CASE REPORT

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A Case Diagnosed with Chronic Granulomatous Disease Presenting with Dactylitis

Daktilit ile Prezente Olan Kronik Granülomatöz Hastalık Tanısı Konulan Bir Olgu

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Abstract

Chronic granulomatous disease is a rare primary immunodeficiency seen in 1/70,000-1/200,000 births. It is a monogenetic disease caused by defects in the nicotinamideadenine-dinucleotide-phosphate oxidase enzyme complex. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase produces reactive compounds necessary for the lysis of phagocytized microorganisms. Defects in the NADPH oxidase enzyme complex predispose to granuloma formation and the development of life-threatening recurrent bacterial and fungal infections. Infections usually occur with involvement of the lungs, lymph nodes, liver, bone and skin. Rarely, it may present with dactylitis. A case of chronic granulomatous disease presenting with dactylitis in the third finger of the left hand and abscess on the wrist. The patient who didn't respond to empirical antibiotic treatment was referred to our hospital. *Serratia marcescens* was detected in the drained abscess. After the detection of *Serratia marcescens,* which we see rarely as a causative agent, in the wound culture, the detection of granulomatous inflammation in the biopsy and the NBT test: 0%; the patient was diagnosed with chronic granulomatous disease. Significant regression was observed in the lesion after ceftriaxone and gentamicin treatment given for 14 days. Recurrent and/or unusually severe infections, particularly abscesses and infections commonly caused by CGD-associated pathogens, should suggest chronic granulomatous disease. Early screening of potentially affected children; early diagnosis as well as timely antimicrobial therapy followed by adequate antimicrobial prophylaxis will prevent infectious relapses and sequelae.

Keywords: Chronic granulomatous disease, CYBB, dactylitis, *Serratia marcescens*

Öz

Kronik granülomatöz hastalık 1/70.000-1/200.000 doğumda görülen nadir bir primer immün yetmezliktir. Nikotinamidadenin-dinükleotit-fosfat oksidaz enzim kompleksindeki kusurların neden olduğu monogenetik bir hastalıktır. Nikotinamid adenin dinükleotid fosfat (NADPH) oksidaz, fagosite edilmiş mikroorganizmaların parçalanması için gerekli reaktif bileşikleri üretir. NADPH oksidaz enzim kompleksindeki kusurlar, granülom oluşumuna ve yaşamı tehdit eden tekrarlayan bakteriyel ve mantar enfeksiyonlarının gelişmesine zemin hazırlar. Enfeksiyonlar genellikle akciğer, lenf bezleri, karaciğer, kemik ve deri tutulumu ile ortaya çıkar. Nadiren daktilite de neden olabilir. Sol el üçüncü parmağında daktilit ve el bileğinde apse ile başvuran kronik granülomatöz hastalık olgusunu sunuyoruz. Ampirik tedaviye yanıt alınamaması üzerine tarafımıza sevk edildi. Boşaltılan apsede *Serratia marcescens* saptandı. Yara kültüründe etken olarak nadiren gördüğümüz *Serratia marcescens*'in saptanması, biyopside granülomatöz enflamasyon saptanması ve NBT testinin %0 olarak saptanması üzerine hastaya kronik granülomatöz hastalık tanısı kondu. On dört gün süreyle verilen seftriakson gentamisin tedavisi sonrasında lezyonda belirgin gerileme gözlendi. Tekrarlayan ve/veya alışılmadık derecede şiddetli enfeksiyonlar, özellikle apseler ve genellikle CGD ile ilişkili patojenlerin neden olduğu enfeksiyonlar, kronik granülomatöz hastalığı düşündürmelidir. Potansiyel olarak etkilenen çocukların erken taranması; erken tanı ve zamanında antimikrobiyal tedavi ve ardından yeterli antimikrobiyal profilaksi, enfeksiyöz relapsları ve sekelleri önleyecektir.

