Clinical spectrum of X-linked hyper-IgM syndrome

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We report the clinical and immunologic features and outcome in 56 patients with X-linked hyper-IgM syndrome, a disorder caused by mutations in the CD40 ligand gene. Upper and lower respiratory tract infections (the latter frequently caused by *Pneumocystis carinii*), chronic diarrhea, and liver involvement (both often associated with *Cryptosporidium* infection) were common. Many patients had chronic neutropenia associated with oral and rectal ulcers. The marked prevalence of infections caused by intracellular pathogens suggests some degree of impairment of cell-mediated immunity. Although lymphocyte counts and in vitro proliferation to mitogens were normal, a defective in vitro proliferative response to antigens was observed in some patients, and additional defects of cell-mediated immunity may be presumed on the basis of current knowledge of CD40-ligand function. All patients received regular infusions of immunoglobulins. Four patients underwent liver transplantation because of sclerosing cholangitis, which relapsed in three. Three patients underwent bone marrow transplantation. Thirteen patients (23%) died of infection and/or liver disease. X-linked hyper-IgM syndrome, once considered a clinical variant of hypogammaglobulinemia, is a severe immunodeficiency with significant cellular involvement and a high mortality rate. (J Pediatr 1997;131:47-54)

Immunodeficiency with hyper-IgM is a rare genetic disorder characterized by recurrent infections in association with markedly decreased serum IgG, IgA, and IgE levels but normal or elevated serum IgM levels.[1] Genetic heterogeneity is indicated by the occurrence of X-linked and autosomal recessive variants. Acquired forms of the disease have been also reported.[1] The molecular pathogenesis of the X-linked form of HIM has been elucidated; several groups of researchers have demonstrated that the defect is caused by mutations in the gene encoding for the CD40 ligand, located at Xq26.3-27.[2-6] Point mutations, insertions, deletions, and splice-site mutations at the CD40L locus have been described in patients with XHIM.[7] The CD40L is a type II integral transmembrane glycoprotein, expressed mainly by activated $CD4^+$ T lymphocytes. It belongs to a novel family of type II proteins that include tumor necrosis factors alpha and beta, nerve growth factor, and the ligands for FAS, CD27, CD30, and 4-1 BB.[8]

See related articles, pp. 8 and 147.

Interactions between activated $CD4^+$ T-cells expressing the CD40L and B lymphocytes (that constitutively express CD40) serve as fundamental membrane signals for B-cell growth and differentiation.[9] In the presence of appropriate costimulatory soluble signals provided by cytokines, CD40-CD40L interaction drives both the isotype switch and memory B-cell generation.[10] Thus CD40L molecules are required for B-cell activation and the production of IgG, IgA, and IgE in response to T cell–dependent antigens, as well as for the formation of germinal centers. Consequently, both the patients with XHIM and the CD40L gene–targeted mice show an inability to mount IgG, IgA, and IgE responses to T cell–dependent antigens and lack germinal centers, but their ability to produce IgM is preserved.

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Table I. Clinical features in 56 patients with X-linked hyper-IgM syndrome

Manifestation	No.	%
Respiratory tract		
URTI	49	87.5
LRTI	46	82.1
Parenchymal infection	29	51.8
Interstitial infection	22	39.3
Gastrointestinal tract		
Diarrhea	31	55.3
Oral ulcers	25	44.6
Liver/biliary tree		
Sclerosing cholangitis	11	19.6
Hepatitis	9	16.1
Cirrhosis	6	10.7
Sepsis	8	14.3
Arthritis	6	10.7
CNS manifestations		
Meningitis/encephalitis	5	8.4
Encephalopathy	2	3.6
Tumors	2	3.6

URTI, Upper respiratory tract infection; *LRTI*, lower respiratory tract infection; *CNS*, central nervous system.

The clinical and immunologic features of patients with HIM, regardless of the genetic basis, have been reviewed.[1, 11-13] However, scant information is available on a representative cohort of patients with a clearly defined CD40L defect. The collection of data through the Registry of the European Society for Immune Deficiency enabled us to analyze clinical and immunologic features, prognosis, and response to treatment in this selected group of patients.

