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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. We describe 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

INTRODUCTION
Chronic granulomatous disease (CGD) is a heterogenous genetic primary immune deficiency disorder originating from 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 p47phox, p67phox, p40phox, 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).

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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 2nd finger 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 1 week, and a consultation from the department of immunology due to worsening of the swelling in the finger was requested after 1 week.

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 splenomegalgy 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/mm3; hemoglobin:11.1 gr/dl; platelets:642000/mm3; absolute neutrophil count:22290/mm3; absolute lymphocyte count:4410/mm3; 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–
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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 also been reported to occur (in approximately 10%) rarely, including systemic lupus erythematosus, antiphospholipid syndrome, autoimmune thrombocytopenia, rheumatoid arthritis, IgA nephropathy, sarcoidosis, and celiac disease (9, 10, 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.

In conclusion, 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.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES


Table 1. Hemogram-immunoglobulins-lymphocyte subgroups

<table>
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<tr>
<th>Hemogram</th>
<th>WBC [mm$^3$]</th>
<th>Hb [gr/dl]</th>
<th>Plt [mm$^3$]</th>
<th>ANC [mm$^3$]</th>
<th>ALC [mm$^3$]</th>
<th>IgG [mg/dl]</th>
<th>IgM [mg/dl]</th>
<th>IgA [mg/dl]</th>
<th>IgE [IU/l]</th>
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<td>22290</td>
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<td>795</td>
<td>126</td>
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<tr>
<td></td>
<td>[633-1466]</td>
<td>[22-87]</td>
<td>[11-14]</td>
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<tr>
<td>Lymphocyte</td>
<td>CD3 [%]</td>
<td>CD4 [%]</td>
<td>CD8 [%]</td>
<td>CD19 [%]</td>
<td>NK [%]</td>
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<tr>
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<td>53.7</td>
<td>44</td>
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WBC: white blood cell, Hb: hemoglobin, Plt: platelet, ANC: absolute neutrophil count, ALC: absolute lymphocyte count

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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.