

# Seven chronic granulomatous disease cases in a single-center experience and a review of the literature

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## Abstract

**Background:** Chronic granulomatous disease (CGD) is a rare primary immunodeficiency caused by defects in the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme system. This disease causes the disordered functioning of phagocytic cells. It is characterized by life-threatening and/or recurrent infections by bacteria and fungi. CGD has one X-linked recessive subtype (X-CGD) and four autosomal recessive subtypes (AR-CGD), and the differential diagnosis is important in such chronic inflammatory disorders.

**Objectives:** To report the clinical and laboratory characteristics of our CGD patients based on their genetic characteristics.

**Methods:** Seven boys with CGD were reviewed based on clinical findings and genetic results. Dihydrorhodamine-1,2,3 (DHR) assay with flow cytometry was used as a diagnostic test. Genetic analysis was conducted to establish definitive diagnoses in all patients with CGD.

**Results:** The age of diagnosis varied between 1.5 years and 15 years. The most frequent clinical presentation was pneumonia, and two patients had BCG-itis. Four patients had the AR-CGD phenotype, and three patients had the X-CGD phenotype. Severe invasive infections due to *Aspergillus*, *Staphylococcus*, and *Serratia* species were reported. Frequent lung and lymph node involvement was observed during follow-up of the cases.

**Conclusions:** CGD is life-threatening disease that involves deep-seated infection. In our patients, the most commonly affected organs were the lungs and lymph nodes. Phagocytic disorders should be considered in cases of recurrent infectious diseases, invasive fungal diseases, BCG complications that are not self-limiting, unexplained lymphadenitis or osteomyelitis, and chronic inflammatory disorders.

**Keywords:** Children, chronic granulomatous disease, invasive fungal disease, NADPH oxidase, primary immunodeficiency

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## Introduction

Chronic granulomatous disease (CGD) is a congenital disorder of the innate immune system. Phagocytotic functions are impaired, and thus, recurrent bacterial and fungal infections occur.<sup>1</sup> It is characterized by the defective functioning of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme complex, which is found in phagocytic cells such as macrophages, neutrophils, monocytes, and eosinophils. This enzyme is responsible for respiratory burst, which has an

antimicrobial effect due to the formation of reactive oxygen intermediates (ROIs).<sup>2-4</sup>

NADPH oxidase (phagocyte oxidase -phox-) is an enzyme complex with five subunits. One of these subunits is the gp91<sup>phox</sup> protein, which is encoded by *CYBB* in the X chromosome and is the part of the enzyme linked to the cell membrane. This protein is the catalytic part of the enzyme. X-linked chronic granulomatous disease (X-CGD) occurs when this protein

is defective. The other four subunits of this enzyme complex are the p22<sup>phox</sup>, p47<sup>phox</sup>, p67<sup>phox</sup>, and p40<sup>phox</sup> proteins. These four subunits are encoded by *CYBA*, *NCF1*, *NCF2*, and *NCF4*, respectively, which are located in the autosomal chromosomes. Autosomal recessive chronic granulomatous disease (AR-CGD) occurs due to a defect in these proteins.<sup>2,5</sup> These four proteins form the cytosolic part of the enzyme. The p22<sup>phox</sup> protein also links the membrane component of the enzyme and the cytosolic component. The glucose-6-phosphate dehydrogenase (G6PD) and *Rac2* genes also affect NADPH oxidase activity.<sup>5</sup>

The most important symptom of this disease is recurrent and/or invasive infections, especially those caused by catalase-positive bacteria and fungi.<sup>6</sup> The most frequently isolated agents are *Aspergillus* species, *Staphylococcus aureus*, *Serratia marcescens*, *Burkholderia cepacia*, *Nocardia*, and *Salmonella* species.<sup>7</sup> Some CGD patients are predisposed to BCG or *Mycobacterium tuberculosis* infection.<sup>8</sup> Thus, CGD has clinical heterogeneity, as well as genetic heterogeneity. In addition, extreme inflammatory reactions that cause granuloma formation can occur. However, infectious diseases, especially fungal infections, are the most common cause of death among CGD patients.<sup>2,7</sup> Thus, the differential diagnosis of chronic inflammatory disorders is important.