Anahtar kelimeler: CYBB, daktilit, kronik granülomatöz hastalığı, *Serratia marcescens*

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Introduction

Chronic granulomatous disease is a rare primary immunodeficiency seen in 1/70,000-1/200,000 births. It is a monogenetic disease caused by defects in the nicotinamide-adeninedinucleotide-phosphate (NADPH) oxidase enzyme complex. NADPH oxidase produces reactive compounds necessary for the lysis of phagocytized microorganisms. Defects in the NADPH oxidase enzyme complex predispose to granuloma formation and the development of life-threatening recurrent bacterial and fungal infections. Infections usually occur with involvement of the lungs, lymph nodes, liver, bone and skin. Rarely, it may present with dactylitis (1,2). Here we present a case of chronic granulomatous disease presenting with dactylitis in the third finger of the left hand and abscess on the wrist.

Case Report

Three-year-old 10-month-old male patient had a lesion that started as dactylitis on the middle finger of the left hand three months ago and gradually became an infected ulcerated wound. He was referred to us after there was no response to the treatment given. He has a history of frequent upper respiratory tract and lower respiratory tract infections, hospitalization with a diagnosis of sepsis in the neonatal period and infected lesion on the edge of the nose 4 months ago.

Our case was born as the third child of a 27-year-old mother and a 32-year-old father. There is no consanguinity between his parents. He was born at term as 3330 gr.

On physical examination, there was an infected and ulcerated lesion extending from the proximal phalanx to the distal phalanx of the left third finger. Contracture developed in his left hand middle finger (Figure A, B). In the oropharynx examination, there were caries in the anterior upper teeth. He has a left axillary lymphadenomegaly around 1 cm. His chest and cardiac auscultation was normal. He has not organomegaly. Fever was 36 degrees, heart rate was 90/min, respiratory rate was 20/min, blood pressure was 85/55 mmHg. Oxygen saturation was measured at 96% in room air. Body weight: 16 kg (25-50p), height: 96 cm (3-10 p).

Complete blood count; leukocyte count: 9850/mm^3, hemoglobin: 9.5 g/dL, platelet count: 436000/mm^3 neutrophil: 2750/mm^3, lymphocyte: 5690/mm^3, C-reactive protein: 25 mg/L, procalcitonin was 0,02 ng/mL. Biochemical parameters were normal. A 31.5 mm lesion which is located under the skin in the area extending from the proximal phalanx to the distal phalanx of the left hand 3rd finger and 17x20x6 mm wrist abscess was detected in magnetic resonance imaging. *Serratia marcescens* was detected in the drained abscess. Quantiferon was negative. No pathogenic microorganisms were detected in the fungal culture, mycobacterial culture and blood culture. In the biopsy material was taken from the lesion on the finger, granulomatous inflammation was detected. *Serratia marcescens* was detected in tissue culture. IgG: 1348 mg/dL (640-2010), IgM: 194 mg/dL (52-297), IgA:198 mg/dL (44-241), total IgE: 212 mg/dL, anti-HBs positive. In flow cytometry analysis of lymphocyte subgroups: CD 45:99%,

