Case Report / *Olgu Sunumu*

DOI: 10.5578/ced.20229808 • *J Pediatr Inf 2022;16(2):e115-e118*

Chronic Granulomatous Disease with Recurrent Tuberculosis at Adolescent Child

Tekrarlayan Tüberküloz ile Kronik Granülomatöz Tanısı Konulan Adölesan

Şefika İlknur Kökcü Karadağ[1](İD), Şeyhan Kutluğ[1](İD), Oğuz Uzun[2](İD), Mustafa Yavuz Köker[3](İD), Alişan Yıldıran[1](İD)

[1] *Division of Pediatric Immunology and Allergy, Ondokuz Mayıs University Faculty of Medicine, Samsun, Türkiye*
[2] *Department of Chest Diseases, Ondokuz Mayıs University Faculty of Medicine, Samsun, Türkiye*
[3] *Department of Immunology, Erciyes University Faculty of Medicine, Kayseri, Türkiye*

Cite this article as: Kökcü Karadağ Şİ, Kutluğ Ş, Uzun O, Köker MY, Yıldıran A. Chronic granulomatous disease with recurrent tuberculosis at adolescent child. J Pediatr Inf 2022;16(2):e115-e118.

Abstract

Chronic granulomatous disease (CGD) is an a primary immunodeficiency characterized by recurrent severe bacterial and fungal infections due to defects in the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system. Both extracellular and intracellular pathogens such as mycobacterium tuberculosis also cause important infectious diseases in these patients. The diagnosis is usually made in early childhood. However, partial enzyme deficiencies may delay the diagnosis. We presented a patient who first had recurrent tuberculosis infectious disease and later developed pulmonary aspergillosis and was diagnosed with CGD. Primary immune deficiency should be considered in the differential diagnosis in cases of recurrent tuberculosis infectious disease. Patients with primary immunodeficiency, such as CGD, may be contracted by recurrent tuberculous infectious disease before developing invasive pulmonary aspergillosis. In this way, at least in some patients, the infectious disease can be controlled more effectively and the recurrence of the infectious disease can be prevented.

Keywords: Chronic granulomatous disease, recurrent tuberculosis, aspergillosis

Öz

Kronik granülomatöz hastalık (KGH) nikotinamid adenin dinükleotit fosfat (NADPH) oksidaz sistemindeki defektlere bağlı görülen tekrarlayan ciddi bakteriyel ve fungal enfeksiyonlarla karakterize nadir görülen immün yetmezlik hastalıklarından biridir. Çoğunluğunda gp91phox mutasyonu ve X'e bağlı resesif kalıtım mevcuttur. Hem hücre dışı hem de *M. tuberculosis* gibi hücre içi bazı patojenler de bu hastalarda önemli enfeksiyon hastalıkları tablosu oluşturur. Tanı genellikle erken çocukluk döneminde konur ancak kısmi enzim eksiklikleri tanının gecikmesine neden olur. Tekrarlayan tüberküloz tanısıyla izlenen, daha sonra pulmoner aspergilloz gelişen adölesan yaşta KGH tanısı konan bir hastayı sunduk. Tekrarlayan tüberküloz enfeksiyon hastalığı durumlarında ayırıcı tanıda primer immünyetersizlik düşünülmelidir. KGH gibi primer immün yetmezlikli hastalarda invaziv akciğer aspergillozu gelişmeden once tekrarlayan tüberküloz enfeksiyon hastalığı vasıtasıyla yakalanabilir. Bu sayede, en azından bazı hastalarda, enfeksiyon hastalığı hem daha etkin kontrol altına alınabilir hem de enfeksiyon hastalığının rekürensi engellenebilir.

Anahtar Kelimeler: Kronik granülomatöz hastalık, tekrarlayan tüberküloz, aspergilloz

Introduction

Chronic granulomatous disease (CGD) is a heterogeneous, hereditary primary immunodeficiency disease characterized by recurrent life-threatening infections as a result of defects in the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system (1). Although the X-linked recessive form is most frequent, there are also autosomal recessive forms

Correspondence Address / Yazışma Adresi
Şefika İlknur Kökcü Karadağ
Ondokuz Mayıs Üniversitesi Tıp Fakültesi,
Çocuk İmmünoloji ve Alerji Bilim Dalı,
Samsun-Türkiye
E-mail: drilknurkokcu@gmail.com

Received: 31.05.2021 **Accepted:** 07.10.2021 **Available Online Date:** 30.06.2022

which is frequently seen in our country. Mycobacterial disease has been reported in patients with chronic granulomatous disease. Additionally, patients followed with the diagnosis of recurrent tuberculosis may have underlying chronic granulomatous disease (2). We would like to present a patient who first had recurrent tuberculosis infectious disease and later developed pulmonary aspergillosis and was diagnosed with CGD.