The aim of this report is to present the clinical, laboratory, and genetic features of our patients with CGD in light of the recent literature.

## Methods

This retrospective study was based on the patients' medical records. Seven patients from six unrelated families were diagnosed and followed at Ondokuz Mayıs University, Division of Pediatric Immunology and Allergy, from June 2008 to December 2016. Dihydrorhodamine-1,2,3 (DHR) assay has a high sensitivity and specificity in detecting NADPH oxidase deficiency in neutrophils; thus, it was used as a diagnostic tool.<sup>1,2,5</sup> The DHR assay was performed with total leukocytes as described by Köker *et al.*<sup>2</sup> In this test, isolated neutrophils were incubated with DHR, stimulated with phorbol myristate acetate (PMA), and then analyzed via flow cytometry. The results are shown as the stimulation index (SI) i.e. the ratio of the mean fluorescence intensity (MFI) of the stimulated cells to that of unstimulated cells.<sup>2,9,10</sup>

The subgroup analysis and genetic analysis of all families and patients with CGD were performed at the laboratory of the Department of Immunology at the University of Erciyes, which is the Turkish reference center for neutrophil function disorders.<sup>2,5</sup> Genomic DNA was isolated from total blood leukocytes via standard procedures and analyzed for mutations in the *CYBB*, *NCF1*, and *NCF2* genes via the PCR amplification of each exon, followed by sequence analysis with ABI 3500 (Applied Biosystem, CA).<sup>2,9</sup> Genetic analysis was performed on all patients to ensure definitive diagnoses.<sup>2,5</sup> All the parents of the patients were genetically analyzed to detect carriers and for the sake of genetic counseling. Infections that required hospitalization or parenteral treatment were accepted as severe infections. When invasive fungal disease (IFD) was considered but not proven microbiologically, the patient was diagnosed with a *probable* or *possible* IFD based on clinical and imaging criteria.<sup>11</sup>

## Results

There were seven patients from six unrelated families in this study. The mean age of diagnosis was  $6.7 \pm 4.4$  years and age at diagnosis ranged between 1.5 and 15 years. The data on demographic and clinical features are shown in **Table 1**. Diagnoses were performed via DHR assay for all patients. Three patients with the carrier mother pattern (bimodal histogram) upon DHR assay were accepted as X-CGD cases. Three patients with a p47<sup>phox</sup> defect had residual activity, with an average SI of 3 upon DHR assay. Three patients with X-CGD and one patient with a p67-phox defect had oxidase null activity, with an SI of 1 (**Table 2**).

**Table 2** shows the mutations found in *CYBB* in the X-CGD patients and the mutations found in *NCF1* and *NCF2* in the AR-CGD patients. All mothers of X-CGD patients were found to be heterozygous carriers of the mutations observed in their children. These results were correlated with their carrier status in the DHR assay. All investigated parents of AR-CGD patients with homozygous mutations were heterozygous carriers of those mutations.

### Medical Histories of the Patients

Patient 1 suffered from anemia and lymphadenopathy at one month old and had severe BCG lymphadenitis at 3 months old. An interleukin 12-interferon gamma axis defect was considered initially because this patient also exhibited high induration (27x25 mm) on a tuberculin skin test (TST) and he was given tuberculosis treatment. Subsequently, lymphadenitis and multiple ulcers developed on his face. Then, he was diagnosed as X-CGD via DHR assay, and his mother was found to have the carrier pattern on DHR assay. Genetic analysis also confirmed the diagnosis in both patient and mother. He exhibited recurrent IFD in the lung, despite antifungal prophylaxis. His parents did not accept hemopoietic stem cell transplantation (HSCT). He died due to non-ameliorating fungal pneumonia during follow-up.

Patient 2 suffered from pneumonia twice. IFD was detected in the lung during the third pneumonia attack. Then he was diagnosed with CGD. He had congenital glaucoma and bilateral retinal atrophy; the infection markers for *Toxoplasma gondii*, *Rubella*, *Cytomegalovirus* and the *Herpes Simplex Virus* (TORCH) were negative. He also had selective IgA deficiency. He received HSCT at the age of six. He is still being followed up, with no problems.

