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A Case of Recurrent Granulomatous Disease

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Abstract
Chronic granulomatous disease (CGD) is an extremely rare genetically heterogeneous disorder characterized by serious life-threatening infections. CGD is caused by a defect of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system. The disease is characterized by increased inflammation and granuloma formation secondary to recurrent infections. CGD typically involves the lungs, liver, and lymph nodes. Most patients with CGD are diagnosed in childhood. In this case report, we aimed to present a patient with recurrent granulomatous diseases who could not be diagnosed despite reaching adulthood. A nineteen-year-old male patient who was previously diagnosed with granulomatous inflammation and lymphadenopathy and had consanguineous parents was examined for persistent fever and cough and diagnosed with chronic granulomatous disease. This case is presented to show that in countries where consanguineous marriage is common, this genetic disorder can also be diagnosed in adulthood.
Key words: Fever, Genetic Disorders, Granuloma, Lymphadenopathy, Pneumonia

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Introduction

Chronic granulomatous disease (CGD) is a genetic disorder characterized by recurrent, life-threatening bacterial and fungal infections, and granuloma formation. Phagocytic cells are programmed to show rapid response to cells invaded by microorganisms. With the innate immune response system, called phagocytosis, reactive oxygen intermediates are produced due to proteolytic destruction of phagosomes (1). Monocytes and neutrophils use oxygen as phagocytic cells by physical and chemical reactions, leading to respiratory burst. In this burst, NADPH (nicotinamide adenine dinucleotide phosphate) oxidase protein pathway is used (2). The NADPH oxidase complex is activated by phagocytosis and electrons are transferred from NADPH to oxygen to kill intracellular bacteria and fungi by forming lytic enzymes such as superoxide radicals and hydrogen peroxide. Due to genetic defects of NADPH oxidase, phagocytes cannot destroy these pathogens (3). These genetic defects arise from mutations that result in loss or functionally inactivation of one of the subunits of the NADPH oxidase complex (gp91phox, p47phox, p22phox, p67phox, p40phox) (4).

Although CGD is usually inherited as an X chromosome-linked trait, there are also forms inherited through autosomal recessive mode. Therefore, the disease can be seen in both sexes. The frequency of CGD in the USA is about 1 in 200,000 live births. The disease primarily affects men since most mutations are X-linked. However, in societies where consanguineous marriage is common, autosomal recessive forms of the disease are more common than X-linked forms, with a higher overall incidence rate (5). Patients diagnosed with CGD may present with growth retardation, abnormal wound healing, diarrhea, and infected dermatitis. Patients may have hepatomegaly, splenomegaly, and lymphadenitis on physical examination. Patients with CGD can present at any age from infancy to adulthood, but the majority of patients present before 5 years of age (5).

Laboratory findings may include anemia, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, hypoalbuminemia, and hypergammaglobulinemia (6). The diagnosis is made by neutrophil function test and genotyping (3).

In this case report, we present a patient suffering from recurrent granulomatous lymphadenopathies from childhood to adulthood who was diagnosed with chronic granulomatous disease.

Case

A nineteen-year-old male patient who was dealing with farming presented to our clinic with cough, fever, and loss of appetite. The patient's history revealed that he had undergone submandibular lymph node excision fifteen years ago and received antituberculosis treatment for ten months after his pathology result was reported as caseating granulomatous inflammation. Because his chest imaging showed mediastinal lymphadenopathies and tree-in-bud pattern in the lower lobe of the right lung when examined for similar complaints six years ago, he received antituberculosis treatment again. His family history revealed that his parents had consanguineous marriage. The patient's general condition was poor, he was cachectic, his body temperature was 38ºC, heart rate was 98/min, respiratory rate was 24/min, blood pressure was 140/90 mmHg, and crackles were auscultated on respiratory examination. The laboratory test results were as follows: Hgb, 12 g/dL; WBC, 10.9 thousand/uL; neutrophil, 8.29 thousand/uL; CRP, 27 mg/dL; ESR, 76 mm/hour; albumin, 2.5 g/dL; total protein, within normal range. According to his test results, he had anemia, hypoalbuminemia with elevated CRP and ESR. The patient's chest imaging showed irregular coarse septal thickening in both lungs, alveolar ground-glass opacities, and mediastinal lymphadenopathy (Figure 1).

