 was started on immunoglobulin therapy for nonspecific hypogammaglobulinemia at the age of 1 year in 2006. At the age of 6 years, he and his brother received a diagnosis of XHIGM based on absent CD40L expression on peripheral lymphocytes. He had severe interstitial pneumonitis requiring intensive care and likely caused by *P jirovecii* and was therefore treated with trimethoprim-sulfamethoxazole. A lung biopsy showed signs of lymphocytic interstitial pneumonitis. He also manifested protracted diarrhea and failure to thrive, and *Cryptosporidium* species was detected in the stools by using PCR.

Treatment with azithromycin, paromomycin, and nitazoxanide was attempted for the *Cryptosporidium* species infection without effect. He underwent an mMUD HSCT from bone marrow (match 9/10) at the age of 7 years after reduced-intensity conditioning with fludarabine, treosulfan, and ATG. The dose of $CD34^+$ cells was 5.8×10^6/kg. Engraftment was successful, but he had grade IV GvHD involving the gut and liver. Other post-HSCT complications included adenovirus infection, *Klebsiella* species urinary tract infection, catheter-related sepsis, chronic esophagitis and feeding problems, and severe liver dysfunction. Liver biopsies showed chronic cholestasis and cellular infiltrate around the bile ducts that could be attributed to both GvHD or persistent *Cryptosporidium* species infection. Significant immunosuppression was attempted with steroids, MMF, infliximab, sirolimus, and ATG, without effect. Extracorporeal photopheresis was then started with very slow beneficial effects, but because of the irreversible liver damage, a deceased-donor orthotopic LT with ABO matching was finally performed at the age of 10 years. Steroid and tacrolimus were used as immunosuppressive treatment during transplantation, and he experienced no complications.

The patient is now 12 years old and alive and well, with a mixed donor chimerism of 64% on granulocytes ($CD15^+$), 84% on B cells ($CD19^+$), and 80% on T cells ($CD3^+$). He is still immunosuppressed with tacrolimus and steroids, and immunoglobulin substitution and antibiotic prophylaxis have recently been stopped.

P4

Patient P4 had recurrent upper and lower respiratory tract infections, hypogammaglobulinemia, and neutropenia and received a diagnosis of XHIGM at the age of 2 years. A mutation in *CD40L* was identified (c.120delA),[E2] and immunoglobulin substitution and prophylaxis with trimethoprim-sulfamethoxazole were started. At the age of 5 years, he had liver disease in the form of sclerosing cholangitis, and *Cryptosporidium* species infection was detected. He underwent an MUD HSCT from peripheral blood stem cells at the age of 7 years after myeloablative conditioning with busulfan, cyclophosphamide, and ATG. The $CD34^+$ cell dose was 5.5×10^6/kg. After transplantation, he had hypertension and acute mucocutaneous, intestinal, and hepatic GvHD (grade III), which continued in chronic form. He was treated with steroids, ATG, cyclosporine, and MMF. A year later, he received a deceased-donor orthotopic LT. The immunosuppressive treatment consisted of steroids, tacrolimus, and MMF. Etanercept was added 14 months after LT because of persistent skin and oral chronic GvHD. The course of LT was complicated by transient renal and liver insufficiency. Immunoglobulin substitution could be suspended soon after HSCT.

Patient P4 is now 18 years old, alive and well, and still immunosuppressed with tacrolimus and MMF.

P5

Patient P5 presented with diarrhea and failure to thrive since the age of 8 months in 2008. At the age of 3 years,

hypogammaglobulinemia and an increase in levels of liver enzymes were noted for the first time. He received a diagnosis of sclerosing cholangitis and liver cirrhosis at 5 years of age. *C parvum* was repeatedly isolated in stool and did not respond to treatment with paromomycin. CD40L expression was absent on peripheral lymphocytes, and genetic analysis confirmed the diagnosis of XHIGM caused by a mutation in *CD40LG* (c.773T>G, p.L258X).[E3] His healthy sister was heterozygous for the same mutation, whereas their mother was genotypically normal, implying a germinal mosaicism. He was started on immunoglobulin substitution, prophylactic trimethoprim-sulfamethoxazole treatment, paromomycin, and ursodeoxycholic acid, and he never experienced recurrent infections.

