CASE REPORT

Chronic Granulomatous Disease Presenting With Hypogammaglobulinemia

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Abstract

Chronic granulomatous disease (CGD) is a primary immunodeficiency disorder caused by inherited defects in the nicotinamide adenine dinucleotide phosphate oxidase complex. The neutrophils of patients with CGD can ingest bacteria normally, but the oxidative processes that lead to superoxide anion formation, hydrogen peroxide production, nonoxidative pathway activation, and bacterial killing are impaired. Serious infections result from microorganisms that produce catalase. Immunoglobulin levels of patients with CGD are usually normal or elevated. We describe a patient with CGD associated with hypogammaglobulinemia, an unusual co-occurrence.

Key words: Chronic granulomatous disease (CGD). B-cell subsets. Hypogammaglobulinemia. Memory B cell.

Resumen

La enfermedad granulomatosa crónica (EGC) es una inmunodeficiencia primaria causada por defectos hereditarios en el complejo NADPH (nicotinamida adenina dinucleótido fosfato) oxidasa. Los neutrófilos de los pacientes con EGC pueden fagocitar bacterias con normalidad, pero hay una disfunción en los procesos oxidativos que dan lugar a la formación de aniones superóxido, la producción de peróxido de hidrógeno, la activación de la vía no oxidativa y la eliminación de bacterias. Las infecciones graves se deben a microorganismos que producen catalasa. Los niveles de inmunoglobulina de los pacientes con EGC suelen ser normales o elevados. En este artículo se describe un paciente con EGC asociada a la hipogammaglobulinemia, una rara asociación.

Palabras clave: Enfermedad granulomatosa crónica (EGC). Subconjuntos de linfocitos B. Hipogammaglobulinemia. Linfocito B de memoria.

Introduction

Chronic granulomatous disease (CGD), previously known as fatal granulomatosis of childhood [1], is a primary immunodeficiency disorder resulting from the absence or malfunction of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase subunits in phagocytic cells [2-4]. A defect in any one of 4 components of the NADPH oxidase complex (gp91-phox, p22-phox, p47-phox, p67-phox) encoded by the X-linked *CYBB* gene and the autosomal *NCF1, NCF2, CYBA*, and *Rac2* genes abolishes the activity of the oxidase and leads to CGD [4-7]. The major clinical manifestations of CGD are pneumonia, lymphadenitis, liver abscess, pyoderma, inflammation of the gastrointestinal tract, and osteomyelitis [3]. Severe recurrent life-threatening infections develop due to bacteria and fungi that produce catalase, such as *Staphylococci* species, *Burkholderia cepacia, Serratia marcescens, Nocardia* species, and *Aspergillus* species. *Salmonella* species, bacille Calmette-Guérin (BCG), and *Mycobacterium* and *Candida* species are also important infectious agents [2-5]. Another important manifestation of CGD is an enhanced and persistent inflammatory response, which presents as hypergammaglobulinemia and anemia (hemoglobin, 8-10 g/dL) [6,8]. However co-occurrence of CGD and hypogammaglobulinemia is an unusual condition, with only 4 cases reported in the literature [9-12]. We report a patient diagnosed with CGD associated with hypogammaglobulinemia.

Case Report

A 20-year-old woman had been referred to Hacettepe University Faculty of Medicine İhsan Dogramacı Children's Hospital (Division of Immunology) at the age of 10 with persistent vaginal candidiasis and recurrent oral candidiasis She had had a 4-year history of yellow-white vaginal discharge, hyperemia, genital itching and discomfort, and dysuria, all of

which had persisted despite appropriate therapy. Her medical history revealed recurrence of oral candidiasis since infancy, lymphadenitis following BCG vaccination, upper respiratory tract infections, otitis media, and intermittent diarrhea during the 3 months before attending the hospital.

She is the fourth child of consanguineous parents. Her mentally retarded sister had recurrent pyoderma and died of unknown causes at the age of 5. Her brother died from fungal pneumonia at the age of 12. She also has a deaf sister who is currently 30 years old.

