

Letter to the Editor

Hodgkin lymphoma in 2 children with chronic granulomatous disease

To the Editor:

Chronic granulomatous disease (CGD) is a rare primary immunodeficiency (PID) characterized by a lack of reactive oxygen species caused by a defect of the nicotinamide dinucleotide phosphate oxidase in phagocytes and other cells,¹ resulting in severe recurrent pyogenic and fungal infections early in life.² A number of PIDs are known to predispose to certain cancers.³ Patients with CGD have been reported to have a high risk of developing solid tumors.^{4,5} Two cases of hematologic malignancies—one of acute lymphoblastic leukemia in a boy with X-linked CGD⁶ and the other of splenic Hodgkin lymphoma in a 20-year-old man⁷—have also recently been reported. We describe here 2 cases of lymphoma in patients with CGD: a man with X-linked CGD and a girl with autosomal-recessive CGD.

The first patient was born in 1987 to nonconsanguineous parents living in France. He had an early history of repeated upper respiratory tract infections, chronic eczema, cheilitis, gingivitis, cervical lymphadenitis, and recurrent otitis media by the age of 3 years. *Staphylococcus aureus* was isolated from a lymph node. He developed bronchiectasis by the age of 7 years, chronic restrictive lung disease at 13 years, and diffuse inflammatory colitis at 19 years. This patient was diagnosed with CGD at the age of 7 years on the basis of a nitroblue tetrazolium reduction assay (0%) and an absence of gp91^{phox} expression on immunoblots. RT-PCR and gene sequencing revealed a hemizygous nonsense point mutation in exon 7 of *CYBB*, affecting the NTERM domain (c.676[C>T], p.R226X). Prophylactic treatment with trimethoprim/sulfamethoxazole and itraconazole was started. The patient was hospitalized at the age of 14 years after 2 weeks of general decline, weight loss, dyspnea, and dry cough. Chest radiographs and computed tomography showed a mediastinal (left parahilar) mass. A thoracoscopy-guided transbronchial biopsy revealed abnormal cells: a lymphocyte-rich inflammatory infiltrate consisting of large lacunar cells with large, round, eosinophilic nucleoli (Reed-Sternberg cells), together with eosinophils, histiocytes, and macrophages in a granulomatous, fibrous background.

Immunophenotyping identified CD30⁺, LMP⁺, CD20[−], CD3[−], CD15[−], and ALK[−] cells. Stage 2Bb scleronodular-type Hodgkin lymphoma was diagnosed on the basis of regional localization with constitutional B symptoms but no visceral involvement. A multiple chemotherapy regimen consisting of procarbazine, adriamycin, and prednisone was initiated for 2 sessions, followed by cyclophosphamide, prednisone, and procarbazine without vincristine for 4 more sessions.

Prophylactic radiotherapy was also administered, with 30 Gy external beam irradiation in the mantle field and 20 Gy of lumbosplenic radiation, achieving complete remission. Follow-up has shown no signs of recurrence 8 years after radio-chemotherapy. The patient is alive and generally well.

The second patient, a girl from Mauritius, was born in 1994 to consanguineous parents of Indian ancestry. She had no history of serious infections in early childhood. At the age of 10 years, the patient presented with a 3-year history of cervical and axillary lymphadenopathy, intermittent low-grade fever, and weight loss. She had been given several regimens of antituberculous

medication with poor results. On examination, the patient had diffuse, bilateral cervical and axillary lymphadenopathies, 20 to 40 mm in diameter, including an ulcerated retro-auricular lymph node. Lymph node needle biopsies showed granulomatous inflammation. No acid-fast bacilli were detected, and culture was negative for bacteria, fungi, and mycobacteria. Neck and chest radiographs revealed multiple bilateral nodular calcifications along the trajectory of the cervical lymph node chains and mediastinum. Computed tomography scan showed several enlarged nodes below the diaphragm and a multinodular pattern in liver and spleen. Laboratory tests reported persistent inflammation, moderate hypergammaglobulinemia, normal cellularity of the bone marrow, and serologic evidence of chronic EBV infection. *Nocardia* sp. grew in a culture of fluid sampled during an episode of septic arthritis of the elbow.