Because of the progressive liver disease, at the age of 8 years, he underwent deceased-donor orthotopic LT with ABO matching complicated by reactivation of CMV and an episode of mild-to-moderate rejection, which responded to steroids. The immunosuppressive regimen used during LT comprised basiliximab and tacrolimus. Four weeks after LT, he received an MUD HSCT from bone marrow after reduced-intensity conditioning with treosulfan, fludarabine, and thiotepa. The dose of $CD34^+$ cells was 5.1×10^6/kg. Neutrophil engraftment was seen at day +15, and platelet engraftment was seen at day +20. He experienced CMV reactivation; bilateral optic neuritis probably associated with tacrolimus, which was then replaced by cyclosporine; and acute cutaneous GvHD (grade II), which was successfully treated with steroids. During treatment with cyclosporine, he had hepatic GvHD, for which MMF was started. A full donor chimerism (>97% donor) was observed on day +75 and is still stable to date. Finally, he had limited chronic cutaneous GvHD 15 months after HSCT.

The patient is now 11 years of age and alive and well. He has no signs of liver dysfunction or GvHD and is still immunosuppressed with cyclosporine and MMF.

P6

Patient P6 was given a diagnosis of XHIGM in 1995, at the age of 6 months, after his older brother died because of progressive panencephalitis in the context of XHIGM. CD40L expression was absent on peripheral lymphocytes, and genetic analysis identified the causative mutation in *CD40LG* (c.500delG, p.G167fs*24). He was immediately treated with immunoglobulin substitution and trimethoprim-sulfamethoxazole prophylaxis, but despite this, he had recurrent bacterial sinusitis throughout childhood. He also manifested recurrent neutropenia requiring granulocyte colony-stimulating factor treatment, oral aphthosis treated with thalidomide, and an episode of cryptococcal meningoencephalitis. He was given a diagnosis of sclerosing cholangitis and *Cryptosporidium* species infection at the age of 18 years not responding to treatment with azithromycin, paromomycin, and nitazoxanide.

At 21 years of age, he underwent deceased-donor orthotopic LT with ABO matching, followed 4 weeks later by a matched sibling HSCT from bone marrow, after reduced-intensity conditioning with fludarabine and melphalan. The dose of $CD34^+$ cells was 4.28×10^6/kg. Immunosuppressive treatment during LT consisted of steroids and tacrolimus. He did not experience any complications or GvHD and is now 23 years old and alive and well, despite recurrence of *Cryptosporidium* species infection (detected in the stools).

P7

Patient P7, who had respiratory tract infections, was given a diagnosis of XHIGM at the age of 3 years in 1984 based on absent CD40L expression on peripheral lymphocytes. His younger brother was also affected and died of *P jirovecii* pneumonia. Genetic analysis later demonstrated a small deletion causing a frameshift mutation in *CD40LG* (c.465delGAGCAinsC to c.444delGAGCAinsC adapted to the current reference genome).[E4] He was treated with immunoglobulin replacement therapy, trimethoprim-sulfamethoxazole, and paromomycin prophylaxis.

Since the age of 5 years, he manifested liver involvement, and at 10 years, he had sclerosing cholangitis, without detection of *Cryptosporidium* species infection. He then progressed to liver cirrhosis, having ascites and portal hypertension with esophageal varices, which required sclerotherapy and banding. Therapy with ursodeoxycholic acid and diuretics was started. *Pseudomonas* species and *Streptococcus mitis* were isolated from bile culture.

At 18 years of age, he underwent deceased-donor orthotopic LT with ABO matching, followed 5 weeks later by an MUD HSCT, after reduced-intensity conditioning with fludarabine, melphalan, and ATG. The dose of $CD34^+$ cells was 6.55×10^6/kg. Immunosuppressive treatment during LT consisted of steroids and tacrolimus. Mild skin and gut GvHD developed in the second week after HSCT and was successfully treated with steroids. He did not experience any other significant complications and is now 37 years old and alive and well.

