

CASE REPORT

Two Chronic Granulomatous Disease Diagnosed in Adult Age

Fatma Tokgöz Akyıl¹, Tülin Sevim¹, Safa Barış², Emine Aksoy¹, Dilem Anıl Tokyay¹, Yasemin Bodur¹, Oğuz Aktaş¹

¹Clinic of Chest Diseases, Süreyyapaşa Chest Diseases and Chest Surgery Training and Research Hospital, İstanbul, Turkey

²Clinic of Pediatric Allergy and Immunology, Marmara University Hospital, İstanbul, Turkey

Abstract

Chronic granulomatous disease (CGD) is a rare, inherited primary immunodeficiency that is usually diagnosed at adulthood and is presented with recurrent bacterial and fungal infections. In this case report, two adult cases of CGD have been presented. A 29-year-old woman was referred to our clinic with hypoxic respiratory failure, with a pre-diagnosis of multidrug resistant tuberculosis (TB). Her lung biopsy had been reported as granulomatous inflammation, she hadnot responded to a 5 month anti-TB treatment. A complete medical history consisted of 4 occasions of treatment with anti-TB drugs and that her sister and brother had undergone TB therapy. However, since childhood, a TB bacilli had never been isolated microbiologically in the siblings. Patient's parents were third degree consanguineous. The patient still had a purulent drainage around the operation site. Microbiological studies of the wound drainage and respiratory tract have not encountered any specific microorganism. Investigation of an immunodeficiency has proved CGD through nitroblue tetrazolium test. Her siblings has been diagnosed as CGD as well.

Second case, a 19-year-old male, has been admitted to our clinic with complaints of fever, chest pain and an abscess lesion in the anterior chest wall. His medical history comprised 3 recurrences of pneumonia within last 2 years. In physical examination, a 3 x 5 cm fluctuant swelling lesion on the anterior chest wall. Radiologically, new pneumonic consolidations were detected. Sputum specimens did not provide any specific microorganism, cultures of the chest-wall abscess fluid grew aspergillus. His parents had been living in the same village but no consanguinity was known. Due to recurrent infections, immunodeficiency tests had been investigated. He was diagnosed as CGD due to dihydrorhodamin test. These two cases signify that, in our country where consanguinity is common, etiology of recurrent unexplained infections, abscesses and granulomas should be investigated and CGD should be in differential diagnosis list.

KEYWORDS: Abscess, chronic granulomatous disease, granuloma, immunodeficiency, tuberculosis

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INTRODUCTION

Chronic granulomatous disease (CGD) is a genetic primary immunodeficiency characterized by the formation of granuloma, where defense mechanisms against bacteria and fungi infections are weakened. The reported incidence from the United States of America is 1/200.000: however, there is no incidence data reported from our country. The disease may show X-linked or autosomal recessive heredity, and autosomal recessive forms are mostly encountered in consanguineous marriages [1].

The disease manifests itself with serious bacterial and fungal infections recurring since childhood [2]. The most frequently affected organ in CGD is the lungs. Skin involvement that progress with skin infections and subcutaneous abscess, suppurative adenitis, sinusitis, liver abscess, osteomyelitis, and necrotizing fungal infections can be seen. Granulomatous infection, autoimmune events and rheumatologic diseases can be detected.

Diagnosis is made under the age of 3 in X-linked inherited form and under the age of 8 in autosomal recessively inherited form [3-5]. There are reported cases where diagnosis is rarely made late and CGD is detected after the third or fourth decades of life [6,7].

In company with the literature, this case report aimed to present two CGD cases diagnosed in adult ages by having received their informed consent.

Address for Correspondence: Fatma Tokgöz Akyıl, Süreyyapaşa Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Kliniği, İstanbul, Türkiye Phone: +90 216 421 42 00/1175
E-mail: fatmatokgoz86@gmail.com

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CASE PRESENTATION

Case 1

The 26-year-old female patient was referred to our clinic with respiratory failure and a preliminary diagnosis of multidrug-resistant (MDR) tuberculosis (TB). The patient presented with complaints such as dyspnea, cough, sputum, fever, weight loss and night sweating. It was found out from her history that the patient had applied to another hospital with the same complaints five months prior and that she had been examined with suspected tuberculosis (Figure 1). Acid-fast bacillus (AFB) had been detected negative in her three sputum samples and bronchial lavage. Standard antituberculosis treatment had been started with isoniazide, rifampicin and ethambutol upon having detected granulomatous inflammation on lung biopsy. Due to the development of hypoxemic respiratory failure in the third month of treatment, corticosteroid was added to the treatment regimen. The patient had been referred to our clinic with a preliminary diagnosis of MDR-TB by having detected clinical and radiological progression in the fifth month of treatment. The posteroanterior (PA) chest radiography during this period is seen on Figure 2.



