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Chronic Granulomatous Disease in a Boy Who Presented With Dactilitis Caused by *Serratia Marcescens*, Mimicking Rheumatic Monoarthritis in the Newborn Period: A Case Presentation

CASE REPORT

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ABSTRACT

Chronic granulomatous disease (CGD) is a heterogenous genetic primary immune deficiency disorder, characterized by life-threatening infections and granulomas secondary to increased inflammatory responses. Most infections involve the lungs, skin, lymph nodes, and liver. Wedescribe a child diagnosed with CGD and the p67phox mutation presenting with *Serratia marcescens* arthritis without osteomyelitis in the newborn period.

Keywords: Chronic granulomatous disease, dactilitis, *Serratia marcescens*

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INTRODUCTION

Chronic granulomatous disease (CGD) is a heterogenous genetic primary immune deficiency disorder originating from the defects in nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system, and characterized by life-threatening infections, and granulomas secondary to increased inflammatory responses (1).

CGD is caused by the mutations in four different genes involved in the NADPH oxidase system (i.e., gp91phox, p22phox, p47phox, and p67phox). CGD inherited X-linked or autosomal recessive. Most patients (65%) have gp91phox mutation with X-linked recessive inheritance in Western countries, while in the region with high rate of consanguinity, such as Turkey, Iran and Israel, autosomal recessive (AR) form of disease is prevalent (2).

A mutation in the *CYBB* gene, located in X chromosome, encoding the membrane-dependent gp91-phox protein(cytochrome b558)causes X-linked CGD phenotype in males. The cases of AR CGD results from genetic defects in NCF1, NCF2, NCF4, or CYBA genes encoding p47*phox*, p67*phox*, p40*phox*, or p22phox, respectively, three regulatory proteins associated with each other, and a smaller subunit of membrane protein (p22phox) associated with gp91phox (1, 2).

Most infections involve the lungs, skin, lymph nodes, and liver. The diagnosis is based on medical history, clinical signs, and neutrophil function test demonstrating the absence of respiratory burst, and it is confirmed by genotyping (1-3).

Currently, main therapeutic measures include antibiotics and antifungal prophylaxis, interferon-gamma prophylaxis, treatment of acute infectious and inflammatory complications, hematopoietic stem cell transplantation, and the gene therapy (3).

In addition to infections, patients with CGD may also suffer complications resulting from increased inflammation and auto-immunity (4).

In this case report, a, AR-CGD patient with a mutation in NCF2gene resulting in p67phox defect and presenting with arthritis in newborn period is described. Written informed consent was obtained from the parents of the patient.

CASE REPORT

Twenty-four-days-old male infant was referred to the pediatric rheumatology unit with swelling in the left-hand 2ndfinger with a potential diagnosis of inflammatory arthritis. The laboratory work-up did not suggest any rheumatologic conditions. The patient was followed up without treatment for approximately 1week, and a consultation from the department of immunology due to worsening of the swelling in the finger was requested after 1week.