Case Report

A eighteen-year-old male patient was consulted to our clinic because of unhealed treatment-resistant pneumonia with possible fungal infection findings in a lung radiography. It was elucidated that the patient was a construction worker.

He was born into a consanguineous Turkish family, living in central Anatolia. He had a history of progressive axillary lymphadenopathy after receipt of BCG vaccination, recurrent skin abscess and long term antituberculosis treatment in his childhood. Patient was admitted to our clinic with complaints of coughing, night sweats, weight loss, signs of lower respiratory tract infection however, *M. tuberculosis* could not be demonstrated microbiologically and serologically. PPD was found to be 16 mm. The patient was diagnosed with tuberculosis and anti-tubeculosis treatment was given. A tomography showed diffuse calcifications and nodular infiltrations in right lung. In his physical examination, he was pale and exhausted, 167 cm (3-10 percentile) in height, 54 kgs (<3 percentile) in weight, his respiratory rate was 28/min, heart rate of 130/min, an arterial blood pressure of 100/60 mmhg, and a body temperature of 38.1°C.

His immunological examination revealed the following results: WBC= 11800/mm^3, lymphocyte= 4560/mm^3, neutrophil= 7240/mm^3, hb= 10.3 g/dL, PLT= 436.000, IgG= 2830 mg/dL (907-1958), IgA: 373 mg/dL (96-465), IgM= 123 mg/dL (83-282), IgE= 3100 IU/mL, and normal lymphocyte subgroups. Due to possible fungal pneumonia with high IgG level and recurrent skin abscess in his history, we suspected CGD. We checked neutrophil oxidative function with dihydrorhodamine test assay. The stimulation index (SI) was found as three-fold (normal 60-90-fold). In this way, we showed that the oxidase activity was decreased in the patient. His mother don't havea carrier pattern in dihydrorhodamine assay. In light of these findings, the patient was followed up with a preliminary diagnosis of CGD with residual oxidase activity SI> 3. A blood sample was sent to XXXXX , Department of Immunology, which is a molecular diagnosis center of CGD, to confirm functional and genetic diagnoses. CGD subgrup analysis was performed with flow cytometry. We found that p47-phox expression was lost. So, for the rapid genetic diagnosis, hotspot mutation (dGT deletion) at the beginning of exon two of NCF1 gene was checkwith fragment analysis (gene scan) by ABI3500 x L infrastructure. Gene-scan showed only a pseudogen peak in the patient and pesudogen/gene was 5/1 at parentsmeans heterozygot carrier (normal; 2/1 pseudogen/gene ratio). These data revealed that there was a homozygous c.75_76 delGT deletion in NCF1 Exon 2 in the patient (Figure 1). Mutation cause stop codon, leads to the discontinuation of an aminoasit synthesis at the p.Tyr26HisfsX26 point and loss of expression of p47-phox protein. P47-phox, is the activity-enhancing molecule in the NADPH oxidase complex, p47-phox deficiency causes the mild disease phenotype with residual oxidase activity. Residual oxidase activity may be the couse of late diagnosis and mild phenotype. No other mutations were detected in the primary immunodeficiency panel.

A chest X-ray showed infiltration covering the main bronchus on the right middle lobe (Figure 2a). A tomography showed diffuse calcifications and nodular infiltrations (Figure 2b). Acid-resistant bacteria (ARB) in gastric aspirates, tuberculosis PCR and tuberculosis culture in sputum tests were all negative.

