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CASE REPORT

Chronic granulomatous disease; Three different clinical presentation

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Abstract
Chronic granulomatous disease is an inherited disorder of nicotinamide-adenine dinucleotide phosphate oxidase and results in a defect in intracellular killing of ingested microorganisms characterized by recurrent life threatening bacterial and fungal infections. The disease is classified by mutations in specific subunits of the NADPH oxidase enzyme. There are one X-linked and four autosomal recessive forms of disease. The organisms cultured from lesion of patients with chronic granulomatous disease are generally catalase-producing including Staphylococci, Escherichia coli, Serratia; or fungi such as Aspergillus species. Recurrent or serious infections usually lead to diagnosis of disease in early childhood. We report three male patients who were diagnosed 5, 10, 13 years old, respectively and showed different clinical presentation.

Keywords: Chronic Granulomatous Disease; İmmunodeficiency; Hepatic Abscess; Sepsis.

INTRODUCTION

Chronic granulomatous disease (CGD) is a hereditary immunodeficiency characterized by the absence of NADPH oxidase subunits or dysfunctions. Microorganisms are phagocytosed normally; however, they continue to live in cells and they are protected against antibiotics with extracellular effect and antibodies. The frequency of the disease is between 1/200000 and 1/250000 (1).

Since intracellular microorganisms are not killed in patients with CGD, they develop predisposition to infections such as catalase positive Staphylococcus aureus, Klebsiella pneumoniae, Salmonella spp, Burkholderia cepacia, Aspergillus, Candida, Nocardia (2). This case report presents three different male patients with different clinical presentations who were diagnosed at the age of 5, 10 and 15, respectively.

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CASE REPORT

Case 1.
5-year-old male patient was admitted to our clinic with complaints of fever that had been going on for 6 weeks, cough and dyspnea. There were no frequent or serious infections in his anamnesis. His parents had a consanguineous marriage.

His physical examination showed tonsillar tissue and BCG scar. His respiratory rate was 60/min, body temperature was 37.3 °C, pulse was 76/min. He had tachypneic and dyspneic respiration. His respiratory sounds were normal and tuber sufl was heard on the left side of his back. Other system examinations were normal.

Laboratory findings were as follows: hemoglobin, 10.9 g/dL; haematocrit, 31.0%; RBC, 4.61 million/uL; leukocyte, 19580/mm3; lymphocyte, 5240 /uL; platelet, 923000 /mm3; C reactive protein, 303 mg/L; erythrocyte sedimentation rate, 91 mm/h; AST, 30.9 U/L; ALT, 19.1 U/L; Na, 128 mEq/L; K, 4.43 mEq/L; Ca, 9.4 mg/dl; BUN, 7.4 mg/dL; creatinin, 0.23 mg/dL. The patient's PPD was measured as 16 mm, acid fast bacilli was not found in his sputum and his tuberculosis PCR was negative. Serum immunoglobulin levels were as follows: IgG, 18.3 (7.45-18) g/L; IgA, 5.96 (0.57-2.82) g/L; IgM, 2.3 (0.78-2.61) g/L; IgE, 48 IU/mL; sweat test, 60 mmol/L (60-80). Isohemoagglutinins were 1/256 positive, direct combs test was positive. Postero-anterior (P-A) lung graphy

showed bilateral pneumonic infiltration, which was more obvious on the right upper lobe (Figure 1). Thorax computed tomography showed bilateral patchy consolidation (Figure 2). Aspergillus hyphae were found in lung biopsy and his nitroblue tetrazolium test (NBT) and phagoburst test were in accordance with chronic granulomatous disease.

Aspergillus pneumonia of the patient was taken under control with three-month-long voriconazole theraphy. Bone marrow transplantation was performed on the patient who was being followed up with cotrimoxazole, voriconazole and interferon-gamma prophylaxis.