METHODS

The names and addresses of European physicians taking care of patients with HIM were obtained from the Registry of Primary Immunodeficiencies of the European Society for Immune Deficiency (Huddinge, Sweden). The physicians answered a detailed questionnaire, and clinical, genetic, and immunologic data were gathered and analyzed with Excel (Microsoft Corp.) and SPSS (SPSS, Inc.) software. Data on immunoglobulin serum levels, total lymphocyte count, and enumeration of $CD4^+$ and $CD8^+$ T cells and of B cells, and on the in vitro proliferative response to phytohemagglutinin and tetanus toxoid, were requested. These assays were performed by means of standard laboratory techniques. For the analysis of CD40L expression, peripheral blood mononuclear cells were activated in vitro with phorbol-myristate acetate and ionomycin, as described,[14] and stained with CD40-immunoglobulin construct (kindly provided by Dr. J. Y. Bonnefoy, Glaxo Wellcome, Geneva, Switzerland) and with the anti-CD40L monoclonal antibody TRAP1 (kindly provided by Dr. R. Kroczek, Robert-Koch Institute, Berlin, Germany), as described.[7, 14] In all cases a similar degree of reactivity was observed with either reagent.

CD	Cluster distribution
CD40L	CD40 ligand
CMV	Cytomegalovirus
HIM	Hyper-IgM syndrome
HLA	Human leukocyte antigen
IVIG	Intravenously administered immunoglobulin
PCP	*Pneumocystis carinii* pneumonia
XHIM	X-linked hyper-IgM syndrome

Survival analysis was performed by the Kaplan-Meier product-limit method.[15] The starting time for all survival analyses was the date of birth. For survival analysis, death from any cause was considered a treatment failure.

The identification of patients by initials and birth date was adopted to avoid the risk of including any patient more than once.

RESULTS

Ninety-eight patients were identified as having HIM. Of these, 56 (from 47 families) fulfilled the criteria for XHIM. The inclusion criteria were evidence of specific CD40L gene mutation (48 patients) and/or clear X-linked inheritance (with multiple affected males in multiple generations) in association with defective CD40L expression (8 patients). An X-linked pattern of inheritance was evident from the pedigree of 32 patients, who belonged to 23 unrelated families. The mean age at presentation was 12.9 months (range, birth to 96 months of age).

Clinical Features

The most common clinical signs in the cohort of patients with XHIM are shown in Table I. Infections were the most prominent clinical feature of the disease, and most of the patients had multiple infections. Although positive identification by culture of common, uncomplicated infections was obtained relatively infrequently, severe infections were also common and were more actively investigated. Bacterial sepsis occurred in eight patients (14%), five of whom had chronic neutropenia, and was the cause of death in one. *Escherichia coli* was the predominant pathogen involved (four cases); one patient had multiple episodes of sepsis of bacterial origin. Disseminated *Mycobacterium tuberculosis* and cytomegalovirus infections were recorded in one patient each.

RESPIRATORY TRACT INFECTIONS

Upper and lower respiratory tract infections were the most common clinical manifestation of the disease. Among the 46 patients with LRTI, 20 (43.8%) had

multiple parenchymal (11 patients), interstitial (5 patients), or both parenchymal and interstitial (4 patients) infections. Bronchiectases developed in 25% of patients with LRTI. *Pneumocystis carinii* accounted for the vast majority of episodes of interstitial pneumonia. It was identified by bronchoalveolar lavage or lung biopsy in 18 of 22 patients with interstitial pneumonia. This pulmonary infection was particularly prevalent in infancy and represented the first clinical sign of XHIM in 16 (43.2%) of 37 patients in whom the clinical onset of the disease occurred within the first year of life. CMV and adenovirus infections were diagnosed in four and two patients, respectively (one of the patients with CMV infection had a disseminated disease, as shown above). Two patients had *Cryptococcus neoformans* lung infection, and three patients had mycobacterial pneumonia (caused by bacillus Calmette-Guérin, *Mycobacterium bovis*, or atypical *Mycobacterium*).

GASTROINTESTINAL PROBLEMS

Thirty-one patients (55.3%) had diarrhea, which followed a chronic course leading to failure to thrive in 20 (64.5%). Total parenteral nutrition was required in 13 patients. Among patients with diarrhea, *Cryptosporidium* was identified in 12, *Giardia lamblia* in 4, and *Salmonella* and *Entamoeba histolytica* in two patients each. Intestinal nodular lymphoid hyperplasia (diagnosed in three patients) and inflammatory bowel disease (in two patients) were the noninfectious causes of chronic diarrhea.