Patient 3 presented with an ankle abscess and talar osteomyelitis based on magnetic resonance imaging (MRI) due to *Aspergillus fumigatus* infection (**Figure 1**). Shortly afterward, he suffered from septicemia, subcutaneous abscess, and vertebral osteomyelitis due to *A. fumigatus* based on blood culture at follow-up, although he had antifungal prophylaxis. Also, he developed a medulla spinalis compression due to vertebral osteomyelitis and a paravertebral abscess (**Figure 1**). HSCT was performed for this reason. He died due to cardiac and respiratory failure after HSCT at the age of eleven.

Patient 4 had suffered from sepsis and lymphadenopathy at one month old. He had also received tuberculosis treatment after BCG lymphadenitis. At four years old, *Aspergillus* pneumonia was detected via a bronchoscopic lung biopsy. He was diagnosed with CGD via DHR assay. Genetic analysis

**Table 1. Demographic and clinical features of the CGD patients.**

Patients (n=7)	P1	P2	P3	P4	P5	P6*	P7*
<b>CGD group</b>	X-CGD	X-CGD	X-CGD	AR-CGD	AR-CGD	AR-CGD	AR-CGD
<b>Sex</b>	Male	Male	Male	Male	Male	Male	Male
<b>Age of onset</b>	1 month	5 y	5 y	1 month	13 y	5 y	4 y
<b>Age of diagnosis</b>	1.5 y	5.5 y	7 y	4.5 y	15 y	10 y	4 y
<b>FTT</b>	No	Yes	Yes	No	No	Yes	Yes
<b>Consanguinity</b>	Yes	Yes	No	Yes	Yes	Yes	Yes
<b>Frequent infection†</b>	Yes	Yes	Yes	No	No	Yes	Yes
<b>Clinical manifestation</b>	Lymphadenitis Anemia	Pneumonia Lap	Abscess Osteomyelitis	Pneumonia	Liver abscess	Pneumonia	Pneumonia Lap
<b>Severe infections at follow-up</b>	Lymphadenitis Abscess Pneumonia Sepsis	Pneumonia Lymphadenitis	Abscess Lymphadenitis Pneumonia Osteomyelitis	Lymphadenitis Pneumonia Sepsis	Abscess Pneumonia Empyema Lymphadenitis	Pneumonia	Pneumonia
<b>Other chronic disease</b>		Congenital glaucoma Retinal atrophy			CLD	CLD, RA Scoliosis	CLD
<b>BMT</b>		HSCT	HSCT	HSCT			
<b>Outcome/ The cause of death</b>	Deceased/ Pneumonia	Alive	Deceased/ CRF	Alive	Deceased/ Pneumonia	Alive	Alive
<b>Current age or the age of death</b>	2 y 7 m	6 y	11 y	9 y	17 y 9 m	22 y	15 y

Abbreviations: CGD, chronic granulomatous disease; DHR, Dihydrorhodamine-1,2,3; FTT, failure to thrive; X-CGD, X-linked recessive chronic granulomatous disease; AR-CGD, autosomal recessive-linked chronic granulomatous disease; Lap, lymphadenopathy; CLD, chronic lung disease; RA, rheumatoid arthritis; BMT, bone marrow transplantation; HSCT, hemopoietic stem cell transplantation; CRF, cardiorespiratory failure.

\* P6 and P7 are brothers.