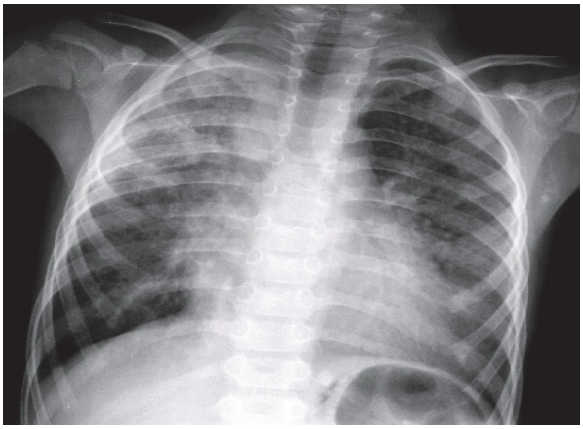

Figure 1. Bilateral pneumonic infiltration, which was more obvious on the right upper lobe of the lung.

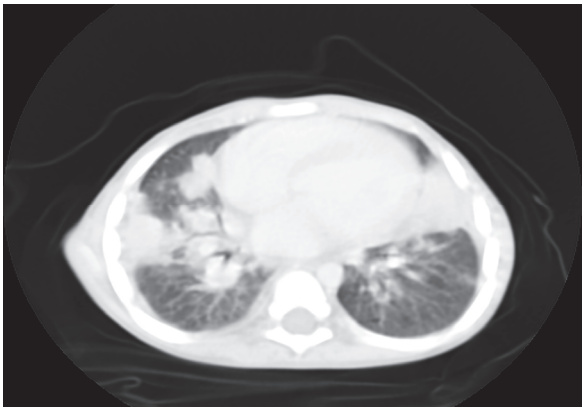

Figure 2. There were paracardiac consolidations accompanied by air bronchograms at right basal lateral and left lobe lingula inferior adjacent to right lung lower lobe bronchi.

Case 2.

5-year-old male patient who was being followed in our clinic for about four years with a diagnosis of chronic granulomatous disease and who was hospitalized with complaints of back pain and swelling on the back. His anamnesis showed that he had undergone spontaneous bacterial peritonitis at the age of three, then he had abscess twice on his neck, he had osteomyelitis on his right ankle at the age of six and aspergillus pneumonia at the same age.

His physical examination showed that blood pressure was 100/60 mmHg, respiratory rate was 20/min, pulse was 80/min. He had tonsillar tissue and BCG scar. He had a 5x5 cm painful swelling on his right thoracolumbar area. His system examinations were normal.

Laboratory findings were as: hemoglobin, 9.7 g/dL; haematocrit, 30.5%; RBC, 4.47 million/uL; leucocyte, 13300/mm3; lymphocyte, 3150 /uL; platelet, 537000 /mm3; C reactive protein, 83 mg/L; erythrocyte sedimentation rate, 70 mm/h; AST, 14 U/L; ALT, 8 U/L; Na, 132 mEq/L; K, 4.6 mEq/L; Ca, 9.8 mg/dl; IgG, 1910 (635-1880) mg/dl; IgA, 433 mg/dl (64-297); IgM, 115 mg/dl (80-328); direct coombs test was negative, Isohemoagglutinins were: Anti-B: 1/16, ANA negative, Anti-dsDNA negative. Salmonella and Brusella scannings were negative. An obvious increase was seen in eosinophilic series in bone marrow aspiration and aspergillus proliferated in bone marrow aspiration material. Thoracic magnetic resonance (MR) imaging showed osteomyelitis at the level of T6-10 vertebra and contrast increase in line with abscess (Figure 3). The patient, whose infection was not taken under control despite a three-month-long intensive theraphy, received haploidentical stem cell transplantation. However, the patient died due to pneumonia during stem cell transplantation.

