

Gingivitis and Very High IgE Level in a Chronic Granulomatous Disease Patient with Unusual Presentation: A Case Report

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Chronic granulomatous disease (CGD) is a rare primary immunodeficiency disease characterized by recurrent bacterial and fungal infections and is due to impaired function of superoxide-producing nicotinamide adenine dinucleotide phosphate oxidase. Patients may have elevated serum IgE levels mainly because of a high incidence of sensitization to *Aspergillus* species. In addition to a predisposition to infections, patients with CGD might have hyperinflammation presenting itself as chronic inflammatory lesions involving gastrointestinal mucosa, skin, lungs, eyes, and brain. Here, we present a case that mainly presented with chronic gingivitis and very high serum IgE levels and had been referred to our hospital with a probable diagnosis of hyper-IgE syndrome, another congenital immunodeficiency that is also characterized by increased susceptibility to bacterial or fungal infections and very high serum IgE levels. Detailed history of the patient revealed recurrent upper and lower respiratory tract and skin infections. He was diagnosed as having CGD by documenting defective phagocyte superoxide production and the diagnosis was then confirmed by mutation analysis. Family screening revealed that a younger brother was also affected. CGD should be considered in the differential diagnosis of patients with recurrent infections, chronic inflammatory lesions, and high serum IgE levels. These cases emphasize the importance of detailed history taking for diagnosis and family screening for identification of other affected members.

Introduction

CHRONIC GRANULOMATOUS DISEASE (CGD) is a rare primary immune deficiency disorder caused by impaired function of superoxide-producing nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which results in deficient respiratory burst in phagocytic cells and increased incidence of severe bacterial and fungal infections.¹

CGD patients generally present with lymphadenitis, liver abscesses, osteomyelitis, pneumonia, or skin infections.^{2,3} However, these patients not only suffer from recurrent infections but also noninfectious complications, namely hyperinflammation. Gastrointestinal (GI) and genitourinary (GU) systems are the most common sites affected by hyperinflammation.⁴ From mouth to anus any part of the GI tract can be involved and CGD patients may suffer from oral hyperinflammation, which is a rare condition.^{3,5} Moreover, CGD patients may have elevated serum IgE levels. Here, we report a patient with CGD who mainly presented with very high IgE levels and gingivitis.

Case Report

An 18-year-old boy was referred to our unit from a dentist because of the presence of chronic gingivitis and elevated serum IgE level with the probable diagnosis of hyper-IgE syndrome (HIES). The gingival biopsy had shown active chronic gingivitis. The medical history of the patient revealed a variety of infections such as pneumonia, pustular skin lesions, and otitis media since 2 months of age. He had pneumonia at 2 months of age requiring hospitalization. At 2 years of age, tonsillectomy was performed. Until 7 years of age he had been free of infections except for recurrent fever attacks for a year for which he had received penicillin prophylaxis. Skin eruptions appeared when he was 8 years old, which did not persist more than a year. Two years later, he had unilateral hearing loss following perforating purulent otitis media despite antibiotherapy. He had been hospitalized for a month at 14 years of age because of fever of unknown origin and received antituberculosis drugs on suspicion of tuberculosis without any objective evidence. He never had allergic complaints such as stuffy or runny nose, itching, sneezing, breathing difficulties, or urticarial rash. He

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had been complaining of gingival problems for the last 3 years. He was born as the second child of first-degree consanguineous parents. He had a brother and a healthy sister. Physical examination was unremarkable except the presence of gingivitis and hypertrophic gingiva.

Routine immunologic workup results were normal (white blood cell count with differentials, serum immunoglobulin levels, antibody production, and lymphocyte subsets) except for very high serum IgE levels ($>10,000$ IU/mL). Because the patient's medical history did not have any clue for allergic symptoms, skin prick tests or serum specific IgE testing was not performed. As the present findings might have been compatible with CGD, nitro-blue tetrazolium (NBT) and dihydrorhodamine (DHR) tests were performed and the results were negative. Mutation analysis revealed that the patient had a mutation in the gene coding the cytosolic component p47 (exon 2, Δ GT) of the NADPH oxidase.⁶ Computed tomography of the lungs showed a 2-cm nodular lesion localized to posterior segment of the left upper lobe and bronchiectasia next to it. Information for the responsible pathogens of his past infections was unavailable and his microbiological workup at our hospital revealed no specific etiologic agent for his infections. He was put on oral trimethoprim-sulphamethaxazole and itraconazole prophylaxis. For the last 2 years, he has been doing well without any infections under antibiotic prophylaxis but still having some periodontal problems.

The patient's 12-year-old brother was found to have CGD during the screening of the family to identify other potential affected members. His physical examination was normal but medical history revealed recurrent pulmonary infections beginning at 3 months of age and development of bronchiectasis for which lobectomy was performed. He had been followed at another center as potential pulmonary tuberculosis regarding the biopsy finding of granulomatous reaction without documentation of acid fast bacilli at the age of 5 years. He also never had experienced any allergic symptoms. Laboratory results revealed normal leukocyte count and serum IgA, IgM, and IgG levels and a very high IgE level (2,300 IU/mL). The Mantoux ppd tuberculin skin test was negative. His NBT and DHR test results were also consistent with the diagnosis of CGD. He benefited from prophylactic oral trimethoprim-sulphamethaxazole and itraconazole treatment, and for the last 2 years he has been doing well without any severe infection.