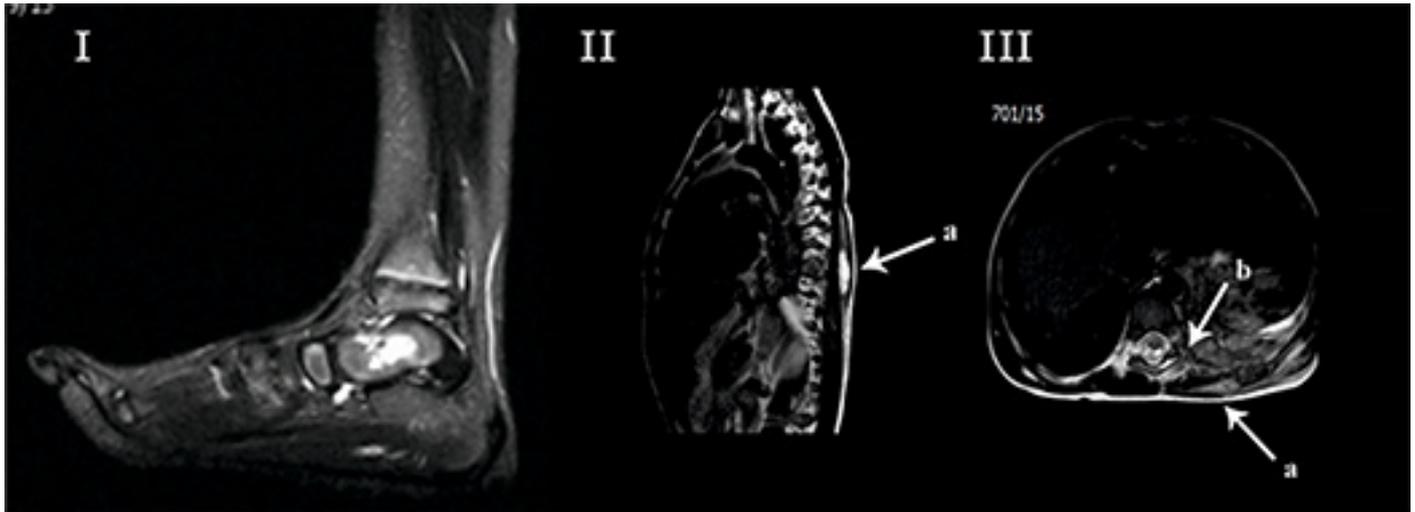
† Patients who have more than eight respiratory tract infections per year.

**Table 2. Laboratory features of the CGD patients.**

Patients (n=7)	P1	P2	P3	P4	P5	P6*	P7*
<b>CGD subtype</b>	X91	X91	X91	A67	A47	A47	A47
<b>CGD gene</b>	CYBB	CYBB	CYBB	NCF2	NCF1	NCF1	NCF1
<b>Diagnostic test / SI</b>	DHR / 1	DHR / 1	DHR / 1	DHR / 1	DHR / 4	DHR / 3	DHR / 3
<b>Continuous laboratory findings</b>	Anemia Increased CRP	Anemia Increased CRP	Anemia Increased CRP	Anemia Increased CRP	Anemia	Anemia Increased CRP	Anemia
<b>IgG (mg/dL)</b>	1940 (463-1006)	1440 (745-1804)	1502 (764-2134)	1830 (745-1804)	3050 (876-2197)	1810 (842-1943)	1930 (640-2010)
<b>Infective agent</b>	S.marsescens S.hominis	No detectable	Aspergillus spp	Aspergillus spp	S.aureus	Aspergillus spp	No detectable
<b>Mutation</b>	Missense	Nonsense	Missense	Missense	Deletion	Deletion	Deletion
<b>Nucleotide change</b>	c.301C>A	c.676C>T	c.897G>T	c.279C>G + intron4+1G>C	c.75_76delGT	c.75_76delGT	c.75_76delGT
<b>Aminoacid change</b>	p.[His101Asn]	p.[Arg226X]	p.[Lys299Asn]	p.[Asp93Glu]	p.[Tyr26HisfsX26]	p.[Tyr26HisfsX26]	p.[Tyr26HisfsX26]

Abbreviations: CGD, chronic granulomatous disease; DHR, Dihydrorhodamine-1,2,3; X-CGD, X-linked recessive chronic granulomatous disease; AR-CGD, autosomal recessive-linked chronic granulomatous disease; X91, X-linked gp91<sup>phox</sup> deficiency; A67, autosomal recessive-linked p67<sup>phox</sup> deficiency; A47, autosomal recessive-linked p47<sup>phox</sup> deficiency; SI, stimulation index; TST, tuberculin skin test; CRP, C-reactive protein.

\* P6 and P7 are brothers.