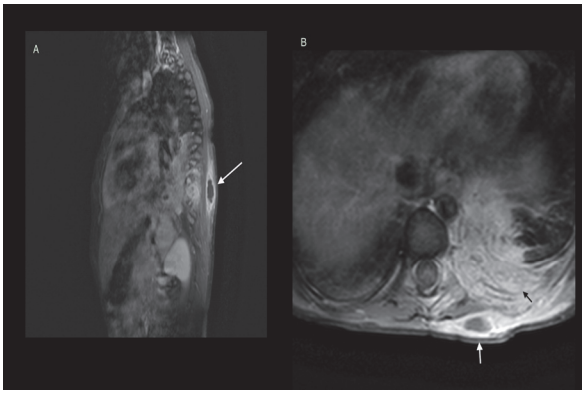

Figure 3. Heterogeneity and contrast increase were seen at A T1 contrasted sagittal B T1 contrasted axial sections, left paravertebral, posterior diaphragm and pleural surface (black arrow). In addition, there were images with a hypointense centre, peripherally contrasted, in accordance with abscess in subcutaneous adipose tissue.

Case 3.

15-year-old male patient was consulted with our clinic due to liver abscess that did not respond to postoperative antibiotics. His anamnesis showed that he had abscesses on his neck and wounds on his nose two years ago and his abscesses were drained. There were no frequent infections in his anamnesis and his parents had a consanguineous marriage.

In his physical examination, his general condition was good and he did not have growth retardation. He had tonsillar tissue and BCG scar. His respiratory rate was 26/min, body temperature was 36.3 °C, pulse was 74/min. Other system examinations were normal.

His laboratory findings were: Hemoglobin, 10.7 g/dL; haematocrit, 33.6%; RBC, 4.39 million/uL; leukocyte, 14360/mm3; lymphocyte, 730/uL; platelet, 644000/mm3; C-reactive protein, 236 mg/L; erythrocyte sedimentation rate, 74 mm/h. Echinococcus screening, anti-HIV, ANA and AntiDs-DNA were negative. PPD was measured as "0" mm. IgG was 30.5 (8.76-21.97) g/L, IgA was 4.25 (1.0-4.07) g/L, IgM was 1.59 (0.75-4.48) g/L, IgE was 2300 IU/mL, Isohemoagglutinins were: 1/128 positive, direct combs test was positive. His abdominal ultrasonography showed a 94x74 mm marked heterogeneous mass lesion with semi solid areas and milimetric cystic areas surrounded by hypoechogenic areas in the right liver lobe. Abdominal computed tomography showed views on both parenchyma of the liver, which were compatible with abscess (Figure 4). S. Aureus was proliferated in the exudate culture and sultamicillin, clindamycin and teicoplanin therapy were started. Exudate fluid continued to come from drainage and his therapy was changed into vancomycin, meropenem and amikacin. No oxidative burst was found in the phagoburst test of the patient whose treatment was completed to 6 weeks. The patient was followed with a treatment of cotrimoxazole, voriconazole and interferon-gamma prophylaxis with a diagnosis of chronic granulomatous disease.

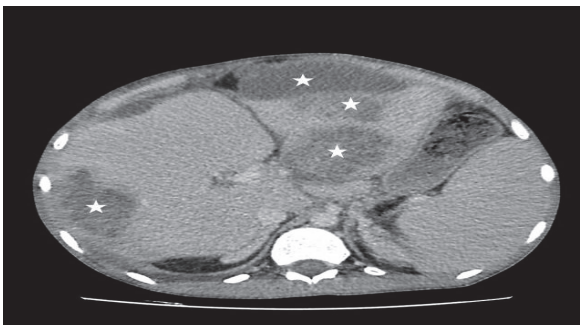

Figure 4. There were images with heterogeneous center, peripherally contrasted, in accordance with hypodense abscess in both lobe parenchyma of the liver, and in the marked subcapsular area of the both lobe anteriors. Abscees was shown with a white star.

DISCUSSION

Sixty percent of CGD cases occur as a result of mutation in gp91phox gene located in Xp21.1(CYBB). While 30% of the cases are autosomal recessively inherited and characterized by the absence of cytosolic p47phox protein, the rest are associated with defects in p67phox protein, which is another cytosolic factor and membrane associated p22phox protein (1). While the two third of CGD cases in Western society are found to be X-dependent CGD, this rate is around 40% in our society. One of the primary reasons for this is more frequent autosomal recessive CGD cases due to consanguineous marriage (3). The first two patients in our study were found to have mutation in X-dependent gp91phox gene. In the third case who was admitted with liver abscess, no mutation was found despite examinations. However, p67phox mutation was considered since he was autosomal recessive and he had residual oxidase activity.