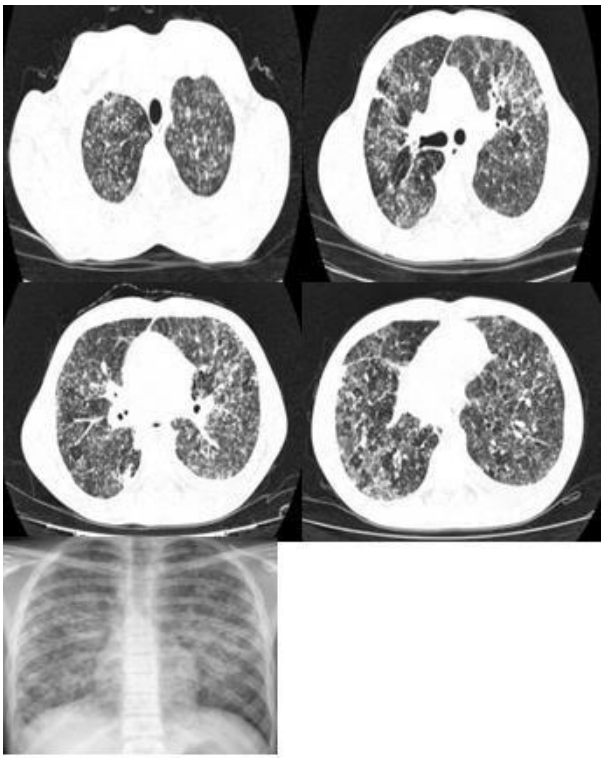


Figure1. Admission chest radiography and chest computed tomography

The patient underwent bronchoscopy. Two biopsy samples were taken distal to the anterior segment of the right upper lobe as well as a lavage sample from the right upper lobe for tuberculosis culture, acid-alcohol resistant bacilli (AARB), mycobacterium PCR, and non-specific culture. The bronchial lavage was negative for mycobacterium PCR, AARB with no growth in the nonspecific culture. No specific pathology was observed in the distal biopsy samples. The patient was consulted with thoracic surgery and wedge resection was recommended. The wedge resection pathology result was reported as suppurative necrotizing granulomatous inflammation. Thereupon, the patient was initiated on antituberculosis treatment. Since the patient achieved no clinical or radiological improvement during the follow-ups, methylprednisolone 40 mg/day was added to his current treatment. It was decided to examine the patient with partially regressed complaints after methylprednisolone treatment for hereditary immunodeficiency syndromes because of the history of consanguineous parents. The patient who was found to have no oxidative burst in the dihydrorhodamine (DHR) test was diagnosed with chronic granulomatous disease, and mutation analysis was ordered. The antituberculosis treatment was discontinued, and he was initiated on voriconazole and continued to receive methylprednisolone. His clinical complaints declined in the follow-ups, intravenous voriconazole was completed to 14 days, and the patient was discharged with oral 3 mg kg voriconazole and oral steroid therapy.

The post-discharge 1-month follow-up chest radiograph of the patient with no active complaint showed significantly regressed infiltrations (Figure 2).



Figure 2. Post-discharge 1-month follow-up chest radiograph

Discussion

Chronic granulomatous disease is a disorder with phenotypic and genotypic variations typically characterized by recurrent fungal and/or bacterial infections from infancy. Some patients might present with symptoms in late childhood or even adulthood (4).

The diagnostic tests are based on the assessment of oxidative burst by measuring superoxide production. These tests include direct measurement of superoxide production, ferricytochrome C reduction test, anti-HIV (by chemiluminescence method), nitroblue tetrazolium reduction test (NBT), and dihydrorhodamine-123 (DHR) oxidation method (3). Today, the DHR-123 method is preferred because it helps the differentiation of X-linked and autosomal forms and is sensitive even to a small number of cells. The DHR-123 method is particularly helpful in diagnosing patients with X-linked CGD early and optimizing treatments such as medication, bone marrow transplant and gene therapy (7).

Despite prophylactic treatments, patients might have recurrent infections. For example, a study of three hundred and sixty-eight CGD patients reported the most prevalent infections as pneumonia, suppurative lymphadenitis, cutaneous and subcutaneous abscess, liver abscess, osteomyelitis, and sepsis (5).