The material was found insufficient in the transbronchial lung biopsy. Galactomannan test could not be performed. The patient, who was resistant to specific and nonspecific antimicrobial treatments, was accepted as "probable pulmonary *Aspergillosis*" according to the lung tomography findings. (Figure 2a). Voricanozole was started at 9 mg/kg/dose twice a day

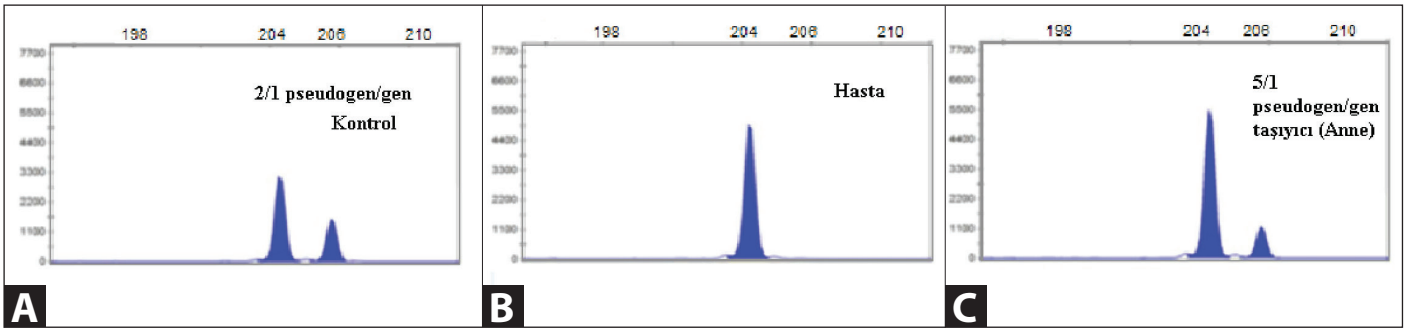

Figure 1. Evaluation of the Dihydrodamine test in flow cytometry.

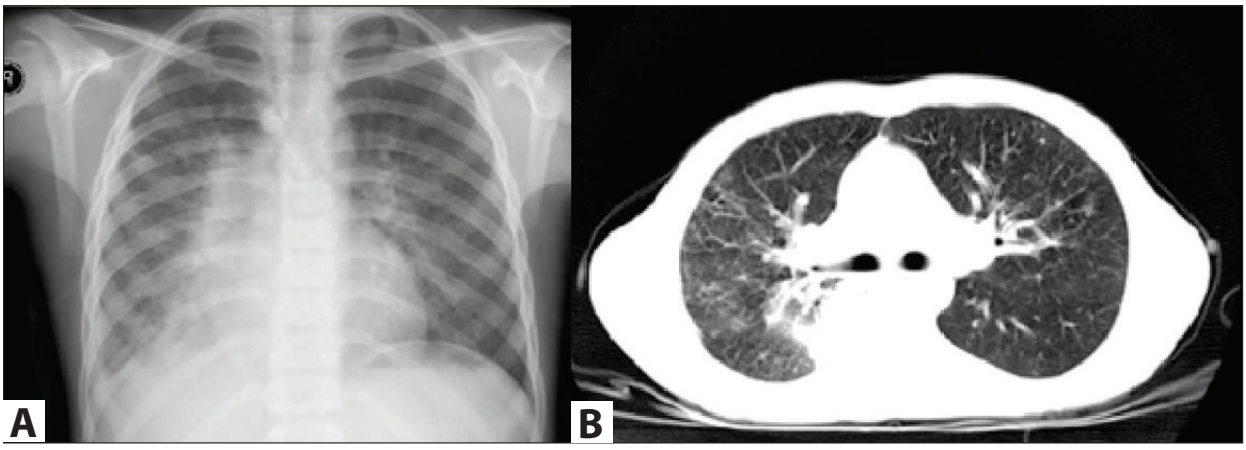

Figure 2. Chest radiography and a thorax CT image, before antifungal treatment.

and continued at 8 mg/kg/dose (3). The patient gave clinical, radiological and serological responses to voriconazole (Figure 2b). After treatment, voriconazole prophylaxis was continued.

Discussion

Chronic granulomatous disease, a bacteria killing defect is apparent. The NADPH oxidase system is an enzyme system consisting of five subunits. CGD with p47phox defects, autosomal recessive disease,caused by mutation in NCF1 gene. While the majority of X-linked recessive patients are diagnosed before the age of two, those with p47phox deficiency diagnosed lately (4,5).

Our patient, who had complaints of lymphadenitis at the age of four, had been treated twice for tuberculosis, but CGD was diagnosed lately at the age of 16. However, disruptions in follow-up and treatment suggest that clinicians should also be mindful of potential treatment disruptions in future cases.

This patient had BCG lymphadenitis and recurrent tuberculosis before pulmonary possible *Aspergillosis* disease. Innate immunodeficiency disease such as CGD should be considered in the differential diagnosis, not only in the presence of skin abscess and *Aspergillus* infection, but also in patients with BCGitis and/or recurrent tuberculosis (6). After BCG vaccination, patients have a skin lesion draining from the vaccination site. It is very rare to be disseminated, as is seen in patients with severe immunodeficiency.

