

lymphoma. A case of splenic Hodgkin lymphoma in a 20-year-old patient with CGD has also recently been reported.⁷

Weel et al⁴ estimated a high relative risk for cancer associated with CGD on the basis of epidemiologic data from The Netherlands. They hypothesized that patients with CGD display deficiencies in cytotoxicity to cancerous cells on the basis of early experiments showing antibody-dependent killing of tumor cells by neutrophils.¹⁰⁻¹² However, the absence of malignancy reports in large CGD cohorts from the United States,¹ Europe,¹³ and Japan¹⁴ and the lack of tumor development in murine models of CGD call this assertion into question.

No direct link between nicotinamide dinucleotide phosphate oxidase and tumorigenesis has been established, although an association between polymorphisms in oxidative stress pathway components (*CYBA* and *AKR1A1*) and the development of non-Hodgkin lymphoma has been reported.¹⁵ Superoxide production in B cells occurs at a level only one tenth that in phagocytes,¹⁶ and reactive oxygen species in B cells are known to act principally as signaling molecules, regulating a number of cell functions, including apoptosis.¹⁷⁻²⁰ It therefore seems most likely that reactive oxygen species act as signaling molecules in B cells, inducing apoptosis and preventing the uncontrolled proliferation of these cells. Our 2 cases contribute to the available evidence for a high degree of susceptibility to malignancy in patients with CGD. Whether this is a true cause-effect relation or just a spurious association of 2 rare diseases remains to be determined.

This article's Table E1, with all primary immunodeficiencies reported to occur in association with Hodgkin lymphoma, and Table E2, listing all solid cancers and hematologic malignancies reported to date in patients with CGD, can be viewed in the Online Repository, together with an extended list of relevant references, at www.jacionline.org.