Oral ulcers were frequently observed (Table I) and were usually associated with neutropenia (87.5%). Gingivitis and perianal ulcers were also frequently observed.

Eleven of the patients with XHIM (19.6%) had sclerosing cholangitis, diagnosed by liver biopsy. In three of them, cirrhosis with hepatic failure required liver transplantation. A fourth patient with sclerosing cholangitis underwent liver transplantation because of severe cholestasis. Among the 11 patients with sclerosing cholangitis, six (55%) had concomitant cryptosporidiosis. Five patients were infected with hepatitis B virus and 1 of 36 investigated by polymerase chain reaction with hepatitis C virus. Of the five patients with hepatitis caused by HBV, three had previously been treated with fresh frozen plasma and one had received multiple blood transfusions. In three patients, chronic hepatitis progressed to liver cirrhosis, and in two of them, fatal hepatocellular carcinoma eventuated. CMV-related hepatitis developed in one additional patient. In two patients, hepatitis of unknown cause, with persistently elevated transaminase activities and no identified infectious agent, was diagnosed.

Table II. Hematologic problems in 56 patients with X-linked hyper-IgM syndrome

Disorder	No.	%
Anemia	18	32.1
Low Fe, high ferritin	12	21.4
Iron deficiency	3	5.3
Aplastic	3	5.3
Coombs positive hemolytic	1	1.7
Neutropenia	38	67.8
Chronic	25	44.6
Cyclic	7	12.5
Episodic	6	10.7

HEMATOLOGIC PROBLEMS

The main hematologic abnormalities observed in patients with XHIM are shown in Table II. Anemia was present in a third (18/56) of the patients and in 12 of them was characterized by low serum iron and elevated ferritin levels (as typically observed in chronic infection). Neutropenia, identified in 38 patients (67.8%), was usually chronic (25 cases). Anti-neutrophil antibodies were sought in six of the patients with chronic neutropenia but were not detected. In four patients, bone marrow studies revealed a maturation arrest of the myeloid lineage at the promyelocyte-myelocyte stage.

MISCELLANEOUS

Seven patients had neurologic problems. Two had degenerative encephalopathy, but exhaustive diagnostic tests failed to identify a causative pathogen. The cause of central nervous system infection in the remaining five patients was variable, with *Toxoplasma*, echovirus, *Cryptococcus*, CMV, and *M. bovis* being responsible in one patient each.

Six patients had seronegative arthritis, in association with oral ulcers in four cases and with proctitis and inflammatory bowel disease in one patient each. Five of these patients had concomitant neutropenia. In none of this group of patients was a pathogen identified, but the presence of etiologic agents such as *Ureaplasma* or *Trichomonas* was not actively investigated.

Seven patients had significant lymphadenopathy. One patient had hypothyroidism.

Immunologic Features

Table III presents the immunologic profile of the study group. Before the initiation of treatment with intravenously administered immunoglobulins, data on serum IgM levels were available in 55 patients. The levels were normal in 29 and were high in 26 (47.3%), with peak levels reaching 13 gm/L. The group with elevated serum IgM levels had a higher mean age (geometric mean, 31.8 months; confidence limits, 23.0 to 40.6 months) than the group with normal serum IgM levels (geometric mean, 20.8 months; confidence limits, 11.7 to 29.8 months), but this difference was not statistically significant. Increased serum IgM levels were recorded in 39 (69.6%) of 56 patients at some point during the course of the disease.

Before substitution therapy, IgG serum levels in all patients were well below the normal range for age-matched control

Table III. Immunologic investigations in patients with X-linked hyper-IgM syndrome

Parameter	N	Mean	Range
IgG (gm/L)	53	1.1	0–2.64
IgA (gm/L)	55	0.2	0–2.92
IgM (gm/L)	55	2.62	0.3–13
B cells/μl	35	888	100–4000
T cells/μl	35	4230	750–16,800
$CD4^+$ cells/μl	33	2766	300–9800
$CD8^+$ cells/μl	33	1106	100–7500

subjects. Of 55 patients in whom serum IgA levels were determined, 51 (92.7%) had very low or undetectable levels; however, 3 patients had elevated levels (2.0, 2.6, and 2.9 gm/L). Serum IgE levels, determined in 27 patients, were less than 5 kU/L in 20 patients but very high (> 1000 kU/L) in one.