The patient was initially examined at our immunology unit at 30 days of age with swelling in the left hand (Figure 1a). His medical history showed that the patient was born to a 29-year-old mother at 39 weeks of gestation with a birth weight of 3350 g. He was the second child of the family, with no prenatal or postnatal health problems. He was born to a cross-cousin marriage. An uncle had died due to acute lymphoblastic leukemia; apart from this, his immunological history was unremarkable. The umbilical cord had fallen off at the 7th day. Physical examination showed anthropometric measurements consistent with age. The liver was palpable 1-2 cm under the inferior costal margin, with no splenomegaly or lymphadenopathy. The patient had marked swelling, redness, and tenderness in the middle phalanx of the left index finger (Figure 1b).The swelling had first started at 24 days of life when a consultation from the rheumatology department was requested. Subsequent anti-nuclear antibody and anti-ds DNA tests were negative, suggesting that a rheumatologic diagnosis was unlikely. Thus, a consultation was requested from our department. In this patient with suspected inflammatory arthritis in the index finger, the following blood tests were performed suspecting immune deficiency: white blood cells: 31580/mm^3; hemoglobin: 11.1 gr/dl; platelets: 642000/mm^3; absolute neutrophil count: 22290/mm^3; absolute lymphocyte count: 4410/mm^3; erythrocyte sedimentation rate: 45 mm/h; C-reactive protein: 130 mg/dl; normal biochemistry, serum IgG: 795 md/dl; IgM: 126 md/dl; IgA: 5.81 md/dl; IgE: 18.5 IU/l. Lymphocyte subtyping was as follows: CD3$^+$: 53.7% (51-79), CD4$^+$: 44% (31-54), CD8$^+$: 14.9% (10-31), CD19$^+$: 9.6% (14-44), and CD16$^+$56$^+$: 30.1% (5-23). CD11-CD18 was normal (Table 1). A dhydrorhodamine test was performed with a low stimulation index (3.5%), establishing a diagnosis of chronic granulomatous disease. Blood sampling was performed for genetic analysis. Also, intra-articular puncture was made to ascertain whether the arthritis associated with chronic granulomatous disorder was of autoimmune or infectious origin. Microscopic examination and the Gram staining of the sample showed no microorganism, but abundance of polymorphonuclear leukocytes were seen. The patient was admitted for intravenous treatment based on a diagnosis of infectious monoarthritis. During his follow up, abscess formation occurred in the arthritic region (Figure 1c).Abscess was drained, and the microbiological culture of the abscess material resulted in the growth of *Serratia marcescens*. No osteomyelitis was detected in bone scintigraphy. Following 14 days of intravenous therapy with meropenem and amikacin, the abscess was completely resolved (Figure 1d).

Figure 1. a-d. (a) The patient presenting with swelling in the left index finger. (b) Arthritis in the left index finger. (c) Abscess formation in the left index finger. (d) Recovering after treatment.

Table 1. Hemogram-immunoglobulins-lymphocyte subgroups

Hemogram	WBC [mm^3]	Hb [gr/dL]	Plt [mm^3]	ANC [mm^3]	ALC [mm^3]
	31.580	11.1	642.000	22290	4410
Immunglobulins	**IgG [mg/dL]**	**IgM [mg/dL]**	**IgA [mg/dL]**	**IgE [IU/l]**	
	795 [633-1466]	126 [22-87]	5.81 [11-14]	18.5	
Lymphocyte Subgroups	**CD3 [%]**	**CD4 [%]**	**CD8 [%]**	**CD19 [%]**	**NK [%]**
	53.7 [51-79]	44 [31-54]	14.9 [10-31]	9.6 [14-44]	30.1 [5-23]

WBC: white blood cell, Hg: hemoglobin, Plt: platelet, ANC: absolute neutrophil count, ALC: absolute lymphocyte count

The genetic analysis showed a homozygote known nonsense mutation c.229C>T caused p. [Arg77X] stop codon in p67phox protein, and this is a prevalent mutation in the Middle Anatolia region. Anti-microbial prophylaxis (trimethoprim-sulfamethoxazole, fluconazole, interferon-gamma) and donor screening for bone marrow transplantation were initiated.

DISCUSSION

As a result of inability to kill intra-cellular microorganisms, patients with CGD are particularly predisposed to infections with catalase-positive *Staphylococcus aureus, Klebsiella pneumoniae, Salmonella spp., Serratia spp., Burkholderia cepaci, Aspergillus, Candida,* and *Nocardia* (5).

Oral prophylactic antibiotics (TMP-SMZ, cephalosporins, quinolones) and antifungal agents (itraconazole) have resulted in a significant improvement in the course of CGD, with efficacy in reducing the number and frequency of infectious episodes (6). In recent years, studies examining the long-term outcomes in these patients have

reported lower mortality rates, that is between 13% and 19.2%, as compared to previous studies (7). Consistent with the published literature, prophylaxis with antibacterial and antifungal prophylaxis resulted in a significant clinical improvement in our patient.

Published data suggest a higher incidence of X-linked CGD with an earlier onset and worse clinical course, although the reported figures for the autosomal-recessive form in our country are much higher (82%). Due to the difference in inheritance patterns, the autosomal-recessive form (p47phox defect) generally tends to have a delayed onset of clinical symptoms as a result of residual NADPH oxidase activity, and is expected to result in a milder clinical course, and longer life expectancy (2, 8).