Saul Oswaldo Lugo Reyes, MD^{a,b}

Felipe Suarez, MD^{b,c}

Rose-Marie Herbigneaux, MD^d

Hélène Pacquement, MD^f

Yves Réguerre, MD^g

Jean-Pierre Riviére, MD^e

Maylis de Suremain, BS^{a,b}

Yoann Rose, BS^{a,b}

Jacqueline Feinberg, PhD^{a,b}

Nizar Malahoui, MD^h

Alain Fischer, MD, PhD^h

Stéphane Blanche, MD^h

Jean-Laurent Casanova, MD, PhD^{a,b,h,j}

Capucine Picard, MD, PhD^{a,b,h,i}

Jacinta Bustamante, MD, PhD^{a,b}

REFERENCES

- Winkelstein JA, Marino MC, Johnston RB Jr, Boyle J, Curnutte J, Gallin JI, et al. Chronic granulomatous disease: report on a national registry of 368 patients. *Medicine* (Baltimore) 2000;79:155-69.
- Jabado N, Casanova JL, Haddad E, Dulieu F, Fournet JC, Dupont B, et al. Invasive pulmonary infection due to *Scedosporium apiospermum* in two children with chronic granulomatous disease. *Clin Infect Dis* 1998;27:1437-41.
- Salavoura K, Kolialexi A, Tsangaris G, Mavrou A. Development of cancer in patients with primary immunodeficiencies. *Anticancer Res* 2008;28:1263-9.
- Weel EA, Redekop WK, Weening RS. Increased risk of malignancy for patients with chronic granulomatous disease and its possible link to the pathogenesis of cancer. *Eur J Cancer* 1996;32A:734-5.
- Aguilera DG, Tomita T, Rajaram V, Fangusaro J, Katz BZ, Shulman S, et al. Glioblastoma multiforme in a patient with chronic granulomatous disease treated with subtotal resection, radiation, and thalidomide: case report of a long-term survivor. *J Pediatr Hematol Oncol* 2009;31:965-9.
- Wolach B, Ash S, Gavrieli R, Stark B, Yaniv I, Roos D. Acute lymphoblastic leukemia in a patient with chronic granulomatous disease and a novel mutation in *CYBB*: first report. *Am J Hematol* 2005;80:50-4.
- Geramizadeh B, Alborzi A, Hosseini M, Ramzi M, Foroutan HR. Primary splenic Hodgkin's disease in a patient with chronic granulomatous disease, a case report. *Iran Red Crescent Med J* 2010;12:319-21.
- Tran H, Nourse J, Hall S, Green M, Griffiths L, Gandhi MK. Immunodeficiency-associated lymphomas. *Blood Rev* 2008;22:261-81.
- Robison LL, Stoker V, Frizzera G, Heinritz K, Meadows AT, Filipovich AH. Hodgkin's disease in pediatric patients with naturally occurring immunodeficiency. *Am J Pediatr Hematol Oncol* 1987;9:189-92.
- Clark RA, Szot S. The myeloperoxidase-hydrogen peroxide-halide system as effector of neutrophil-mediated tumor cell cytotoxicity. *J Immunol* 1981;126:1295-301.
- Clark RA, Klebanoff SJ. Studies on the mechanism of antibody-dependent polymorphonuclear leukocyte-mediated cytotoxicity. *J Immunol* 1977;119:1413-8.
- Kindzelskii AL, Petty HR. Early membrane rupture events during neutrophil-mediated antibody-dependent tumor cell cytotoxicity. *J Immunol* 1999;162:3188-92.
- van den Berg JM, van Koppen E, Ahlin A, Belohradsky BH, Bernatowska E, Corbeel L, et al. Chronic granulomatous disease: the European experience. *PLoS One* 2009;4:e5234.
- Hasui M. Chronic granulomatous disease in Japan: incidence and natural history: the study group of phagocyte disorders of Japan. *Pediatr Int* 1999;41:589-93.
- Lan Q, Zheng T, Shen M, Zhang Y, Wang SS, Zahm SH, et al. Genetic polymorphisms in the oxidative stress pathway and susceptibility to non-Hodgkin lymphoma. *Hum Genet* 2007;121:161-8.
- Paclet MH, Coleman AW, Burritt J, Morel F. NADPH oxidase of Epstein-Barr virus immortalized B lymphocytes: effect of cytochrome b(558) glycosylation. *Eur J Biochem* 2001;268:5197-208.
- Nakazato T, Ito K, Ikeda Y, Kizaki M. Green tea component, catechin, induces apoptosis of human malignant B cells via production of reactive oxygen species. *Clin Cancer Res* 2005;11:6040-9.
- Vene R, Delfino L, Castellani P, et al. Redox remodeling allows and controls B cell activation and differentiation. *Antioxid Redox Signal* 2010;13:1145-55.
- Hiraoka W, Vazquez N, Nieves-Neira W, Chanock SJ, Pommier Y. Role of oxygen radicals generated by NADPH oxidase in apoptosis induced in human leukemia cells. *J Clin Invest* 1998;102:1961-8.
- Kim YS, Park GB, Lee HK, Song H, Choi IH, Lee WJ, et al. Cross-linking of B7-H1 on EBV-transformed B cells induces apoptosis through reactive oxygen species production, JNK signaling activation, and fasL expression. *J Immunol* 2008;181:6158-69.

Available online December 18, 2010.

doi:10.1016/j.jaci.2010.10.049

From ^athe Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Institut National de la Santé et de la Recherche Médicale, U980, Paris, France; ^bParis Descartes University, Necker Medical School; ^cthe Department of Hematology, Necker-Enfants Malades Hospital, Paris; ^dthe Hematology-Oncology Unit and ^ethe Pathology Department, Reunion CHU, Saint Denis Reunion, France; ^fthe Department of Medical Oncology, Institut Curie, Paris; ^gthe Hematology-Oncology Unit, Angers CHU, France; ^hthe Pediatric Hematology-Immunology Unit, and ⁱthe Study Center of Primary Immunodeficiencies, AP-HP, Necker Hospital, Paris; and ^jthe St Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, Rockefeller University, New York, NY. E-mail: jacinta.bustamante@inserm.fr.

Supported by BNP-Paribas Fondation, Schlumberger Fondation, Institut Universitaire de France, the ANR, and the Rockefeller University Center for Clinical and Translational Science grant no. 5UL1RR024143-03.

Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

Two new families with X-linked inhibitor of apoptosis deficiency and a review of all 26 published cases

To the Editor:

X-linked lymphoproliferative disease (XLP) is a primary immunodeficiency syndrome characterized by combined lymphoproliferation and inadequacy of immune response. The disease most often manifests after an infection with EBV.

In the majority of cases that have been genetically tested, mutations in the *SH2* domain-containing gene *1A*, which encodes