Figure 1. (Case 1) Before TB treatment, another center.

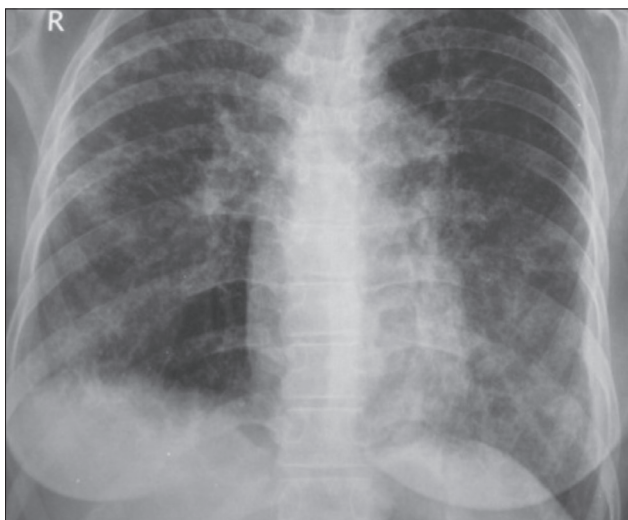


Figure 2. (Case 1) Fifth month of TB treatment.

The patient had a history of receiving treatment for tuberculosis four times before. Her sister was hospitalized in the pediatric service of our hospital with a preliminary diagnosis of MDR-TB. Her brother had also received TB treatment.

The patient was weak and fatigued. Her body temperature was 37.2°C and respiratory rate per minute was 16. Many skin scars were present on her knees and elbows from childhood. On respiratory examination, rales were heard in bilateral lower regions in the inspirium. Purulent leakage still continued from her previous operation site. Micronodular infiltrations were seen in all zones on chest graphy. On high resolution computed tomography (HRCT), an image concordant with small-airway disease accompanied by micronodules, nodules, interseptal thickening and reticular markings (Figure 3A,B) was seen. White blood cell count was 12.25 K/L and hemoglobin was 11 g/dL on complete blood count. Biochemical tests were normal except for a slight albumin fall (3.3 g/dL). On arterial blood gas test, partial oxygen pressure was 54 mmHg and oxygen saturation was 86% in room temperature. C-reactive protein was found as 88 g/L.

Antituberculosis treatment was continued. ARB was (-) on three sputum samples. Growth was not detected in sputum nonspecific culture and fungus culture. There was no growth in the cultures of the leakage from the operation site.

Three detailed histories were taken from the family and patient. First of all, the patient had received tuberculosis

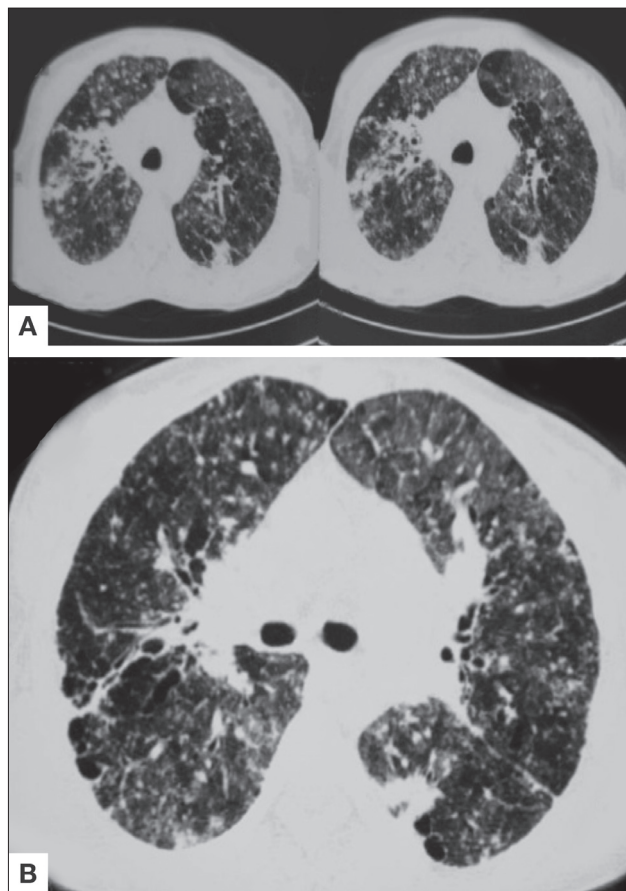


Figure 3. (Case 1) (A) Presenting HRCT, (B) presenting HRCT.