Anti-nuclear antibodies were sought in 21 patients and found in two; three patients had anti-parietal cell and anti-thyroid microsomal autoantibodies. Positivity for autoantibodies was not associated with relevant clinical problems in any of these patients. In contrast, one patient of the five with autoantibodies had Coombs-positive hemolytic anemia subsequently.

B- and T-cell counts were generally normal: low counts of B cells (<200 cells/mm^3), $CD4^+$ T cells (<500 cells/mm^3), or $CD8^+$ T cells (<200 cells/mm^3) were identified in 9.6%, 5.9%, and 2% of patients, respectively. In vitro proliferative responses to phytohemagglutinin, tested in 46 patients, were normal in 43 patients (93%). In contrast, 6 of 16 patients had a reduced (<30% of control values) in vitro proliferative response to tetanus toxoid.

Therapy

IVIG therapy is the treatment of choice in XHIM.[1, 12] In our series, 51 (91.1%) of 56 patients received this treatment on a regular basis; one patient died of *P. carinii* pneumonia after only three IVIG infusions, and four patients were treated with fresh frozen plasma at a dose of 20 ml/kg per month. Of the 51 patients on the IVIG regimen, 31 (60.8%) received 400 to 500 mg/kg every 3 to 4 weeks and 20 patients received 200 to 300 mg/kg every 3 weeks.

Regular use of IVIG resulted in a marked decrease of infectious episodes in 46 (90.1%) of 51 patients; among the other patients, one died of peritonitis, one acquired sepsis caused by coagulase-negative *Staphylococcus*, one had multiple interstitial pneumonias, and two continued to have recurrent URTI and LRTI. All these patients who did not benefit from IVIG therapy were receiving IVIG regularly, at a dosage of 300 to 400 mg/kg every 3 weeks.

In the cohort of 51 patients who received IVIG regularly, serum IgM levels decreased somewhat in 5 and became normal in 9 of 26 patients who had elevated serum levels before the start of IVIG infusions. In 17 additional patients, IgM levels remained normal throughout the course of the disease. In contrast, IgM levels remained high or even increased in 20 patients, despite IVIG therapy. This individual variability in IgM levels during treatment with IVIG was not strictly related to differences in dosages or duration of IVIG substitution therapy. However, patients who maintained normal IgM levels received their first IVIG infusion at an earlier age (geometric mean, 20.2 months; confidence limits, 12.7 to 27.8 months) than did those whose IgM levels remained high or even increased during the course of the disease (geometric mean age, 23.4 months; confidence limits, 12.1 to 35.2 months), although the difference was not statistically significant. In 14 of the 29 patients whose condition was evaluated, neutropenia was corrected by IVIG substitution therapy.

Forty-three patients (76.8%) were treated with antibiotic prophylaxis; 23 of them received life-long treatment, 16 were treated sporadically, and 4 received prophylactic trimethoprim-sulfamethoxazole during their first 2 years of life. In all, 27 patients (48.2%) received trimethoprim-sulfamethoxazole to prevent PCP, including 10 patients in whom PCP was the first clinical sign of the disease. Trimethoprim-sulfamethoxazole prevented further episodes of PCP in all patients but one.

Eleven patients received granulocyte colony-stimulating factor for severe, symptomatic neutropenia. In eight cases normalization of the neutrophil count was achieved. Three patients had a bone marrow transplantation (two from an HLA-matched sibling and a third, more recently, from a matched unrelated donor). Four patients underwent liver transplantation because of sclerosing cholangitis, which was associated with cirrhosis in three of them.

Outcome

Forty-three patients are alive (mean age, 9.7 years; range, 3 to 23 years), and 13 patients (23.2%) have died (mean age, 11.7 years; range, 9 months to 23 years). The causes of death are listed in Table IV. Six deaths were caused by severe infection (CMV infection in two cases, and PCP, staphylococcal sepsis, disseminated *Mycobacterium tuberculosis*, and peritonitis in one patient each). In six patients, death was due to severe liver disease; one patient died of a primitive neuroectodermal tumor of the colon associated with cirrhosis and hepatocellular carcinoma.