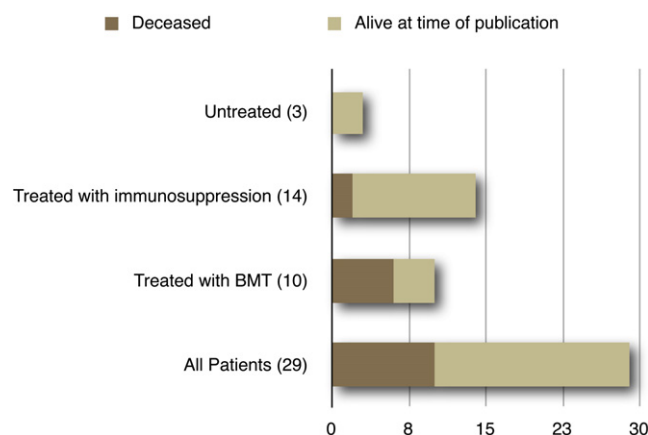


FIG 1. Retrospective mortality in the different treatment groups. The total of 27 patients does not include the 2 deceased relatives of our patients, who have not been diagnosed but may have died from XIAP deficiency–related complications. Data are not adjusted for age of survivors or the fact that chosen treatment likely corresponds to severity of presentation. Groups are formed by patients from the respective publications in the following manner: No treatment group: 3 patients reported by Marsh et al.² Immunosuppression group: 10 patients from the publication by Rigaud et al.,¹ the 3 patients presented here, and 1 patient reported by Zhao et al.³ Bone marrow treatment group: 2 patients from Rigaud et al.,¹ 1 patient reported by S. Latour via correspondence, and 7 patients described by Marsh et al.²

for *SLAM*-associated protein (*SAP*), a signaling adaptor molecule, were found. Mutations in the gene that encodes the X-linked inhibitor of apoptosis (*XIAP*) have been identified in SH2 domain–containing gene 1A—negative patients with XLP.¹ Among other functions, *XIAP* mainly inhibits cellular caspases and is a key regulator of apoptosis. XLP caused by *XIAP* mutations has been termed XLP-2. The clinical implications of *XIAP* deficiency in human beings have not yet been characterized, and a phenotype-genotype correlation for specific mutations is not visible.

A total of 42 DNA samples were selected from a larger collection of 152 patients with suspected XLP; all 42 had tested negatively for *SLAM*-associated protein mutations and were not related among themselves. Informed consent was obtained from all patients before examination of their DNA. Analysis of the samples led to the discovery of 2 new families with *XIAP* mutations. Here we present their clinical and molecular genetic data.

DNA was isolated from patients' blood by using standard methods. A 100-bp sequence located upstream of the initiation codon and the entire genomic region of the baculoviral inhibitor of apoptosis repeat-containing protein 4 gene were obtained by amplifying overlapping fragments via PCR. Direct double-strand sequencing was performed with fragment separation on a capillary sequencer. The sequences of the primer pairs used for PCR and sequencing reactions are available on request.

In family A, a single-nucleotide exchange from C→T was found that resulted in the replacement of an arginine encoding triplet CGA by stop codon TGA at amino acid position 222 (R222X nonsense mutation). The mutation was also found in the patient's mother (heterozygous carrier status).

In patient III-1 of family B, a 4-bp deletion mutation, S347Lfs5X, was identified. This mutation leads to a serine-to-leucine exchange at position 347 and a subsequent frameshift with a stop codon occurring 5 triplets later, at position 352. The same mutation was found in his brother and in his mother (heterozygous carrier status).

Chart reviews and patient interviews were performed to gain information on the disease presentation. Genealogic data and family interviews identified further possible afflicted patients in family B, both of whom had died in the 1970s.

All 3 definitely affected boys had a common history of recurrent or persistent splenomegaly and acute hemophagocytic syndrome during their first years of life. In patient III-2, hemophagocytic syndrome had occurred before EBV infection. For other clinical presentations, please refer to Table I. All 3 were successfully treated once with corticosteroids and/or intravenous immunoglobulins. They are currently 19, 26, and 28 years old, respectively, and have had no serious recurrences.

Review of the clinical progression of the 5 new patients with XLP-2 (a genetic diagnosis was secured in 3) presented here, from 12 patients published in the initial report,¹ 10 patients from Cincinnati,² and 1 additional patient,³ suggests that recurrent/persisting splenomegaly is the most common manifestation of XLP-2 (24 of 25 patients studied; 96%), followed by hemophagocytic syndrome (23 of 26 patients studied; 88.5%) and hypogammaglobulinemia (8 of 24 patients studied; 33%). An association with EBV was found in 16 of 25 patients studied (64%). This is important to note because recent guidelines consider hypogammaglobulinemia and association with EBV to be the distinctive features of XLP.⁴ To date, malignant lymphoma was not observed in any patient with XLP-2. This suggests that the clinical manifestation of XLP-2 differs markedly from X-linked lymphoproliferative disorder type 1 (XLP-1): persisting splenomegaly (alone) is not a typical phenotype in XLP-1. Malignant lymphoma, occurring in approximately one third of all patients with XLP-1,⁵ has not been found in any patient with XLP-2 studied so far. It has been proposed that *XIAP* deficiency may be more closely related to familial hemophagocytic lymphohistiocytosis than *SLAM*-associated protein deficiency.² Although the 2009 primary immunodeficiencies update does not distinguish much between XLP-1 and XLP-2,⁶ we agree that these entities are more distinct than previously believed. The notion that patients with XLP-2 do not seem to develop lymphoma should be emphasized in prognosis and the therapeutic approach.