treatment for six months with TB diagnosis as a result of scars with abscess on her body at the age of ten. At the age of eleven, the patient had been reported to have granulomatous inflammation with liver biopsy and had received TB treatment for six months. The patient had been treated with a diagnosis of pulmonary TB at the ages of twenty-one and twenty-four. The 23-year-old brother of the patient had received TB treatment at the age of nine. Patient's sister had also received TB treatment twice and by having been accepted as clinically unresponsive, she had been referred to the pediatric service of our hospital with a preliminary diagnosis of MDR-TB.

The Tuberculosis Control Dispensary with which the patient is affiliated, was contacted and it was found out that tuberculosis bacilli were detected in the sputum samples of neither our patient nor her siblings. The parents of the patient were third-degree relatives, and their twins died when they were 9-months-old. Deaths at childhood ages were present on the siblings and cousins of the parents.

In the light of this information, our patient was investigated in terms of immunodeficiency; IgG: 21.5 (7-16) g/L, IgA: 10.1 (0.7-3.1) g/L, IgM: 1.1 (0.05-0.3) g/L. Upon contacting the immunology clinic, the patient was asked for nitroblue tetrazolium test (NBT) which was reported as unresponsive.

The patient, who was diagnosed with chronic granulomatous disease, was referred to the immunology department. Her siblings were also diagnosed with CGD. The patient who was started on interferon gamma, trimethoprim-sulfamethoxazole (TMP-SMX) and itraconazole treatment is followed without complications and is in a clinically stable condition in the third year of treatment.

Case 2

The 19-year-old male patient applied to our clinic with fever and chest pain ongoing for a week and swelling on the anterior thoracic wall ongoing for two months. The patient



Figure 4. (Case 2) Presenting PA chest radiography.

had lost 7-8 kg in the last one year. The patient had suffered pneumonia three times for the last two years, but he did not have any additional diseases. Nothing was detected in family history. On physical examination, the patient was weak and he was 1.55 cm tall. His body temperature was 37.4°C. A swollen, rubescent, fluctuating soft tissue lesion, 3 x 5 cm in diameter, which had an increase in temperature was present on the sternum on the anterior wall of the right chest. Other system examinations were normal. White blood cell count was 10.20 K/L and hemoglobin was 8.7 g/dL on complete blood count. Biochemical tests were within normal limits and C-reactive protein was detected as 122 g/L.

On PA chest radiography, peripheral nonhomogeneous density increase was detected on upper right and middle left zone (Figure 4). On thoracic CT, homogenous opacity located on the right upper lobe pleura and fibrotic shrinkage with parenchymal infiltration in its surrounding, which stretched out to the parenchyma from the lower left lobe pleura were monitored (Figure 5A,B). The patient had been treated with a diagnosis of bilateral pneumonia two years prior and had developed pneumonia in different locations six months later. The case was investigated for TB and ARB was detected (-).

Antibiotherapy was started on the patient. Sputum cultures and ARB were (-). ARB was not detected on the lesion taken from the anterior chest wall; there was no growth in nonspecific culture. Dense neutrophils were reported in cytological investigation. *Aspergillus* grew in fungus culture.

The parents of the patient lived in the same village and did not know about any history of consanguineous marriage. Human immunodeficiency virus was negative in the patient who suffered frequent infections. Immunoglobulin values of the patient tested for immunodeficiency were normal. Dihidrorhodamin test was found concordant with CGD.

The patient, who was referred to the immunology department, was started on interferon gamma, voriconazole, cefixime, and TMP-SMX treatment. The clinically responsive patient is followed without complications in the second year of treatment. The 12-year-old sister of our patient, who did not have any complaints, was also diagnosed with CGD and is now under follow-up.