One of the three patients who underwent bone marrow transplantation died of generalized CMV infection, and one patient is alive and well 3 years after transplantation.[16] Limited follow-up is available for the third patient, who recently received bone marrow from a matched unrelated donor. Of the four patients who underwent liver transplantation, two died

of relapse of sclerosing cholangitis and liver failure, one is alive but in poor condition (with a relapse of sclerosing cholangitis), and one is alive and well. The survival curve for our series of patients is shown in the Figure.

Table IV. Causes of death in patients with X-linked hyper-IgM syndrome

Patient No.	Cause of death	Age at death
1	*Pneumocystis carinii* pneumonia, staphylococcal sepsis	9 months
2	*Pneumocystis carinii* pneumonia	14 months
3	Peritonitis	3.5 years
4	Hepatocellular carcinoma, cirrhosis, liver failure	5 years
5	Liver failure, sclerosing cholangitis	11 years
6	Sclerosing cholangitis and liver failure, after liver transplantation	13 years
7	Liver failure, after liver transplantation	14 years
8	Cirrhosis, liver failure	14 years
9	Disseminated mycobacterium tuberculosis infection	15 years
10	CMV encephalitis	16 years
11	Cirrhosis	18 years
12	CMV infection, post bone marrow transplantation	20 years
13	Primitive neuroectodermal tumor of the colon, hepatocellular carcinoma, cirrhosis	23 years

CMV, Cytomegalovirus.

DISCUSSION

Although originally considered a humoral form of immunodeficiency, XHIM was suspected in 1986 to be due to defective T-cell function, when Mayer et al.[17] demonstrated that B cells in XHIM could be driven to undergo isotype switch if cocultured in the presence of $CD4^+$ T cells derived from a patient with Sézary disease. More recently, XHIM was shown to be due to mutations of the gene encoding for CD40L,[2-6, 18] a molecule mainly expressed by activated $CD4^+$ T cells. Several groups have shown that both membrane-bound and soluble trimeric forms[19] of CD40L can induce B-cell activation and isotype switch in vitro.[8-10, 19] Furthermore, CD40L gene–targeted mice share with XHIM patients the inability to mount IgG, IgA, and IgE antibody responses to T cell–dependent antigens and, in addition, lack germinal centers.[20, 21] A few of our patients had elevated serum IgA or IgE levels, indicating that mechanisms other than CD40-CD40L interaction may also induce isotype switch. The patient with an elevated serum IgE level carries an insertion of a single nucleotide at codon 64, resulting in frameshift and premature termination at codon 85, as previously reported.[22] Similarly, two of the three patients with elevated serum IgA levels carry an insertion or a deletion of a single nucleotide that also results in frameshift and premature termination at codons 85 and 144, respectively, abolishing CD40L expression. The third patient with an elevated serum IgA level carries a mutation in the acceptor splice site of intron 2, which results in skipping of exon 3, frameshift, and premature termination. Thus the production of IgA or IgE in these patients did not happen because of the preservation of residual CD40L expression and function. Furthermore, one of the patients with XHIM and an elevated serum IgA level had few affected male relatives with undetectable IgA, which indicated that, although CD40-CD40L interaction has a crucial importance in determining isotype switch, immunoglobulin serum levels may be affected by additional genetic or environmental factors. Moreover, these data show that the diagnosis of XHIM should not be restricted necessarily to patients with a typical immunoglobulin profile. The observed variability in serum IgM levels, which were within the normal range in a substantial proportion of patients, suggests that increased IgM levels are not a genetically determined feature of the disease. CD40L-deficient mice do not have increased serum IgM levels if kept under germ-free conditions.[20, 23] When present, elevated serum IgM levels in patients with XHIM may actually reflect chronic, poorly controlled infections, as suggested also by the fact that higher levels of serum IgM were observed in patients who started IVIG substitution therapy at a later age. However, though high-dose IVIG therapy has been reported to suppress IgM blood levels in patients with HIM,[13, 24] this happened in only 53.8% of the cases in our series, indicating that patients with XHIM do not respond uniformly to this treatment by decreasing the serum IgM concentration.