P8

Patient P8 manifested sclerosing cholangitis in 1990 at the age of 33 years. Three years later, the patient received a diagnosis of XHIGM and was started on immunoglobulin substitutive therapy. The molecular defect was identified as a splice-site mutation downstream of exon 1 in *CD40LG* (c.156+1G>T). Clinically, he only presented with upper respiratory tract infections and neutropenia; *Cryptosporidium* species infection was not detected. Because of the liver disease, he underwent LT at the age of 38 years but died shortly thereafter of transplant-related complications.

P9

Patient P9 presented at the age of 8 months in 1983 with recurrent respiratory tract infections, failure to thrive, and neutropenia and received a diagnosis of XHIGM. Genetic testing later confirmed the diagnosis (genetic details not available). He was treated with immunoglobulin replacement therapy, trimethoprim-sulfamethoxazole prophylaxis, and, for a short period of time, crude thymic extract and fresh frozen plasma. He went on to have chronic lung disease, septic arthritis of the hip, and joint tuberculosis of the shoulder and knee. Sclerosing cholangitis associated with *Cryptosporidium* species infection was diagnosed at the age of 11 years. Cryptosporidiosis was identified by means of direct microscopy on stool samples and bronchoalveolar lavage fluid. He underwent an mMUD HSCT from bone marrow at the age of 16 years, with mismatch of one HLA-A antigen after myeloablative conditioning with cyclophosphamide, alemtuzumab, and total-body irradiation at a total dose of 14.4 Gy. Early engraftment of platelets and neutrophils with 100% donor chimerism was complicated by

acute cutaneous GvHD and followed by complete loss of chimerism and acute liver failure requiring LT. LT was performed in an emergency setting, and the postoperative course was complicated by pulmonary hemorrhage and renal failure. The patient ultimately died a short time after LT of disseminated cryptosporidiosis and hemophagocytic lymphohistiocytosis.

P10

Patient P10 was given a diagnosis of XHIGM at the age of 7 years in 2000. He carried a deletion in *CD40L* (c.676-679del, p.G226fs*15) and had chronic diarrhea and failure to thrive, *Cryptosporidium* species infection, and sclerosing cholangitis. Further details about his infectious and immunologic history are not available. Since the diagnosis, he was treated with immunoglobulin substitution, prophylaxis with trimethoprim-sulfamethoxazole and azithromycin, and ursodeoxycholic acid.

At the age of 12 years, he underwent deceased-donor orthotopic LT, followed by an mMUD HSCT 2 months later. He was conditioned with fludarabine, thiotepa, melphalan, and ATG and received 4.24×10^6/kg $CD34^+$ cells from bone marrow. Engraftment was successful, but the posttransplantation course was complicated by a relapse of *Cryptosporidium* species infection, sclerosing cholangitis, CMV and EBV reactivation, *Candida* species infection, and acute kidney failure. The patient succumbed to complications 2 months after HSCT.

P11

Patient P11 was given a diagnosis of XHIGM in 1983, when he was 6 months old, after his older brother died in infancy from *P jirovecii* pneumonia. A first cousin was also given a diagnosis of the disease. CD40L expression was absent on peripheral lymphocytes, and genetic testing demonstrated the presence of a novel mutation in this family (c.231_232insT, p.78fsX8).[E5,E6] Clinically, he presented with upper and lower respiratory tract infections, chronic diarrhea, failure to thrive, and *Parvovirus* species infection. He was treated with substitutive immunoglobulins since the diagnosis. During childhood, he had *Cryptosporidium* species infection and sclerosing cholangitis that finally evolved into end-stage liver disease. He received an LT at the age of 10 years but died 2 years later from a relapse of sclerosing cholangitis and persistent *Cryptosporidium* species infection.

P12

Patient P12 presented in 2003, at age 7 months, with staphylococcal scalded-skin syndrome and a polymicrobial soft tissue infection. Because of this unusual infection and a family history of a brother who died of pneumococcal sepsis, he underwent an immune deficiency evaluation and eventually received a diagnosis of XHIGM caused by a deletion in *CD40LG* (Xq26.3del[135728471_135730458]). He was treated with immunoglobulin substitution and trimethoprim-sulfamethoxazole prophylaxis.