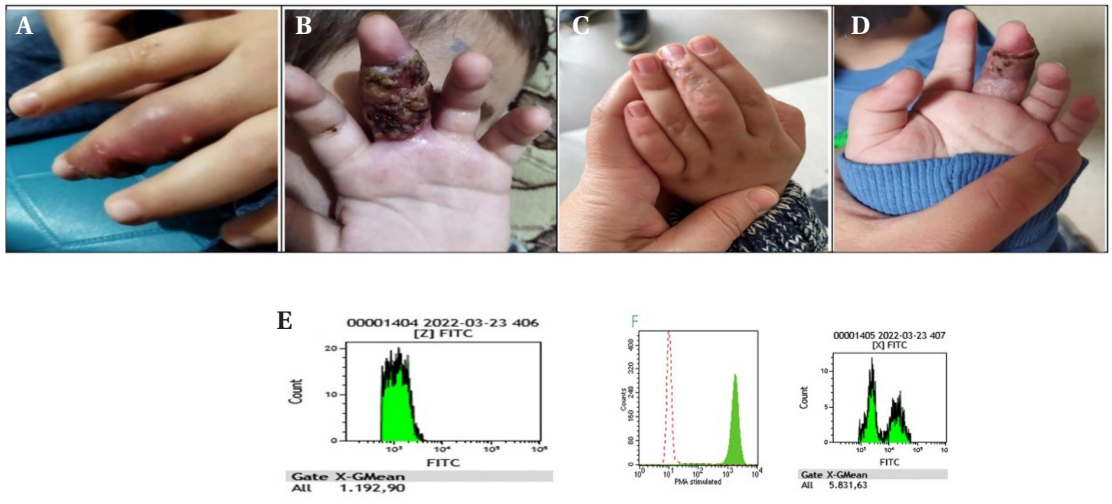

Figure. A, B) An infected and ulcerated lesion extending from the proximal phalanx to the distal phalanx of the left third finger, **C, D)** Patient's finger after treatment, **E)** Histogram image remained on the left in the patient's dihydrorhodamine test, **F)** Histogram images were detected in the dihydrorhodamine test of our patient's mother, one normal and one affected

CD 19: 22 (11-31), CD3: 66% (55-79), CD4: 35% (28-51), CD8: 30% (16-42), CD 16-56 9% (5-28), HLA DR 21.6 (18-38), NBT: 0% in the dihydrorhodamine test, the fluorescent effect we see in healthy people did not occur. While the histogram image remained on the left, two separate histogram images were detected in the dihydrorhodamine test of our patient's mother; one normal and one affected (Figure E, F). With these data, it was thought that there may be a *CYBB* gene mutation with X-linked inheritance and accordingly Gp91 phox deficiency. As a result of the genetic test sent from our patient a hemizygous mutation *CYBB* gene was detected (c.868C>T (p.aRG290*).

After the detection of *Serratia marcescens*, which we see rarely as a causative agent, in the wound culture, the detection of granulomatous inflammation in the biopsy and the NBT test: 0%; the patient was diagnosed with chronic granulomatous disease.

Significant regression was observed in the lesion after ceftriaxone gentamicin treatment given for 14 days (Figure C, D). We started trimethoprim-sulfamethoxazole and itraconazole prophylaxis. Physiotherapy was started for finger contracture. Permission was obtained from the parents of the case to use the pictures and present the case.

Discussion

More than 50 percent of pathogenic variants that cause CGD are X-linked the disease therefore primarily affects men, as in our patient. However, in cultures where consanguineous marriage is common, autosomal recessive forms of CGD are more common than X-linked forms (3). Although autosomal recessive forms of CGD are more common in our country due to the frequent occurrence of consanguineous marriage, X-linked CGD form was seen in our patient. The mother was found to be a CGD carrier.

Patients with CGD often have growth retardation. In a series of 94 patients, approximately 75 percent of the patients had low height and weight values at the time of diagnosis (2). Although our patient's weight was in the normal percentile, his height value was below the 10th percentile.

CGD can occur at any time from infancy to late adulthood. However, most patients are diagnosed before the age of five. Consistent with the literature, our patient was first diagnosed when he was 3 years and 10 months old (2-7). X-linked CGD tends to start earlier and be more severe than p47phox deficiency, which is the most common autosomal recessive form (8). Infections usually occur in organs exposed to the external environment such as the lungs, gastrointestinal tract and skin, as well as in the lymph nodes that drain these areas. In addition to infection and granuloma formation in patients with CGD, autoimmune diseases; including systemic lupus erythematosus, antiphospholipid antibody syndrome, autoimmune thrombocytopenia, rheumatoid arthritis, IgA nephropathy, sarcoidosis and Celiac disease, can also be seen rarely (about 10%) (9-11). Our patient also had an abscess on the left wrist and dactylitis, which is rarely seen in CGD, and an enlargement was detected in the left axillary lymph node that drains this region.

Most commonly, patients with CGD typically present with infections due to catalase-positive organisms. Catalase is an enzyme that can inactivate hydrogen peroxide produced by some bacteria and fungi. It is believed that patients with CGD can use hydrogen peroxide produced by catalase-negative microbes to generate reactive oxidants and, as a result, bypass the intrinsic CGD defect (12).