**Figure 1. I:** Magnetic resonance imaging T2-weighted sagittal view of the talus, demonstrating high signal intensity and enhancement of the talus in Patient 3. **II:** Subcutaneous abscess (a) and vertebral osteomyelitis (b) on magnetic resonance imaging of Patient 3.

showed AR-CGD with p67<sup>phox</sup>-deficiency. His NADPH oxidase activity was very low (Table 2). He experienced recurrent invasive fungal infections in the lung despite antifungal prophylaxis. HSCT was performed at the age of seven, and he is now 9 years old and still under follow-up. It was discovered that Patients 3 and 4, who were found to have *Aspergillus fumigatus* upon culture, kept poultry at home and were frequently exposed to a poultry house in their daily lives.

Patient 5 presented with liver abscesses at the age of 13. He was found to have a p47<sup>phox</sup> deficiency. He had recurrent, treatment-resistant liver abscesses due to *S. aureus* infection (Figure 2). HSCT was recommended, but his parents did not accept it. Later, the patient died due to severe *S. aureus*-linked pneumonia and pleural empyema.

Patients 6 and 7 are brothers. Patient 6 was the index case in their family, and Patient 7 was diagnosed with CGD upon his first pneumonia attack. Patient 6 had recurrent lung infection, and suffered from IFD in the lung due to *Aspergillus spp.* infection. CGD was diagnosed via DHR assay. Patient 6 suffered from rheumatoid arthritis, which developed after interferon-gamma therapy, based on a report by his family.

The most common laboratory findings were anemia and continuously increased C-reactive protein (CRP) (Table 2). Although CRP decreased in non-infectious periods, it usually



**Figure 2. Multiple liver abscesses on axial computed tomography image of Patient 5.**

did not return to normal levels. The presence of familial Mediterranean fever (FMF) was tested in three patients (P1, P3, and P7) due to unexplained abdominal cramps. Patient 1 was found to have a heterozygous mutation of E148Q, while Patients 3 and 7 had a heterozygous mutation of R202Q.

**Table 3. The results of tuberculosis research in our patients.**

	P1 (X91)	P2 (X91)	P3 (X91)	P4 (A67)	P5 (A47)	P6 (A47)	P7 (A47)
BCG-itis	Yes	No	No	Yes	No	No	No
BCG scar	Yes	No	Yes	Yes	Yes	No	No
TST (mm)	27 x 25	15 x 14	Negative	16 x 18	Negative	Negative	Negative
TB culture and TB PCR	Negative	Negative	Not done	Negative	Not done	Negative	Negative
TB treatment	Yes	Yes	No	Yes	No	Yes	No

Abbreviations: X91, X-linked gp91<sup>phox</sup> deficiency; A67, autosomal recessive-linked p67<sup>phox</sup> deficiency; A47, autosomal recessive-linked p47<sup>phox</sup> deficiency; TST, tuberculosis skin test; TB, tuberculosis.

Most of our patients had tuberculosis treatment before CGD diagnosis (Table 3). Co-trimoxazole prophylaxis was begun for all patients upon CGD diagnosis. The most frequent area of severe infection was the lungs, followed by the lymph nodes. *Aspergillus spp.* and *Staphylococcus spp.* were the most frequently detected microorganisms in our patients (Table 2). Although a fungal agent was found in only three patients (Table 2), the other patients had *probable* or *possible* IFD in their lungs based on imaging. Antifungal prophylaxis was begun after IFD. Granulocyte colony-stimulating factor (G-CSF) and/or recombinant interferon-gamma (IFN- $\gamma$ ) prophylaxis was temporarily used in patients with refractory aspergillosis and/or recurrent neutropenic attacks.<sup>12</sup> Hemopoietic stem cell transplantation (HSCT) was recommended for five patients (P1, P2, P3, P4, and P5); however, only three of them accepted (P2, P3, P4). Our mortality rate was 42%.

## Discussion

This report presents seven CGD patients from six unrelated families who were followed at a single center. Although our case number was small, their features are significant because CGD is a rare disease and it is important to consider CGD in the differential diagnosis of other chronic inflammatory and infectious diseases. We have reported that talar and vertebral osteomyelitis occurred together in a X-CGD patient for the first time. Congenital glaucoma and bilateral retinal atrophy have not been reported in CGD patients.