On admission to our hospital, her height and weight were below the third percentile for age. A complete physical examination revealed extensive scarring at the site of the BCG injection, a hyperemic and swollen left ear canal with white secretion, pain when the tragus was moved, and hepatosplenomegaly. Hyperemia, maceration, and small vesicles were observed on the pubis, labia majora, and perianal region. A dense white vaginal discharge was also present.

The immunology workup revealed serum immunoglobulin (Ig) levels to be below the normal range, as follows: IgA, 22mg/dL (normal range 62-390 mg/dL); IgG, 430 mg/dL (normal range 842-1943 mg/dL); and IgM, 67 mg/dL (normal range 54-392 mg/dL) (Table 1). Her lymphocyte subset analysis was normal. Isohemagglutinin titers and specific antibody responses (anti-HBs, poliovirus antibodies, antibody response to unconjugated pneumococcal vaccine) were defective. The results of the nitroblue tetrazolium test and dihydrorhodamine were consistent with CGD. Moreover, the patient was found to have altered B-cell subgroups (Table 2). Molecular analysis revealed a mutation on exon 2 of p22 (70G>A), thus confirming the diagnosis of autosomal recessive CGD.

The patient was prescribed appropriate antibiotic therapy and continuous prophylactic oral trimethoprim-sulphamethoxazole and itraconazole.

Since then, she has had several mild upper respiratory tract infections treated with oral antibiotics. At the age of 16, her growth was retarded and puberty delayed. She has required root canal treatment for tooth abscesses for the past 4 years. Although she responded well to antibiotic prophylaxis, intravenous immunoglobulin (400 mg/kg every 4 weeks) was added to her treatment schedule, as she continued to have marked hypogammaglobulinemia.

Discussion

First described in the 1950s, CGD is a rare immunodeficiency caused by a genetically inherited defect in one of the subunits of the respiratory burst. It results in formation of granuloma and recurrent suppurative infections caused mostly by catalase-positive bacteria and fungi. CGD can be inherited in both an X-linked and autosomal recessive manner.

Age of onset is early, usually during the first year of life in patients with X-linked CGD. However, the disease can manifest later, and patients with milder signs and symptoms usually acquire the disease through autosomal recessive inheritance, as was the case with our patient. Most patients are diagnosed as toddlers and young children [2]. The patient in the present study was referred to our clinic at the age of 10 years complaining of persistent vaginal candidiasis, recurrent oral candidiasis, and lymphadenitis that had been present since infancy. Our group recently analyzed the clinical features of 26 CGD patients from a single center in which the most common presentation was found to be pneumonia (61.5% [n=16]) followed by lymphadenitis (34.9% [n=9]). Vaginal candidiasis was reported to be rare. Our patient's symptoms were mild. The growth retardation observed appears to be a complication of chronic disease, recurrent infections, or both. She did not require hospitalization or parenteral treatment, despite having hypogammaglobulinemia. In addition, prophylaxis with trimethoprim-sulphamethoxazole could have prevented the development of severe respiratory infection, which is common in untreated hypogammaglobulinemia.

Hypergammaglobulinemia has been reported to be a common finding among CGD patients, whereas

Table 1. Immunoglobulin Levels[a]

Patient age intervals at evaluation	IgA, mg/dL		IgG, mg/dL		IgM, mg/dL	
	Median (range)	Range of healthy controls	Median (range)	Range of healthy controls	Median (range)	Range of healthy controls
9-11 y	8 (7-22)	62-390	260 (138-430)	842-1943	35 (18-67)	54-392
16-21 y	16.5 (6-24)	139-378	170 (106-300)	913-1884	27.5 (16-43)	88-322

Abbreviation: Ig, immunoglobulin.
[a]The patient was followed-up at another center between the ages of 11 and 16 years.