In patients with CGD, in addition to infections and granuloma formation, autoimmune diseases have alsobeen reported to occur (in approximately 10%) rarely, including systemic lupus erythematosus, antiphospholipid syndrome, autoimmune thrombocytopenia, rheumatoid arthritis, IgA nephropathy, sarcoidosis, and celiac disease (9-11). Conditions such as pericardial effusion or pericarditis that require for prompt identification and treatment for increased survival have also been reported in CGD patients (12, 13). Although juvenile idiopathic arthritis frequently coexists with immune deficiencies, its co-occurrence with CGD is uncommon. However, patients with CGD in association with juvenile idiopathic arthritis have also been reported (14, 15).

Corticosteroids and immunosuppressive agents (azathioprine, methotrexate, anti-TNF blockers) may be effective in controlling the autoimmune symptoms (4).

Several mechanisms have been proposed to explain the co-occurrence of autoimmune conditions and CGD. In such cases, the increase in inflammation was explained on the basis of delayed apoptosis of neutrophils, and a reduced secretion of anti-inflammatory cytokines have also been found (16).

In CGD, in addition to increased occurrence of infections and granulomas, autoimmune conditions may also occur, although rarely. Since autoimmune related symptoms may comprise the first manifestation of the disease, CGD should be considered in the differential diagnosis. Exclusion of possible infections and regular use of anti-inflammatory medications may help achieve symptomatic control (13). Initially, arthritis due to autoimmune conditions was considered, although subsequent tests ruled them out.

From a clinical viewpoint, the lungs, skin, lymph nodes, and liver represent the most common sites of infection in CGD (3). Typical infections include purulent bacterial pneumonia, sinusitis, liver abscess, or necrotizing fungal infections in deep tissues or bone (17). In the study by Köker et al. (2) involving 89 patients, the most frequent type of infections were pneumonia and lymphadenitis, with no patients presenting with arthritis. Also, there was one case report for a 3-month-old patient with metacarpal osteomyelitis due to *Serratia marcescens*, and another newborn patient with osteomyelitis; however, both of these cases presented with osteomyelitis without arthritis (18). Similar to the patients described above, our patient presented with signs of the disease during the newborn or early infancy period, although the disease first manifested itself with arthritis without osteomyelitis. Therefore, to our knowledge, this is the first reported patient clinically presenting with arthritis.

Neonatal-onset multisystem inflammatory disease (NOMID) should be considered in the differential diagnosis. NOMID has been described as the most severe form and also one of the most severe monogenic autoinflammatory diseases. It has more chronic and persistent course. Patients display ongoing fever, continuous rash, optic disc edema, uveitis, abnormal bony overgrowth of the knees, and a variety of central nervous system manifestations (19). These findings were not observed in our case.

CONCLUSION

Chronic granulomatous disease (CGD) is an immune deficiency condition that may present with variable systemic signs and symptoms, characterized by recurrent infections. With the case report, our goal was to point out that CGD should be kept in mind in the differential diagnosis of rheumatic monoarthritis in the newborn period.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Conceived and designed the experiments or case: MC, NK. Performed the experiments or case: MC, NK, TP. Analyzed the data: TP, YK. Wrote the paper: MC, NK. All authors have read and approved the final manuscript.