The most prominent clinical feature of the study group was the increased occurrence of opportunistic infections (*Cryptosporidium*, *P. carinii*, mycobacteria, and CMV). Though susceptibility to *Cryptosporidium* and *P. carinii* have been reported previously,[1] the occurrence of mycobacterial infections in patients with XHIM is new. These infections are uncommon in pure humoral immunodeficiencies and are frequently associated with severe defects of cell-mediated immunity. Though ineffective CD40-CD40L interaction readily explains the unique immunoglobulin profile observed in XHIM, the basis for the increased susceptibility to opportunistic infections has long remained elusive. As also shown in this study, the in vitro proliferative response to T-cell mitogens is normal in patients with XHIM. In contrast, a defective T-cell proliferative response to specific antigens (tetanus toxoid) was observed, though in a smaller proportion of patients. These data need to be confirmed in a larger series using multiple antigens and standardized protocols; however, it is noteworthy that antigen-specific T-cell priming is defective in CD40L-deficient mice also.[25]

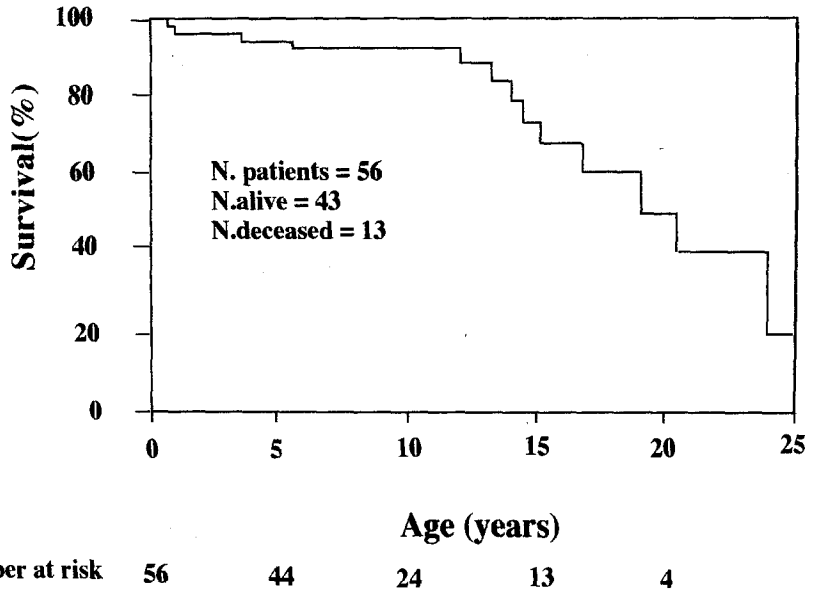

Figure. Kaplan-Meyer survival curve resulting from a retrospective analysis of 56 patients with X-linked hyper-IgM syndrome.

It has been shown that expression of CD40L facilitates T-cell activation.[26] This may be due to a direct stimulatory role of CD40L itself[27, 28] or to the involvement of costimulatory signals elicited after CD40-CD40L interaction. In particular, signaling through CD40 induces de novo expression of CD80/CD86 by B cells, which may then bind to CD28 (expressed by T lymphocytes), generating an important costimulatory signal for T cells.[29] More recently, several groups have shown that interaction between activated $CD4^+$ T cells, expressing CD40L, and macrophages (that express CD40) is crucial to the immune defense against *Leishmania*[30, 31] and *P. carinii*.[32] In particular, signaling through CD40 would result in increased production of interleukin 12 by macrophages, which would then stimulate T cells to release interferon gamma.[33] The latter cytokine would, in turn, activate macrophages to kill the pathogen. The crucial role of this pathway is illustrated by the fact that CD40- or CD40L-deficient mice have an increased susceptibility to infections caused by *Leishmania* and *P. carinii*.[30-32, 34] Indeed, T cell–mediated macrophage activation is impaired in CD40L-deficient mice.[35]

Finally, CD40L has been shown to exert antiviral activity, although by mechanisms that are still poorly understood.[36] In particular, it has recently been shown that CD40L-deficient mice have an impaired memory cytotoxic T-cell response.[37] Defective CD40L expression in XHIM might thus also contribute to the increased occurrence of CMV infection; on the other hand, it should be noted that patients with XHIM do not appear to be at high risk of having other herpesvirus infections.