The patient experienced mild respiratory tract infections throughout his life but experienced severe pulmonary disease with *M avium* complex and *Aspergillus* species since the age of 13 years, resulting in chronic lung disease and bronchiectasis. He also manifested mild neutropenia, diarrhea, and failure to thrive, and at the age of 13 years, he was given a diagnosis of *Cryptosporidium* species infection and sclerosing cholangitis. He received treatment with pentamidine, azithromycin, rifabutin, rifampin, ethambutol, voriconazole, liposomal amphotericin, and nitazoxanide.

At age 14 years, he underwent deceased-donor orthotopic LT, which was complicated by hepatic artery stenosis and recurrence of *Cryptosporidium* species infection, with concern for graft failure caused by chronic rejection. He never recovered from the LT well enough to be able to undergo HSCT and finally passed away 1 year after LT from fulminant liver failure.

P13

Patient P13 presented with *P jirovecii* pneumonia at the age of 2 months and subsequently experienced chronic interstitial lung disease, diarrhea, and failure to thrive. He was given a diagnosis of XHIGM at age 11 years, and immunoglobulin substitution and prophylaxis with trimethoprim-sulfamethoxazole were started. Immunologically, he manifested neutropenia. He had sclerosing cholangitis, with documented *Cryptosporidium* species infection, which led to LT at 24 years of age. He received a deceased-donor orthotopic LT, and immunosuppressive treatment consisted of steroids, tacrolimus, and MMF. He experienced several posttransplantation complications, among which were hemorrhagic shock after a biopsy, *Enterococcus* species bacteremia, CMV reactivation, and pericarditis. He had a relapse of cryptosporidiosis 2 months after LT and succumbed to sepsis in the context of evolving *Cryptosporidium* species infection in the first year after transplantation.

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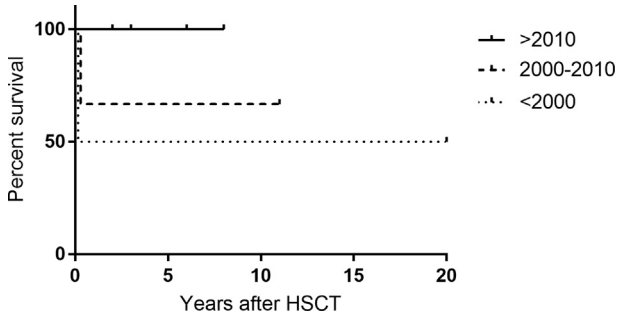

FIG E1. Kaplan-Meier curve of survival of 9 patients with XHIGM treated with HSCT and LT based on year of HSCT.

TABLE E1. Clinical, genetic, and immunologic characteristics of 13 patients with XHIGM treated with LT