The most common pathogens detected in 268 patients followed in a single center over a 40 year period were *Aspergillus species, S. aureus, Burkholderia (Pseudomonas) cepacia complex, Serratia marcescens, Nocardia* (13). In another series of 27 patients followed in a different center in North America from 1985 to 2013, it was found that the most common severe infections, in order of frequency, were due to *S. aureus, Serratia, Klebsiella Aspergillus,* and *Burkholderia* (14). In our case, *Serratia marcescens*, which is among the most common organisms CGD, was detected in wound culture. Overall, *Serratia* spp. has low virulence and is considered an opportunistic pathogen (12). In infants with CGD, *Serratia marcescens* infections often present as bone and soft tissue infections, whereas in older children and adults with CGD, they present as abscesses and large, poorly healing ulcerated skin infections. Osteomyelitis is rare (15,16).

Patients with CGD are prone to make granuloma formation. These may affect the lumen organs, but they are more common especially in the gastrointestinal and genitourinary tracts (17). Other tissues and organs, such as the retina, liver, lungs, and bone, may also be affected, to a lesser extent by granuloma (18). In our patient, granulomatous inflammation was detected in the lesion on the finger with atypical presentations. The causes of granuloma formation in CGD are unknown.

However, CGD cells normally disrupt chemotactic and inflammatory signals and fail to lyse apoptotic cells normally, which can lead to persistent and excessive

inflammation (19). Up to 20 percent of cells with normal respiratory burst activity are sufficient to prevent serious bacterial and fungal infections. Therefore, most female carriers of X-linked gp91 phox CGD variants can generate adequate immune responses against infections (19-22). In a large series of X-linked carriers, those with <20% DHR+ cells had severe infectious complications, while all carriers had increased rates of inflammatory and autoimmune complications, regardless of the percentage of DHR+ cells (23).

Although the mother of our patient had a history of frequent upper respiratory tract infections, there was no history of serious infection, autoimmune or chronic disease detected so far.

It is very important to identify the complicated infectious agent in the treatment of infections in CGD. Early and aggressive treatment is essential to prevent the spread of infection.

Infections that do not respond to treatment within 24 to 48 hours, additional diagnostic procedures should be used to identify the microorganism (24). Unfortunately, the starting of effective treatment was delayed in our patient, and therefore a contracture developed in his finger.

Cotrimoxazole is the antimicrobial of choice for bacterial prophylaxis in CGD, because of its broad spectrum and activity against *Nocardia* spp. It also reaches a good concentration in polymorphonuclear cells and does not affect the intestinal anaerobic microbiota (25). It is the most common cause of fungal infection in *Aspergillus* spp. CGD, but has been less frequently identified in different pathogens. Itraconazole has traditionally been the azole of choice for prophylaxis. It was observed that invasive fungal disease had seen less frequently in patients who received prophylaxis compared to those who did not (26).

We started trimethoprim-sulfamethoxazole and itraconazole prophylaxis for our patient whose intravenous treatment was completed in the hospital. No serious infection was observed in our patient after discharge.

Conclusion

Recurrent and/or unusually severe infections, particularly abscesses and infections commonly caused by CGD-associated pathogens, should suggest chronic granulomatous disease. Early screening of potentially affected children; early diagnosis as well as timely antimicrobial therapy followed by adequate antimicrobial prophylaxis will prevent infectious relapses and sequelae.

Ethics

Informed Consent: Permission was obtained from the parents of the case to use the pictures and present the case.

Authorship Contributions

Concept: S.U., I.T., Ç.A., Design: S.U., I.T., Ç.A., Data Collection or Processing: S.U., G.K., M.H.Ç., Analysis or Interpretation: S.U., Ç.A., S.N., Drafting Manuscript: S.U., I.T., S.N., G.K., Critical Revision of Manuscript: Ç.A., M.H.Ç., Final Approval and Accountability: S.U., S.N., I.T., Ç.A., G.K., M.H.Ç., Writing: S.U., S.N., I.T., Ç.A., G.K., M.H.Ç., Technical or Material Support: S.U., Supervision: S.U.

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