Discussion

CGD is a genetically heterogeneous disease characterized by recurrent severe infections with bacteria and fungi as well as dysregulated inflammatory response.⁴ It is a disease involving the multicomponent NADPH oxidase system. A defect in one of its 4 components (ie, gp 91-phox, p22-phox, p47-phox, p67-phox) encoded by the X-linked *CYBB* gene and the autosomal *CYBA*, *NCF1*, and *NCF2* genes abolishes the activity of the enzyme.^{2,7}

It has been reported that in about 70% of the patients, disease is inherited as X-linked and the remaining 30% as autosomal recessive (AR).^{2,8} However, probably because of the high consanguineous marriage rate in Turkey, AR form of the disease is more frequent in our CGD patients.⁹ In general, X-linked CGD appears to have more serious clinical phenotype than the AR form based on the features such as

earlier onset, higher prevalence of bacteremia or fungemia and a higher mortality rate. The presence of the milder form of the disease and the parental consanguinity were in favor of the AR form of the disease in our patients.

CGD patients usually present within the first years of life with recurrent life-threatening infections and excessive granuloma formation involving lungs, skin, soft tissues, and reticuloendothelial system.¹⁰ Patients with CGD also suffer from an increased inflammatory response whose mechanism remains poorly understood.⁵ The genetic variant of the disease that causes the most severe infections (X-linked form) also causes more inflammatory complications. It is not well known why these complications are more prominent in the membrane-bound NADPH oxidase system deficiency than the other forms. Although reactive oxygen species (ROS) production is associated with inflammation, absence of ROS leads to hyperinflammatory state paradoxically. ROS production seems to play a role in termination of inflammatory responses via degradation of phagocytosed material, suppression of pro-inflammatory signals, or impaired survival of proinflammatory cells.⁵ It has been shown that defective ROS production results in increased phagocytic cell recruitment due to an increase in IL-8 response and synthesis of increased pro- and decreased anti-inflammatory mediator production.^{11,12} The typical inflammatory response is persistent inflammation with or without granuloma formation. Hollowed viscera, such as the GI and GU tract, are the most commonly affected sites in terms of dysregulated inflammation. Inflammatory GI system (GIS) involvement presents itself in 2 ways: focal obstructive lesions or diffuse inflammation. Inflammatory bowel disease, oral ulcers, gingivitis, esophagitis, gastric outlet obstruction, villous atrophy, and perirectal abscesses have been reported so far.⁴ From mouth to anus any part of the GI system may be affected.⁵ Other tissues that may be influenced by hyperinflammation are brain, skin, eyes, and lungs.

CGD patients may suffer from sterile hyperinflammation of the oral cavity. Severe gingivitis,¹³⁻¹⁵ granulomatous mucositis, geographic tongue, and periodontitis are examples of oral hyperinflammation. The reported frequency rate of oral hyperinflammatory lesions varies between 0% and 35%.^{2,16-19} However, Dar-Odeh et al. reported presence of oral complications in 58% of their 12 CGD patients and biopsies of 2 showed chronic nonspecific mucositis.²⁰

Our patient presenting with the AR form of CGD had troublesome periodontal complaints and came to medical attention by the presence of chronic gingivitis, although he had a crowded history of serious infections. His serum IgE levels were high and he was referred to our unit with the probable diagnosis of HIES. Recurrent infections and elevated serum IgE levels are common in HIES and CGD. Patients with both disorders have markedly elevated IgE levels mainly because of a high incidence of sensitization to *Aspergillus* species.²¹

The HIES is a primary immunodeficiency characterized by infections of the lung and skin, eczema, eosinophilia, and elevated serum IgE. Nonimmunologic features of HIES include characteristic facial appearance and skeletal and dental abnormalities (eg, scoliosis, retained primary teeth, bone fractures following minimal trauma, and joint hyperextensibility). Sporadic, autosomal dominant (AD) and AR forms have been described. Skeletal and dental symptoms are associated with the AD form, whereas AR disease is

characterized by molluscum contagiosum and other severe cutaneous viral infections and neurological complications.^{22,23} Mutations in *STAT3* (the signal transducer and activator of transcription 3) have been shown to be a cause of AD-HIES, whereas mutations in *Dock8* (dedicator of cytokinesis 8) are responsible for many cases of AR-HIES.^{23,24} The diagnosis of HIES is usually made based on characteristic clinical phenotype. Because of the lack of a confirmative test, a clinical scoring system, known as NIH score, was suggested by Grimbacher et al. and has been used to screen HIES.²⁵ Scores of at least 40 points suggested HIES, whereas a score of below 20 made the diagnosis unlikely. For intermediate values, no firm conclusion could be reached. Our patient had a HIES-NIH score of 25, which comprises points for clinical features of recurrent pneumonia, parenchymal lung abnormalities, otitis media, and high serum IgE. He did not have distinctive facial appearance, skeletal or dental abnormalities as seen in AD-HIES, or increased susceptibility to severe cutaneous viral infections or neurological complications as in AR-HIES; moreover, he had no eczema or eosinophilia. DHR test and molecular analysis results were consistent with the diagnosis of CGD and this diagnosis explained all features of our patient.

In conclusion, although presentation of CGD mainly with inflammatory oral lesions is not common, a patient with severe, chronic periodontal lesions, especially in the presence of history of recurrent pyogenic infections, should be screened for CGD along with other potential immunodeficiencies, for example, neutropenia and HIES. The present cases emphasize the importance of detailed history taking for diagnosis and family screening for discovering others affected in the family.

Author Disclosure Statement

No competing financial interests exists.

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