Over the next few months, the patient's condition worsened, with weight loss, hepatosplenomegaly, ascites, and jaundice. On admission at the age of 10 years, the patient was found to be cachectic and severely jaundiced, with respiratory distress and rales on auscultation. Lymphadenopathy was generalized, with retro-auricular spontaneous fistulization-ulceration and marked hepatosplenomegaly on palpation. The patient was febrile, anemic, and thrombocytopenic. Thrombin time was moderately prolonged, and serum fibrinogen concentration was low. PCR for EBV revealed acute reactivation (15,800 viral copies/mL).

Burkholderia cepacia was grown from blood cultures. All other cultures were negative. An excisional biopsy of a cervical lymph node showed caseous tuberculous lesions and calcified fibrocaseous scars, with aberrant lymph node architecture, admixed inflammatory infiltrate, thick collagen fibers, and numerous Reed-Sternberg cells. Immunophenotyping of these slides confirmed the presence of mixed cellularity-type Hodgkin lymphoma: CD30⁺, CD15^{−/+}, CD20[−], CD79a[−], CD3[−]. A review of the previous biopsies provided no evidence of overlooked tumor cells. The patient's condition deteriorated rapidly, with progressive respiratory distress, refractory shock, renal and hepatic failure, and diffuse multiple hemorrhages. She died on her fifth day in the hospital. Cytochrome-c reduction assay in EBV-transformed B cells showed no superoxide production. Immunoblotting showed an absence of p47^{phox}. RT-PCR and sequencing of *NCF1* revealed the mutation most commonly found in autosomal-recessive CGD, a homozygous GT deletion at the beginning of exon 2. Both the patient's younger sisters have also since been diagnosed with the same homozygous mutation and are currently receiving prophylaxis with oral antibiotics.

Lymphomas have been associated with a number of PIDs,⁸ particularly those affecting lymphocytes and immune regulation. Hodgkin lymphoma is a malignant proliferative disorder of monoclonal B-cell origin. The scleronodular type is more common in younger subjects, whereas the mixed cellularity and lymphocyte-depleted subtypes are most frequent among patients with PID.⁹ Isolated reports of solid cancers and hematologic malignancies in patients with CGD to date include retinoblastoma,⁴ malignant melanoma,⁴ rhabdomyosarcoma of the liver,⁴ glioblastoma multiforme,⁵ T-cell acute lymphoblastic leukemia,⁶ and Hodgkin 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.

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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 polynuclear 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.