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REFERENCES

1. Patiroglu, T., et al. "The clinical features and genetic mutations of chronic granulomatous disease: results from a reference centre at middle Anatolia."-*Genetic counseling [Geneva, Switzerland]*-24.3 [2012]: 327-335.
2. Köker MY, Camcıoğlu Y, van Leeuwen K, Kılıç SŞ, Barlan I, Yılmaz M, Metin A, de Boer M, Avcılar H, Patıroğlu T, Yıldıran A, Yeğin O, Tezcan I, Sanal Ö, Roos D. Clinical, functional, and genetic characterization of chronic granulomatous disease in 89 Turkish patients. J Allergy Clin Immunol.2013Nov; 132[5]: 1156-1163.e5. [CrossRef]
3. Filiz, Serkan, Dilara Fatma Kocacık Uygun, and Olcay Yeğin. "Kronik granülomatöz hastalık."-*Turk J Immunol*-1 [2013]: 22-31.
4. De Ravin SS, Naumann N, Cowen EW, Friend J, Hilligoss D, Marquesen M, et al. Chronic granulomatous disease as a risk factor for autoimmune disease. J Allergy Clin Immunol 2008; 122: 1097-103. [CrossRef]
5. Keleş S, Soysal A, Özdemir C, Eifan AO, Bahçeciler N, Bakır M ve ark. İnvaziv aspergilloz infeksiyonu ve hipogamaglobulinemi ile başvuran kronik granülomatözlü bir olgu. Asthma Allergy Immunol 2009; 7: 189-93.
6. Seger RA. Modern management of chronic granulomatous disease. Br J Haematol 2008; 140: 255-66. [CrossRef]
7. Turul-Ozgür T, Türkkani-Asal G, Tezcan I, Köker MY, Metin A, Yel L, et al. Clinical features of chronic granulomatous disease: a series of 26 patients from a single center.Turk J Pediatr 2010; 52: 576-81.
8. van den Berg JM, van Koppen E, Ahlin A, Belohradsky BH, Bernatowska E, Corbeel L, et al. Chronic granulomatous disease: the European experience. PLoS One 2009; 4: e5234 [CrossRef]

9. De Ravin SS, Naumann N, Cowen EW, Friend J, Hilligoss D, Marquesen M, et al. Chronic granulomatous disease as a risk factor for autoimmune disease. J Allergy Clin Immunol 2008; 122: 1097-103. [CrossRef]
10. Schmitt CP, Scharer K, Waldherr R, Seger RA, Debatin KM. Glomerulonephritis associated with chronic granulomatous disease and systemic lupus erythematosus. Nephrol Dial Transplant 1995; 10: 891-5.
11. Narsipur SS, Shanley PF. IgA nephropathy in a patient with chronic granulomatous disease. J Nephrol 2002; 15: 713-5.
12. Barış S, Özen A, Kıykım A, et al. Kronik granülomatöz hastalıklı olgularımızın değerlendirilmesi. Asthma Allergy Immunol 2014; 12: 26-34.
13. Barış S, Çağan HH, Kıykım A, ve ark. Kronik granülomatöz hastalık: Her zaman infeksiyonla ilişkili midir? Asthma Allergy Immunol 2012; 10: 48-52.
14. Sadrosadat T, Ziaee V, Aghighi Y, Moradinejad MH, Movahedi M. Presence of aJuvenile Idiopathic Arthritis and Chronic Granulomatous Disease in a Child. Iran J Pediatr. 2015 Apr; 25[2]: e365 [CrossRef]
15. Lee BW, Yap HK. Polyarthritis resembling juvenile rheumatoid arthritis in a girl with chronic granulomatous disease. Arthritis Rheum. 1994; 37[5]: 773. [CrossRef]
16. Brown JR, Goldblatt D, Buddle J, Morton L, Thrasher AJ. Diminished production of anti-inflammatory mediators during neutrophil apoptosis and macrophage phagocytosis in chronic granulomatous disease [CGD]. J Leukoc Biol 2003; 73: 591-9. [CrossRef]
17. Stasia MJ, Li XJ. Genetics and immunopathology of chronic granulomatous disease. Semin Immunopathol 2008; 30: 209-35. [CrossRef]
18. Salfa I, Cantarutti N, Angelino G, Di Matteo G, Capo V, Farinelli G, Cancrini C, Aiuti A, Palma P, Finocchi A. Serratia marcescens osteomyelitis in a newborn with chronic granulomatous disease. Pediatr Infect Dis J. 2013 Aug; 32[8]: 926. [CrossRef]
19. Sag E, Bilginer Y, Ozen S. Autoinflammatory Diseases with Periodic Fevers. Curr Rheumatol Rep. 2017 Jul; 19(7): 41. [CrossRef]