Pneumonia is the most common type of infection in CGD and typically causative pathogens are Staphylococcus aureus, Aspergillus species, Burkholderia cepacia and enteric gram-negative bacteria. Aspergillus and other fungal infections of the lung also present difficult challenges as they typically require long-term treatment (3-6 months). Cutaneous abscesses and lymphadenitis represent the next most common types of infection in CGD and are typically caused by S. aureus, followed by various gram-negative organisms, including B. cepacia complex and Serratia marcescens. Hepatic abscesses are also quite common in CGD and are typically caused by S. aureus. Likewise, perirectal abscesses are common and, once formed, can persist for years despite aggressive antimicrobial therapy and rigorous local care. Osteomyelitis is another important infection in CGD and is caused by hematogenous spread of microorganisms (S. aureus, Salmonella spp., S. marcescens). Other common microbial agents are Escherichia coli spp., Listeria spp., Klebsiella spp., Nocardia and Candida spp. (8)

In a study evaluating the incidence of severe infections in patients followed up by a single-center, Aspergillus species (2.6 cases per 100 patient-year), S. Aureus (1.44 cases per 100 patient-year),

Burkholderia (Pseudomonas) cepacia complex (1.06 cases per 100 patient-years), Serratia marcescens (0.98 cases per 100 patient-years), Nocardia species (0.81 cases per 100 patient-years) could be isolated as causal pathogens of infections (9).

While infections caused by bacterial factors manifest themselves with symptoms such as fever and leukocytosis, fungal infections can be asymptomatic and can be noted during routine screenings or in an advanced stage (10). Infections caused by fungal factors are less common than bacterial infections but have a more fatal course. Novel antifungal agents such as lifelong itraconazole prophylaxis, voriconazole and posaconazole have reduced the frequency of infection and the risk of death. Lung infection can develop by inhalation of fungal pathogens, especially aspergillus species (5).

Especially individuals dealing with farming can develop mulch pneumonitis due to Aspergillus species with the inhalation of organic substances such as piles of hay and dead leaves. This entity is a hypersensitivity reaction characterized by a sudden shortness of breath, fever, and radiological pulmonary infiltrates due to inhalation of organic substances and fungi. In such cases, steroid therapy should be given in addition to antifungal treatment, and even if the infection is controlled, steroid therapy should be continued for a long time (11).

Besides infections, non-infectious complications such as inflammation and granuloma formation and autoimmune diseases may also develop in CGD (12). Non-caseating granulomas form especially in the brain, lung, liver, gastrointestinal and genitourinary tracts. In many granulomas, the causal pathogen is not identified and rapid response is achieved to steroid therapy (13).

In chronic granulomatous disease, trimethoprim-sulfamethoxazole (TMP-SMX) is given prophylactically in two divided doses of 5 mg/kg/day, while dicloxacillin, oral cephalosporin, or fluoroquinolone is preferred as an alternative for allergic patients (14). TMP-SMX prophylaxis should be applied for life. In the case of acute infection, treatment should be initiated in the form of oral ciprofloxacin and intravenous meropenem empirically until the causal pathogen is identified. In addition, TMP-SMX initiated at a prophylaxis dose should be doubled, and voriconazole should be added to the treatment in the presence of pneumonia (15).

With the use of TMP-SMX treatment for routine prophylaxis, the incidence of bacterial infections, especially staphylococci, has decreased. While the incidence of pneumonia due to mycobacterial infections has been reported as 6% in the United States, this rate has been reported to be higher in countries where tuberculosis is endemic (16).

Although antimicrobial drugs and immunomodulatory agents are primarily utilized to prevent or treat developing infections, hematopoietic stem cell transplantation is the only definitive cure for CGD (17). Allogeneic stem cell transplantation has been increasingly used in recent years with enhanced preparative treatment, 'graft-versus-host' disease prophylaxis, high-resolution matching of tissue groups, and the adjustment of pre-transplant and post-transplant therapies, and has become an appropriate and successful treatment method for CGD patients with infectious and inflammatory complications.

Our patient was suspected of having the diagnosis of CGD because of persistent fever despite antibiotic and antituberculosis treatment, the presence of mediastinal lymphadenopathy and pulmonary parenchymal infiltrates, and the consanguineous marriage of the parents. The fact that our patient benefited from steroid therapy in addition to antifungal treatment, was dealing with farming, and especially had contact with the barn suggests that the lung findings are consistent with the "mulch pneumonitis" clinic due to Aspergillus. Our patient who had granulomatous lung diseases caused by an unidentified pathogenic agent, especially since childhood, and who did not benefit from treatments was examined for immunodeficiency syndromes and was diagnosed with CGD as the dihydrorhodamine (DHR) test revealed the absence of oxidative burst.

Conclusion

It should be kept in mind that albeit rarely, CGD can also be diagnosed in adulthood in countries where genetic conditions are common due to the high prevalence of consanguineous marriages such as our country. Patients with recurrent infectious/non-infectious granulomatous lesions should be evaluated for CGD.

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Peer-review: Externally peer-reviewed.
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