Although chronic granulomatous disease can be seen in any age from early childhood to adulthood, the diagnosis is generally made under the age of five (4). Lungs, skin, lymph nodes and liver are the most involved infection areas (5). The agents primarily responsible for pneumonia in CGD are Aspergillus species (especially A. nidulans), Burkholderia spp, other gram negative bacteria, Staphylococcus aureus and Nocardia spp. In addition, tuberculosis or non-tuberculosis Mycobacteria spp. can be seen in undeveloped societies. Focal invasive fungal pneumonia have insidious onsets, however, they have high mortality; they extend to pleura and thoracic wall bones in 1/3 of the patients. Clinical and radiological findings are non-specific. Mixed infections can be found with rare organisms and microbiological diagnosis can be difficult. Thus, increasing the possibility of diagnosis can require bronchoalveolar lavage or CT guided transthoracic needle inspiration (1). Our first two cases developed aspergillus induced pneumonia. Our first case was admitted for advanced respiratory distress. Since tuber sufl was found in physical examination and bilateral consolidation was found in PA lung graphy, he was hospitalized with a pre diagnosis of bacterial pneumonia. Empirical ampiciline- sulbactam and clarithromycin therapy was started. Since the patient did not respond to three-week-long therapy and no recovery was seen in respiratory distress, empirical triple tuberculosis therapy was added. However, no recovery was seen in the following days. Thus, lung biopsy was made. Primary immunodeficiency was considered when aspergillus proliferated in lung biopsy material culture. No oxidative burst was found in phagoburst test and voriconazole therapy was started with a diagnosis of CGD. The patient's complaints regressed with a therapy of three months. Lung graphy recovered completely. The patient was referred for bone marrow transplantation when a suitable donor was found. In our second patient, aspergillus pneumonia had developed four years before thoracolumbar osteomyelitis development.

In chronic granulomatous disease, osteomyelitis is generally seen in the small bones in hands and feet. Serratia marcescens, Aspergillus spp. and Staphylococcus aureus are frequently the agents responsible. Although local infections are rule in chronic granulomatous disease, sepsis is seen in some patients with Salmonella spp. and other gram negative bacteria (for exp; Burkholderia cepacia and Serratia marcescens) and Staphylococcus aureus (1). In our second patient, osteomyelitis was seen not in small bones, but in thoracolumbar area at the level of T6-T10. In addition, Aspergillus-induced sepsis was found for the first time in literature instead of gram negative bacteria because Aspergillus proliferated in the aspirate of the bone marrow taken. The patient, who did not respond to voriconazole theraphy, received bone marrow transplantation. However, the patient died due to pneumonia during treatment regime.

Some cases are diagnosed with unusual infections that are recurrent in late childhood or early adulthood (6). Liver abscesses are clinically diagnosed with difficulty since they do not show intense inflammatory reaction.

The best treatment method is CT. Frequently, Staphylococcus aureus is the responsible organism and it can be detected with needle biopsy (1). Patients with residual NADPH oxidase activity in neutrophiles give clinical findings in later periods and less intense infections when compared with those who do not have activity (7). Our third case did not have any serious infection and he was presented with Staphylococcus aureus-induced liver abscess in the adolescence. This case had residual NADPH oxidase activity, which was in line with the literature.

In chronic granulomatous disease, prophylaxis consists of a triad of cotrimoxazole, itraconazole and immunostimulant IFN-γ therapy (8). In case of acute infection, oral ciprofloxacin and intravenous meropenem therapy should be started until culture results come out. In addition, cotrimoxazole dose should be doubled and in case of the presence of pneumonia, voriconazole should be added in the therapy as antifungal (9). Today, the only known definitive treatment option in CGD is allogenic stem cell transplantation (10). Gene treatment in patients that cannot find suitable donor is still at experimental stage (11).

As a conclusion, immunodeficiency should be considered as preliminary diagnosis in patients who do not recover despite long term broad spectrum antibiotic therapy and whose infections have atypical presentation.

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