Successful stem cell transplantation is the only curative therapy in XLP-1. Historical mortality using myeloablative conditioning regimens in XLP-1 in 1 study was 29%.⁵ Whether stem cell transplantation is the most apt treatment option for XLP-2 is currently controversially discussed. In 2 *XIAP*-deficient patients from France, stem cell transplantation failed.¹ Both patients died rapidly after being transplanted. A third *XIAP*-deficient patient from the Czech Republic who was transplanted died shortly after the transplant (Sylvain Latour, Paris, personal communication, April 8, 2010). In the study from Cincinnati, 7 patients underwent allogeneic hematopoietic cell transplant, with 3 deaths related to complications.² All in all, we are aware of 10 *XIAP*-deficient patients who received stem cell transplantation, of whom 60% (6/10) died shortly after transplantation. An overview of treatment regimens *XIAP* patients have received is given in Fig 1. However, there is no evidence of complications specifically related to deficiency of *XIAP*, and bone marrow transplant can be successful in these patients.⁷

The hemophagocytic syndrome in the 3 patients reported here responded well and completely to treatment with immunoglobulins or corticosteroids, respectively. Furthermore, the Cincinnati study² reports 3 patients who, because of a lack of a diagnosis, received only supportive care. All 3 survived.

TABLE I. Clinical summaries of patients with XIAP deficiency reported to date, updated from Filipovich et al⁷

	Rigaud group	Zhao group	Marsh group	Our patients	Total
Number of patients	12	1	10	3	26
Patients with HLH	11 (92%)	1	9 (90%)	3 (100%)	24 (92%)
Patients with splenomegaly	9 (75%)	1	9 (90%)	3 (100%)	22 (85%)
Patients with EBV infection associated HLH	8 (67%)	1	3 (30%)	3 (100%)	15 (58%)
Patients with recurrent HLH or HLH-like illness	6 (50%)	1	6 (60%)	0	13 (50%)
Patients with hypogammaglobulinemia	4 (33%)	0	2 (20%)	1 (33)	7 (27%)
Patients with colitis	2 (17%)	0	0	0	2 (8%)
Patients with lymphoma	0	0	0	0	0

HLH, Hemophagocytic lymphohistiocytosis.

At this point, therapy remains an individual decision, and further experience with these patients is necessary to find a conclusive therapeutic approach.

Peter C. Horn, MD^{a,c}
Bernd H. Belohradsky, MD^d
Christian Urban, MD^e
Daniela Weber-Mzell, MD^e
Alfons Meindl, PhD^b
Volker Schuster, MD^f

From the Departments of ^aMedicine and ^bObstetrics and Gynecology, Technical University of Munich; ^cthe Department of Ophthalmology, University of Freiburg; ^dUniversity Children's, Ludwig-Maximilians University Munich; ^ethe Division of Pediatric Hematology/Oncology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Austria; and ^fthe Hospital for Children and Adolescents, University of Leipzig, Germany. E-mail: volker.schuster@medizin.uni-leipzig.de.

Supported in part by a grant of the Medical Faculty of Leipzig to V.S. (grant no. 78261 101).

Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

REFERENCES

1. Rigaud S, Fondaneche MC, Lambert N, Pasquier B, Mateo V, Soulas P, et al. XIAP deficiency in humans causes an X-linked lymphoproliferative syndrome. *Nature* 2006;444:110-4.
2. Marsh RA, Madden L, Kitchen BJ, Mody R, McClimon B, Jordan MB, et al. XIAP deficiency: a unique primary immunodeficiency best classified as X-linked familial hemophagocytic lymphohistiocytosis and not as X-linked lymphoproliferative disease. *Blood* 2010;116:1079-82.
3. Zhao M, Kanegane H, Ouchi K, Imamura T, Latour S, Miyawaki T. A novel XIAP mutation in a Japanese boy with recurrent pancytopenia and splenomegaly. *Haematologica* 2009;95:688-9.
4. Oliveira JB, Fleisher TA. Laboratory evaluation of primary immunodeficiencies. *J Allergy Clin Immunol* 2009;125:S297-305.
5. Schuster V, Terhorst C. X-linked lymphoproliferative disease (XLP) due to defects of SH2D1A. In: Ochs H, Smith C, Puck J, editors. *Primary immunodeficiency diseases, a molecular and genetic approach*. Oxford: Oxford University Press; 2007. p. 470-84.
6. Notarangelo LD, Fischer A, Geha RS, Casanova JL, Chapel H, Conley ME, et al. Primary immunodeficiencies: 2009 update. *J Allergy Clin Immunol* 2009;124:1161-78.
7. Filipovich AH, Zhang H, Snow AL, Marsh RA. Lymphoproliferative syndromes: brothers or distant cousins? *Blood* 2010;116:3398-403.

doi:10.1016/j.jaci.2010.11.040