DISCUSSION

History of suffering frequent infections was present in our first case and granulomas were detected histopathologically. TB bacilli had never been proven for the patient and her siblings but treatment had been received many times. Our second case had suffered from infections frequently in recent years and presented to us with skin abscess. These cases emphasize the necessity to question hereditary immunodeficiency in inexplicable resistant infections which the person suffers frequently especially in a country, like ours, where consanguineous marriages are often seen. Moreover, although tuberculosis is the first thing that comes to mind in granulomatous lesions, differential diagnosis should be definitely made.

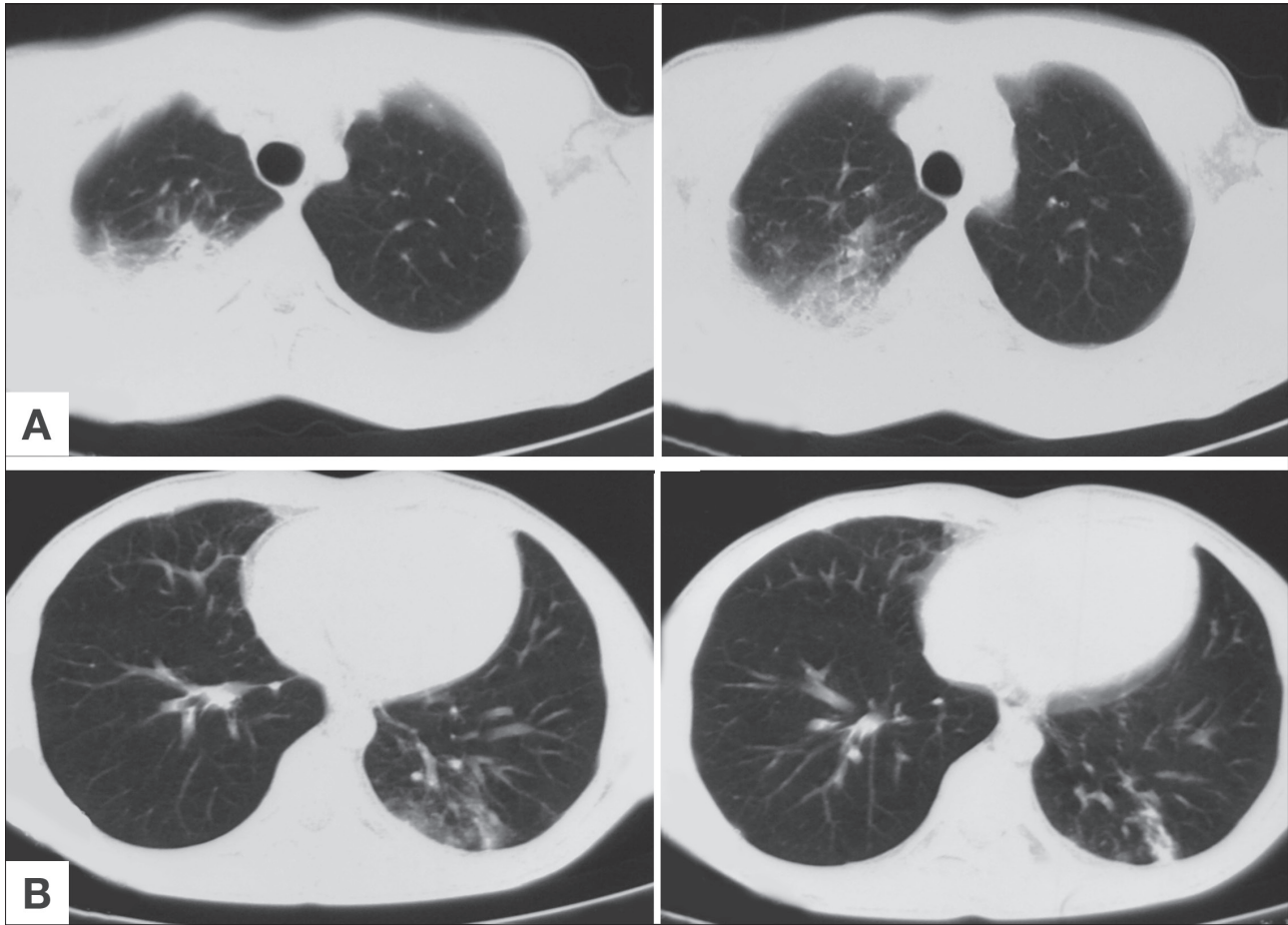


Figure 5. (Case 2) (A) Presenting thoracic CT, **(B)** presenting thoracic CT.

Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system plays the basic part in killing catalase-positive microorganisms after phagocytosis of neutrophilia and monocytes. Due to the mutation in the genes coding the proteins in NADPH oxidase enzyme complex in CGD, superoxide radicals are not formed and respiratory burst does not happen [1]. Fever and leucocyte response occur during infection; however, the microorganism is not killed [8,9]. The most frequently determined agents are microorganisms that produce catalase, such as *Staphylococcus aureus* and *Aspergillus* types. In addition, infection can develop with *Serratia marcescens*, *Burkholderia cepacia* kcomplex and *Nocardia* types [5].

Growth and developmental delay can be seen in patients and increase in length can be late [10]. The most frequent involvement region in CGD is the lungs; recurrent pneumonia and pulmonary abscess can be seen. Due to recurrent infections, bronchiectasis, obliterative bronchiolitis, hypoxia and respiratory failure can develop [11]. Since granulomatous lesions can be detected in the lungs histopathologically, sarcoidosis or tuberculosis can also be considered. Skin is the second most involved organ. Although staphylococcus is the most frequently isolated pathogen, the agent cannot be isolated all the time [5]. The first case that we reported had been started on TB treatment as a result of widespread skin abscesses and having detected granulomas in liver biopsy

afterwards. Finally, the case had been using TB medication upon detecting granulomas in the lungs. Pulmonary failure was present during her application to our clinic. This patient is important in terms of emphasizing microbiologic diagnosis and culture positivity as golden standards in TB diagnosis when every granulomatous inflammation may not be TB or sarcoidosis.

The other case did not have a history of infection or any other disease until two years prior. It has been reported in the literature that a history of infection may not be present until early adult period and these patients have been accepted as mild forms of CGD according to mutation type [2]. This case had also suffered frequent pulmonary infections in recent years and applied to our clinic due to skin abscess.

Apart from infections, granuloma formation, autoimmune events and rheumatologic disease may manifest in chronic granulomatous disease (CGD). Inflammatory intestinal disease, bladder granulomas and genitourinary system complications have been reported most frequently in X-linked heredity. Increase in liver enzymes, splenomegaly, hepatomegaly, portal hypertension and thrombocytopenia may also develop [7,12]. Depending upon recurrent infections, hypergammaglobulinemia, chronic disease anemia and high C-reactive protein levels are frequently observed [11,13]. Granulomas were detected in the liver

when our first case was eleven years old. Both cases had anemia and C-reactive protein elevation.

The most important point for diagnosis is that the disease should come to mind. CGD should come to mind in a history of recurrent, serious and unusual infection and in individuals suffering from hepatosplenomegaly, diarrhea and delay in wound healing. Exclusion of infectious diseases, other immunodeficiencies, and diseases like cystic fibrosis, hyperimmunoglobulin E syndrome and Crohn's disease is of grave importance for differential diagnosis. The siblings should also be scanned when CGD diagnosis is made [11,13]. Neutrophil functions and superoxide production are evaluated for diagnosis. To this end, direct superoxide production measurement, ferrocycytochrome C reduction test, nitroblue tetrazolium (NBT) reduction test and dihidrodamin-123 (DHR) oxidation methods are used [1]. CGD diagnosis was made with TMP-SMX test in our first case and DHR-123 test in our second case.

When diagnosis is made, TMP-SMX, itraconazole and prophylaxis, interferon-gamma as immunomodulatory (IFN- γ) treatments are applied. The patients should be vaccinated for measles, chicken pox, and annual flu, and BCG should be performed due to the risk of disseminated disease [14]. Rapid and aggressive treatment is necessary once the infection develops. Surgical treatment may be necessary in persistent and recurrent cases [5]. Most frequent cause of mortality has been reported as pneumonia and sepsis due to *Aspergillus* or *Burkholderia cepacia* [15]. Both cases are followed with IFN, TMP-SMX and itraconazole treatments without complications.

In conclusion, patients with inexplicable frequent infection attacks, abscess, and granuloma presence should be examined and tested for chronic granulomatous disease. It is important in terms of prognosis if this disease is listed in differential diagnosis in adult age in our country where consanguineous marriages are frequently observed.

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