In western countries, about 70% of CGD cases have been reported to be X-CGD.<sup>3,4</sup> However, in a recent multicenter study conducted in our country, 55% of CGD patients had an autosomal recessive (AR) genotype, 38% had an X-linked genotype, and 7% had a suspected AR genotype.<sup>2</sup> AR-CGD patients were more often reported than X-CGD patients in Iran and Israel, as well as in Turkey.<sup>13,14</sup> AR-CGD was likely more common than X-CGD in countries that have higher rates of consanguineous marriage.<sup>2,13,14</sup> In our series, consanguineous marriage was seen in six out of seven patients. X-CGD patients were reported to have earlier onsets and higher morbidity and mortality rates when compared with autosomal recessive patients.<sup>2,4,15-17</sup> Severe infectious diseases in the first year of life were also reported in X-CGD patients with the same mutations, as in Patient 1.<sup>2,9,18</sup> However, Patient 2 had a later presentation than other X-CGD patients with the same mutation,<sup>2,16</sup> and he also had congenital glaucoma and retinal atrophy, which has not been reported in the literature. Recent studies have reported that residual ROI production, which can be measured by flow cytometry, is helpful in diagnosis and management.<sup>2,10</sup> In a case series of 27 patients in the United States of America, asymptomatic patients that have X-CGD were also reported.<sup>15</sup> Four of our patients (P1-P4) that had oxidase-null activity with an SI of 1 were found to have earlier disease onsets, earlier diagnosis ages, and a higher mortality rate than the other patients. Flow cytometry analysis is easy to use and faster than genetic analysis, so early diagnosis may depend on the availability of laboratory facilities.

In general, the age of diagnosis was reported to be before the age of five in the X-CGD group, while it was reported to

be around the age of eight in the AR-CGD group.<sup>2,3,4</sup> In our series, the age of diagnosis for both CGD groups was higher than that seen in the literature. Initially, we tested our five patients who had non-ameliorating pneumonia and/or BCG complications for tuberculosis because tuberculosis is still common in our country. Although *M. tuberculosis* could not be found in these patients, four of them received tuberculosis treatment. Therefore, CGD diagnosis may be delayed. Although our AR-CGD patients (P5-P7) who have the *NCF1* mutation had residual oxidase capacity, we detected chronic lung disease based on their thorax CT scans. Pulmonary complications may develop as survival time increases in CGD patients. AR-CGD patients with a p47phox defect have a hot-spot mutation in exon 2 of the *NCF1* gene, and their disease manifested at a later age compared to other AR-CGD patients.<sup>2,9,19</sup> In contrast with the literature, one of our patients with a hot-spot mutation in the *NCF1* gene presented with multiple liver abscesses during adolescence. Phenotypic and genetic heterogeneity have been reported in *NCF1* mutations.<sup>20,21</sup>

The most frequent clinical presentation was pneumonia, as in the other series published in the literature.<sup>2-4,13,21</sup> Lymphadenitis and deep organ abscesses were also common clinical presentations, while osteomyelitis was a rare clinical presentation in patients with CGD.<sup>2-4</sup> *Aspergillus spp.* and *Serratia marsescens* are the most common pathogens responsible for osteomyelitis in CGD patients.<sup>3,4</sup> It has been reported that the most frequently affected bones are the ribs, vertebra, femur, talus, and tibia.<sup>4</sup> However, Patient 3 (X-CGD), who presented with osteomyelitis, had talar and vertebral osteomyelitis due to *Aspergillus spp.* infection; these have not previously been reported together in a CGD patient.

Although all our patients had received the BCG vaccine during their first year of life, Patient 1 (X-CGD) and Patient 4 (p67phox defect) suffered from BCG lymphadenitis. These two patients had clinical presentations at the age of one month. Seventy-one patients with CGD who were suspected of having mycobacterial infection were examined in a very recent retrospective study published by Conti *et al.*<sup>8</sup> In most of the patients in this study, BCG complications were reported as the initial findings. Tuberculosis infection was found in 44% of these CGD patients. Tuberculosis infection could not be found in any of our patients. The oxidase activity levels of the patients who developed BCG-itis were lower than those of other patients. In a large multicenter case series study conducted in our country, BCG-itis was reported to have developed in 22.4% of all CGD patients.<sup>2</sup> No adequate information was found regarding the oxidase activity of CGD patients who suffered from BCG-itis in the literature. The BCG vaccine is not recommended for patients with CGD.<sup>20</sup> However, there are no studies in the literature regarding why BCG-itis does not develop in all CGD patients who received the BCG vaccine or the association between BCG complication severity and CGD. Thus, CGD patients who have experienced BCG vaccine complications should be followed up. Prolonged lymphadenopathy and late neonatal sepsis have been reported in AR-CGD patients with the same *NCF2* mutation as Patient 4, but not reported with BCG-itis, as in our patient with a *NCF2* mutation.<sup>23</sup>