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REFERENCES

- E1. Bernstein R, Pinto M, Jenkins T. Ataxia telangiectasia with evolution of monosomy 14 and emergence of Hodgkin's disease. *Cancer Genet Cytogenet* 1981;4:31-7.
- E2. Dugois P, Amblard P, Imbert R. [Ataxia telangiectasia and Hodgkin's disease (apropos of a case)]. *Bull Soc Fr Dermatol Syphiligr* 1967;74:507-10.
- E3. Harris VJ, Seeler RA. Ataxia-telangiectasia and Hodgkin's disease. *Cancer* 1973; 32:1415-20.
- E4. Yalcin B, Kutluk MT, Sanal O, Akyuz C, Anadol D, Caglar M, et al. Hodgkin's disease and ataxia telangiectasia with pulmonary cavities. *Pediatr Pulmonol* 2002;33:399-403.
- E5. Niehues T, Schellong G, Dorffel W, Bucky P, Mann G, Korholz D, et al. Immunodeficiency and Hodgkin's disease: treatment and outcome in the DAL HD78-90 and GPOH HD95 studies. *Klin Padiatr* 2003;215:315-20.
- E6. Periman P, Callihan TR, Lessin L, King GW, Blaese M. Hodgkin's disease occurring in a patient with the Wiskott-Aldrich syndrome. *Cancer* 1980;45:372-6.
- E7. Sasahara Y, Fujie H, Kumaki S, Ohashi Y, Minegishi M, Tsuchiya S. Epstein-Barr virus-associated Hodgkin's disease in a patient with Wiskott-Aldrich syndrome. *Acta Paediatr* 2001;90:1348-51.
- E8. van den Berg A, Maggio E, Diepstra A, de Jong D, van Krieken J, Poppema S. Germline FAS gene mutation in a case of ALPS and NLP Hodgkin lymphoma. *Blood* 2002;99:1492-4.
- E9. Peters AM, Kohfink B, Martin H, Griesinger F, Wormann B, Gahr M, et al. Defective apoptosis due to a point mutation in the death domain of CD95 associated with autoimmune lymphoproliferative syndrome, T-cell lymphoma, and Hodgkin's disease. *Exp Hematol* 1999;27:868-74.
- E10. Poppema S, Maggio E, van den Berg A. Development of lymphoma in autoimmune lymphoproliferative syndrome (ALPS) and its relationship to Fas gene mutations. *Leuk Lymphoma* 2004;45:423-31.
- E11. Roberts MA, Arnold RM. Hodgkin's lymphoma in a child with cartilage-hair hypoplasia: case report. *Mil Med* 1984;149:280-1.
- E12. Taskinen M, Ranki A, Pukkala E, Jeskanen L, Kaitila I, Makitie O. Extended follow-up of the Finnish cartilage-hair hypoplasia cohort confirms high incidence of non-Hodgkin lymphoma and basal cell carcinoma. *Am J Med Genet A* 2008; 146A:2370-5.
- E13. Christopoulos C, Papadaki T, Vlavianos P, Kokkini G. Hodgkin's disease in a patient with common variable immunodeficiency. *J Clin Pathol* 1995;48:871-3.
- E14. Zenone T. Hodgkin's disease and common variable immunodeficiency. *J Clin Pathol* 1996;49:1021.
- E15. Kashef MA, Kashef S, Handjani F, Karimi M. Hodgkin lymphoma developing in a 4.5-year-old girl with hyper-IgE syndrome. *Pediatr Hematol Oncol* 2006;23: 59-63.
- E16. Lin SJ, Huang JL, Hsieh KH. Hodgkin's disease in a child with hyperimmunoglobulin E syndrome. *Pediatr Hematol Oncol* 1998;15:451-4.
- E17. Jovanovic A, Minic P, Seckic-Guc M, Djuricic S, Cirkovic S, Weemaes C, et al. Successful treatment of Hodgkin lymphoma in Nijmegen breakage syndrome. *J Pediatr Hematol Oncol* 2009;31:49-52.
- E18. Soucek P, Gut I, Treny M, Skovlund E, Grenaker Alnaes G, Kristensen T, et al. Multiplex single-tube screening for mutations in the Nijmegen breakage syndrome (NBS1) gene in Hodgkin's and non-Hodgkin's lymphoma patients of Slavic origin. *Eur J Hum Genet* 2003;11:416-9.
- E19. Filipovich AH, Mathur A, Kamat D, Kersey JH, Shapiro RS. Lymphoproliferative disorders and other tumors complicating immunodeficiencies. *Immunodeficiency* 1994;5:91-112.
- E20. Zenone T, Souquet PJ, Cunningham-Rundles C, Bernard JP. Hodgkin's disease associated with IgA and IgG subclass deficiency. *J Intern Med* 1996;240:99-102.
- E21. 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.
- E22. 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.
- E23. 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.
- E24. 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.

TABLE E1. PIDs associated with Hodgkin lymphoma

Hodgkin lymphoma and PIDs	References
Ataxia-telangiectasia	E1-E5
Wiskott-Aldrich syndrome	E6,E7
Autoimmune lymphoproliferative syndrome	E8-E10
Cartilage-hair hypoplasia	E11,E12
Common variable immunodeficiency	E13,E14
Autosomal dominant hyper-IgE syndrome	E15,E16
Nijmegen breakage syndrome	E5,E17,E18
Severe combined immunodeficiency	E19
X-linked hyper-IgM syndrome	E19
IgA and IgG subclass deficiencies	E19,E20
CGD	This report ^{E21}

TABLE E2. Solid organ cancers and hematologic malignancies reported to date in patients with CGD

Cancers reported in patients with CGD	Reference
Retinoblastoma	E22
Malignant melanoma	E22
Liver rhabdomyosarcoma	E22
Glioblastoma multiforme	E23
(T-cell) acute lymphoblastic leukemia	E24
(B-cell) Hodgkin lymphoma	E21