Table 2. B-Cell Components for Our CVID Group, Control Group, and the Present Patient[a]

	Patient, %	Control group (n=20), % mean (SD, range)	CVID patient group (n=15),% mean (SD, range)
Sm B cell/BL	2.5	19.46 (8.47, 6.65-35.78)	1.20 (2.37, 0.8-8.58)
Sm B cell/TL	0.25	1.91 (0.87, 0.14-3.54)	0.072 (0.12, 0-0.46)
Mz B cell/TL	0.47	1.51 (0.98, 0.05-4.04)	39.1 (21.4, 0.6-68.7)

Abbreviations: BL, B lymphocyte; CVID, common variable immunodeficiency; Mz, marginal zone; Sm, switched memory; TL, total lymphocytes.
[a]Values for control and CVID patient groups are obtained from our unpublished study on B lymphocyte subgroups in CVID patients.

hypogammaglobulinemia is very rare, with only 3 reports of CGD and selective IgA deficiency and 1 of hypogammaglobulinemia, low IgG, and IgA [9-12].

The differential diagnosis for hypogammaglobulinemia includes primary T-cell and B-cell immunodeficiency and secondary immunodeficiency caused by drugs, infectious diseases, certain types of cancer, and systemic diseases leading to hypercatabolism or excessive loss of immunoglobulin [13]. We ruled out secondary immunodeficiency in our case. The patient had normal T-cell and B-cell counts, which enabled us to rule out autosomal recessive agammaglobulinemia and severe combined immunodeficiency (SCID). Bleesing et al [14] demonstrated that patients with CGD have an altered B-cell compartment, characterized by increased $CD5^+$ B-cell counts, and marked reduction in $CD27^+$ memory B-cell counts. The lowering effect is mainly due to prominent reduction in non–isotype-switched memory B cells ($IgM^+IgD^+CD27^+$), also known as marginal zone B cells rather than isotype-switched ($IgM^-IgD^-CD27^+$) memory B cells. Nevertheless, it remains to be determined whether or how this alteration relates to B-cell function and Ig production in patients with CGD and normal Ig levels and antibody production. Our patient had a significant reduction in isotype-switched memory B-cell counts, which accounted for 2.5% of total B cells and 0.25% of total lymphocytes, and the ratio of marginal zone B cells to total B cells was slightly lower (0.47%) than the normal range (Table 2).

Our patient may well have associated common variable immunodeficiency (CVID). Alternatively, the B-cell subset pattern represents the B-cell alteration seen in CGD. Most patients with CVID have reduced switched memory B-cell counts [15,16]. In the present case, the isotype-switched memory B-cell count was low, as occurs in patients with CVID, but the marginal zone B-cell count was also reduced, unlike our unpublished findings and those of Sánchez-Ramón et al [16]. However, similar reductions in the marginal zone B-cell population in CVID patients have also been reported [15]. The findings for B-cell subgroups are not consistent with those of Bleesing et al [14] in CGD or for diagnosis of associated CVID. Hypogammaglobulinemia is an additional burden to the already immunocompromised patient. However, the hypogammaglobulinemia in the present case had a good prognosis even before therapy with intravenous immunoglobulin, probably because the patient took antibiotic prophylaxis.

Co-occurrence of multiple immunodeficiencies has received little attention in the literature. To date, 3 cases of CGD and selective IgA deficiency have been reported, with chronic progressive pneumonia caused by *Pseudomonas cepacia* [9], multiple autoantibodies and progressive pulmonary dysfunction [10], and refractory immune thrombocytopenic purpura in a patient who developed an intracranial hemorrhage [11]. Keles et al [12] reported the case of a 5-year-old boy diagnosed with CGD presenting with disseminated aspergillosis and hypogammaglobulinemia (low IgA and IgG) who died 63 days after admission. B-cell subgroups are not described in these case reports; therefore, we cannot compare our results for switched memory B cells and/or marginal zone B cells. Further analysis of genes known to be involved in CVID could help to reveal the underlying pathology.

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