In a study of 71 cases in which Bustamante et al. examined chronic granulomatous disease and mycobacterial diseases, 31 patients (44%) had tuberculosis, 53 (75%) suffered the negative effects of BCG vaccines, and 13 (18%) had both tuberculosis and BCG-itis. None of these patients had clinical diseases caused by environmental mycobacteria, *Mycobacterium leprae* or *Mycobacterium ulcerans*. A common feature in these patients was that they developed tuberculosis at an early age. Mycobacterial disease was the first clinical finding of CGD in 60% of their patients (7). Our patient also received antituberculosis treatment twice for BCG lymphadenitis and pulmonary tuberculosis.

Camcıoğlu et al reported that the infectious agents found in their study on 32 CGD patients were *S. aureus* (32.2%), *Aspergillus fumigatus* (16.1%), and *M. tuberculosis* (12.5%). In this series of patients, P47 phox defect was present in six cases (6). These patients were followed and treated with tooth abcess, skin abscess, perianal abscess, liver abscess, lymphadenitis, otitis media, mycobacterium tuberculois, haemophilus influenza Type B pneumoniae, inflammatory bowel disease. In accordance with the literature, Our case also had tuberculosis and aspergillosis infectious disease.

A P47-phox defect was also found in three patients, previously reported as a case series in our clinic (8). This case differs from others, in that it was thought to be recurrent tuberculosis, and that diagnosis was made at a late age. In conclusion, where consanguineous marriages are common, patients with recurrent tuberculosis should be examined for chronic granulomatous disease.

Informed Consent: Patient consent was obtained.
Peer-review: Externally peer-reviewed.
Author Contributions: Concept- ŞİKK, OU, MYK; Design- ŞİKK, ŞK; Supervision- AY, OU, MYK; Resources- ŞİKK, ŞK, MYK; Data Collection and/or Processing- ŞİKK, SK; Analysis and/or Interpretation - MYK, AY, OY; Literature Review - ŞİKK, SK, MYK; Writing- ŞİKK, MYK, ŞK; Critical Review - MYK, AY, OU.
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study has received no financial support.

References

1. *Holland SM. Chronic granulomatous disease. Clin Rev Allergy Immunol 2010;38:3-10.* **[CrossRef]**
2. *Ying WJ, Wang XC, Sun JQ, Liu DR, Yu YH, Wang JY. Clinical features of chronic granulomatous disease. Zhonghua Er Ke Za Zhi 2012;50:380-5.*
3. *Warris A, Lehrnbecher T, Roilides E, Castagnola E, Brüggemann RJM, Groll AH. ESCMID-ECMM guideline: Diagnosis and management of invasive aspergillosis in neonates and children. Clin Microbiol Infect 2019;25:1096-113.* **[CrossRef]**
4. *Aygun D, Koker MY, Nepesov S, Koker N, van Leeuwen K, de Boer M, et al. Genetic characteristics, infectious, and noninfectious manifestations of 32 patients with chronic granulomatous disease. Int Arch Allergy Immunol 2020;181(7):540-50.* **[CrossRef]**
5. *Köker MY, Camcıoglu Y, van Leeuwen K, Kılıç SŞ, Barlan I, Yılmaz M, et al. Clinical, functional, and genetic characterization of chronic granulomatous disease in 89 Turkish patients. J Allergy Clin Immunol 2013;132:1156-63.* **[CrossRef]**
6. *Köker MY, Türe Z, Köker N, Metam G. An atypical case wit chronic granulomatosus disease and Kabuki syndrome. Erciyes Med J 2020;42/2:229-32.* **[CrossRef]**
7. *Conti F, Lugo-Reyes SO, Blancas Galicia L, He J, Aksu G, Borges de Oliveira E Jr, et al. Mycobacterial disease in patients with chronic granulomatous disease: A retrospective analysis of 71 cases. J Allergy Clin Immunol 2016;138(1):241-8.* **[CrossRef]**
8. *Kutluğ Ş, Şensoy G, Birinci A, Saraymen B, Köker MY, Yıldıran A. Seven chronic granulomatous disease cases in a single-center experience and a review of the literature. Asian Pac J Allergy Immunol 2018;36:35-41.*