The most frequent invasive pathogen was *Aspergillus spp.*, in accordance with the literature.<sup>2,7,19</sup> Fungal pathogens were found in three of seven of our patients, and the remaining four patients had *potential* IFD in the lungs based on imaging methods.<sup>9</sup> Galactomannan was not assessed, because it is not sensitive in CGD-linked fungal infections.<sup>22</sup> The fungal infections involved the lungs in all patients. Our two patients who had severe IFD due to *Aspergillus spp.* had frequent poultry-house exposure in their daily lives. The second most commonly reported invasive infectious agents are catalase-positive bacteria, such as *Staphylococcus* and *Serratia* species,<sup>6,7</sup> as seen in our patients. *Nocardia* and *Burkholderia* species were reported at lower rates in the literature,<sup>7</sup> but they were not seen in our patients.

One remarkable finding in our patients was the continuously raised CRP. This finding is significant in terms of differential diagnosis. FMF and tuberculosis infection are common in our country. Abscess, lymphadenopathy, fever attacks, and increased CRP may also indicate FMF. Similarly, pneumonia that is unresponsive to conventional treatment, fever, lymphadenopathy, and/or an increased CRP can also indicate tuberculosis. Thus, FMF and tuberculosis should be considered in the differential diagnosis of CGD. Another continuous laboratory finding in all our patients was anemia. This may be related to repeated infections. Anemia due to chronic infection was mentioned in only two studies with large case series, at a rate of 63–65%.<sup>2,14</sup> In our case series, the rate of anemia may be high due to the small number of cases. Anemia was seen to occur earlier and was more severe in the two patients (P1, P4) who had very early ages of disease onset. They had also suffered from BCG-itis and hypergammaglobulinemia. There was no anemia in the five other patients before disease onset. It is possible that a continuous inflammatory response caused chronic anemia and hypergammaglobulinemia in these patients.<sup>2,20</sup>

Non-infectious inflammatory or autoimmune complications are reported more commonly in CGD patients compared with the general population.<sup>2,4</sup> The frequencies of these complications differ from those seen in large case series. These complications have been reported at rates of 6–69% in western countries.<sup>2-4,13,21,25</sup> These differences may depend on the type of complication and the various CGD subtypes included in a given study. Only one of our patients (P6) had an autoimmune complication, which was rheumatoid arthritis. The frequency of inflammatory or autoimmune complications may be low in our study due to the small number of cases. It has been suggested that these complications increase as age increases,<sup>21</sup> and that these complications may have emerged because survival has increased due to antimicrobial therapy and prophylaxis.<sup>6</sup>

## Conclusions

In CGD patients, the organs most commonly affected by specific microorganisms are the lungs and lymph nodes. Primary immune deficiency should be considered in patients with invasive infectious diseases or deep tissue abscesses, even without growth retardation or a history of frequent infection at the age of diagnosis, especially in countries where consanguineous marriage is frequent. Innate immune system deficiencies, such as CGD, should be considered as a differential

diagnosis in patients with BCG-itis that is not self-limiting, treatment-unresponsive infectious diseases associated with the phagocytic cells, unexplained osteomyelitis, and chronic inflammatory disorders. The early diagnosis and follow up of CGD patients are important for their survival. HSCT is a method of treatment that can be used before pulmonary complications cause damage to the lungs. Repeated alveolar infection causes fibrotic tissue in the lung, and alveolar macrophages can effectively control the fibrotic area. This fibrotic area may be a good place for inoculation with *Aspergillus spp.* and other pathogens. Thus, the prevention of lung infections via procedures such as prophylaxis is an efficient therapy, and preventing mold-containing environmental conditions and periodic examinations by a physician may prolong survival in CGD.

## Conflict of interest

None declared.

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