Patient no.	Age	Age at diagnosis of XHIGM	Familial cases	Genetic diagnosis	Lack of CD40L expression	Ig levels	Neutropenia	Anemia	PJP	Chronic LD	Other infections	Chronic diarrhea	FTT	Rx	HSCT	Current Rx	Outcome
P1	27 y	5 mo	No	Yes c.-191A>C	Yes	IgM, 1.85 g/L IgG, 1.98 g/L IgA, <0.04 g/L	No	No	Yes	No	HHV-6	Yes	No	Ig Cotrim Nitaz	Yes	Tacro	A/W
P2	25 y	7 y	No	No	Yes	IgM ↑ IgG ↓ IgA ↓	No	No	No	No	*Staphylococcus aureus*	Yes	Yes	Ig Cotrim	Yes	Ig	A/W
P3	13 y	6 y	Yes Brother	No	Yes	IgM ↑ IgG NA* IgA ↓	No	No	Suspected	Yes	-	Yes	Yes	Ig Cotrim Azithro Nitaz Paromo High-dose CS	Yes	Tacro CS	A/W
P4	18 y	2 y	No	Yes c.120delA	Yes	IgM, 2.7 g/L IgG, 2.7 g/L IgA, <0.06 g/L	Yes	No	No	No	Respiratory tract infections	No	No	Ig Cotrim	Yes	Tacro MMF	A/W
P5	11 y	5 y	No	Yes c.773T>G	Yes	IgM, 0.8 g/L IgG, 3 g/L* IgA, 0.1 g/L	No	No	No	No	-	Yes	Yes	Ig Cotrim Paromo	Yes	Cyclo MMF	A/W
P6	23 y	6 mo	Yes Brother	Yes c.500delG	Yes	IgM, 0.48 g/L IgG, 0.99 g/L IgA, 0.01 g/L	Yes	No	No	No	Sinusitis, cryptococcal meningoencephalitis	No	No	Ig Cotrim Paromo Nitaz G-CSF Thalido	Yes	Tacro Thalido	A/W
P7	38 y	3 y	Yes Brother	Yes g.11880_11884 delGAGCA	Yes	IgM ↑ IgG ↓ IgA ↓	Yes	Yes	No	No	*Pseudomonas* species and *S mitis* biliary infection	No	No	Ig Cotrim Paromo UDCA Diuretics	Yes	Tacro	A/W
P8	38 y†	36 y	No	Yes c.156+1G>T	NA	IgM ↑ IgG ↓ IgA ↓	Yes	No	No	No	Respiratory infections	No	No	Ig	No	—	Deceased aged 38 y
P9	16 y†	8 mo	No	Yes	Yes	IgM ↑ IgG ↓ IgA ↓	Yes	No	No	Yes	Respiratory tract infection, septic arthritis of the hip, joint tuberculosis of shoulder and knee	No	Yes	Ig Cotrim Crude thymic preparation FFP	Yes	—	Deceased aged 16 y
P10	12 y†	7 y	No	Yes c.676-679del	NA	IgM ↑ IgG ↓ IgA ↓	NA	NA	NA	NA	-	Yes	Yes	Ig Cotrim Azithro UDCA	Yes	—	Deceased aged 13 y

(Continued)

TABLE E1. *(Continued)*

Patient no.	Age	Age at diagnosis of XHIGM	Familial cases	Genetic diagnosis	Lack of CD40L expression	Ig levels	Neutropenia	Anemia	PJP	Chronic LD	Other infections	Chronic diarrhea	FTT	Rx	HSCT	Current Rx	Outcome
P11	13 y†	6 mo	Yes Brother Cousin	Yes c.231_232insT	Yes	IgM, 1.12 g/L IgG, 1.38 g/L IgA, <0.05 g/L	No	No	No	No	Respiratory infections, parvovirus and *Leishmania donovani* infection	Yes	Yes	Ig	No	—	Deceased aged 13 y
P12	15 y†	1 y	Yes Brother	Yes Xq26.3 del (135728471_135730458)	NA	IgM ↑ IgG ↓ IgA ↓	Yes	No	No	Yes	Respiratory tract infections, pulmonary *M avium* and aspergillosis	Yes	Yes	Ig Cotrim Penta Azithro Rifabutin Rifampin Ethamb Vorico L-AMB Nitaz	No	—	Deceased aged 15 y
P13	25 y†	11 y	NA	NA	NA	NA	Yes	No	Yes	Yes	—	Yes	Yes	Ig Cotrim	No	—	Deceased aged 25 y

A/W, Alive and well; *Azithro*, azithromycin; *Cotrim*, cotrimoxazole (trimethoprim-sulfamethoxazole); *CS*, corticosteroids; *Cyclo*, cyclophosphamide; *Ethamb*, ethambutol; *FFP*, fresh frozen plasma; *FFT*, failure to thrive; *G-CSF*, granulocyte-colony stimulating factor; *HHV-6*, human herpesvirus 6; *Ig*, immunoglobulin; *L-AMB*, liposomal amphotericin B; *LD*, lung disease; *NA*, not available; *Nitaz*, nitazoxanide; *Paromo*, paromomycin; *Penta*, pentamidine; *PJP*, *P jirovecii* pneumonia; *Rx*, therapy; *Tacro*, tacrolimus; *Thalido*, thalidomide; *UDCA*, ursodeoxycholic acid; *Vorico*, voriconazole.
*During immunoglobulin supplementation.
†Deceased.