The unique susceptibility of patients with XHIM to opportunistic infections has important diagnostic and therapeutic consequences. Infection with *P. carinii* was the first diagnostic sign suggesting XHIM in 43% of our patients. Therefore a diagnosis of XHIM should be considered at the first episode of PCP in all infants with hypogammaglobulinemia, even if the family history is negative. In fact, as many as 43% of our patients represented sporadic cases of the disease. Although PCP is a severe infection and carries a significant risk of death, the prophylactic use of trimethoprim-sulfamethoxazole almost completely eliminated the recurrence of this complication. Furthermore, regular use of IVIG markedly reduced the number of URTI and LRTI episodes.

Neutropenia was associated with systemic infection (sepsis) in five of our patients and may represent the first sign of the disease.[38] Neutropenia may also favor cryptococcal infection, which occurred in two of our patients and was reported previously in other children with XHIM.[39, 40] Contrary to previous reports in which IVIG therapy was highly effective in normalizing the neutrophil count,[11, 41] in our series this was achieved in only 48% of the cases. However, as observed by others,[42] we found that treatment with granulocyte colony-stimulating factor is effective in patients who did not respond favorably to IVIG infusions.

Chronic diarrhea (often leading to growth failure) and severe hepatobiliary disease were common and were often associated with a poor prognosis. *Cryptosporidium* infection was frequent and was associated with sclerosing cholangitis in six patients, as seen in patients with acquired immunodeficiency syndrome.[43, 44] We hypothesize that, in addition to macrophages, other cellular mechanisms, dependent on the CD40-CD40L interaction, participate in the immune defense against *Cryptosporidium*, thus preventing chronic infection and the resulting sclerosing cholangitis. Normal bile duct epithelium does not express CD40, whereas regenerating or inflamed epithelium does.[45] Using an in vitro system, Hayward et al.[45] showed that activation of CD40 on bile duct cells may play a role in protecting against *Cryptosporidium* infection. Persistently impaired cell-mediated immunity to *Cryptosporidium* is probably the cause of the relapse of sclerosing cholangitis after liver transplant, as observed in three subjects with XHIM.

In another group of patients, cirrhosis of the liver developed after viral hepatitis. Two patients with cirrhosis caused by HBV infection subsequently had fatal hepatocellular carcinoma. The appearance of this type of cancer in young individuals might be explained by the association of defective immune surveillance associated with T-cell deficiency in patients with

chronic hepatitis. The use of plasma and multiple transfusions was the likely source of infection in four of the five patients with HBV-related hepatitis. The increased occurrence of carcinomas of the liver, pancreas, and biliary tree has been reported recently.[45] These tumors usually appear in the wake of cholangiopathy or cirrhosis.

The survival rate in our series is poor (20% at 25 years). Severe liver disease has a marked impact on the mortality rate, accounting for half of the deaths. Though the use of uncontrolled, HBV-infected blood products probably contributed to the poor outcome, it should be noted that analysis of the 23 pedigrees with familial presentation of the disease revealed 35 additional boys who died before adolescence, 16 of whom belonged to the same generation as the affected family members included in this study. PCP and severe gastrointestinal manifestations were the predominant causes of deaths in these subjects. These data were not included in the present study because it was not possible to establish the diagnosis by using the strict inclusion criteria that were adopted. Nonetheless, the occurrence of so many deaths at an early age strengthens the observation that XHIM is a devastating disease.

In conclusion, XHIM is characterized by a high incidence of opportunistic infections, cancer, and an unfavorable outcome despite regular substitution therapy with IVIG. These data and the notion that XHIM is a cellular immunodeficiency characterized by the disruption of multiple cellular interactions (T-cells and B cells; T cells and macrophages) have prompted more aggressive therapeutic approaches, including bone marrow transplantation. Three patients underwent this procedure in our series: one was cured,[16] one died, and limited follow-up is available for the third. In another series (including patients with HIM as a whole), three of six patients with HIM (not limited to XHIM) who were treated with bone marrow transplantation were also cured.[46] Though these data are too preliminary to draw conclusions as to the indication and efficacy of this procedure in XHIM, it appears reasonable to consider bone marrow transplantation as a therapeutic option if HLA-matched family donors are available. In all other cases, rigorous use of IVIG therapy, PCP prophylaxis with trimethoprim-sulfamethoxazole, accurate monitoring of gastrointestinal manifestations (including cancer), and management of neutropenia are mandatory to reduce morbidity and mortality rates.

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