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Diagnosis of Chronic Granulomatous Disease in an Adult Patient with Probable Miliary MDR Tuberculosis

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Abstract

Chronic granulomatous disease is a rare inherited disease characterized by severe recurrent bacterial and fungal infections beginning in childhood.

In this report, we describe a case of a 27-year old man with persisting fever, leykocytosis and micronodular image in chest x-ray. The patient showed no response to multiple therapeutic approaches until the addition of second line antituberculous drugs. He eventually showed clinical improvement with that treatment even though all cultures (sputum, BAL, gastric fluid) for Mycobacteria were negative. Because of his unsatisfactory response to treatment and his long history of infections, investigation for Primary Immunodeficiency was performed and autosomal chronic granulomatous disease (CGD) was diagnosed.

Clinicians should consider chronic granulomatous disease as possible background in cases of severe infections in the setting of a medical history of recurrent infections. Furthermore, tuberculosis should be included in the differential diagnosis of infection for patients with chronic granulomatous disease.

Keywords

chronic granulomatous disease; immunodeficiency; tuberculosis; neutrophil disorder

Introduction

The neutrophilic granulocyte is an important cellular component of the innate immune system. For a pathogen to be neutralized, it has to be recognized, phagocytosed, and destroyed by lytic enzymes contained in the neutrophil's granules and reactive oxygen species formed by the enzyme complex NADPH oxidase [1]. In general, lack of functional neutrophils in an individual may lead to infections with Staphylococcus aureus, gram-negative organisms such as Pseudomonas aeruginosa and Burkholderia cepacia, the gram-positive bacterium Nocardia asteroides, as well as fungal infections such as Aspergillus spp. and Candida spp [2,3].

Chronic granulomatous disease (CGD) is a rare genetic disorder, occurring in about one in 250,000 individuals [2]. In Greece it is estimated at 0.90 (95% CI 0.89-0.91) per 100,000 live births in the last decade [4]. It is the most frequent neutrophil function disorder, and is caused by a defective NADPH oxidase enzyme complex which is inherited either in X-linked or one of three existing autosomal recessive

forms [5]. As a result, phagocytosed microorganisms can not be effectively killed, resulting in formation of granulomata [6]. The mostly affected organs are the lungs, skin, gastrointestinal tract, lymph nodes, and liver [7]. Surprisingly, at most clinical cases, no causative pathogen can be isolated, despite the underlying microbial infections [2]. The disorder is caused by a defect in any of the four subunits of the leukocyte NADPH oxidase, gp91phox and p22phox, located in membranes, as well as two cytosolic oxidase components, p47phox and p67phox. Mutations in the gp91phox gene are caused by the X-linked recessive form of the disease that affects the majority of CGD patients (about 70% and most of them males) [8]. The remaining 30% of disease cases is inherited in an autosomal recessive manner, in which males and females are equally affected. These patients have mutations in the genes encoding the other three subunits and may be associated with milder disease [2,9].

The term miliary tuberculosis (TB) refers to any progressive widespread dissemination of *Mycobacterium tuberculosis* via hematogenous spread. Classic miliary TB is defined as milletlike (mean, 2 mm; range, 1-5 mm) seeding of TB bacilli in the lung, as evidenced on chest radiography. This pattern is seen in 1-3% of all TB cases. It is a potentially lethal disease if not diagnosed and treated early [10,11].

We report the case of a young man who was diagnosed with CGD during his hospitalization for possible miliary multi-drug resistant (MDR)-TB.

Case Presentation

A 27-year old man was transfered to our department after one week in a regional hospital due to persisting fever, fatigue, anorexia, weight loss, tachycardia and abnormal chest x-ray. He had been treated for community acquired pneumonia with ampicillin-sulbactam and azithromycin but showed no clinical or radiological improvement.

The patient was smoker, HCV positive, HIV negative, former iv heroin user and current cannabis smoker. Regarding his medical record, he had been diagnosed with prostatitis and treated with ciprofloxacin for 20 days until one month before admission to the regional hospital. He also had a history of meningitis at the age of nine years, for which he had empirically received antituberculous agents.

On admission his clinical examination revealed white skin lessions from past Staphylococcus infection on the spots of intravenous heroin injections. The patient presented with tachycardia (125 bpm), hypoxemia (PO_2=62mmHg) and fatigue. The white blood cell count (WBC) (27000 x 10^9/l, 87% neutrophils, 12% lymphocytes), erythrocyte sedimentation rate (85mm/h) and levels of C-reactive protein (15mg/l) were elevated. Mantoux test was negative. His chest x-ray on admission showed a micronodular pattern compatible with miliary tuberculosis and was confirmed by a chest Computer Tomography (CT) scan (Figure 1). Heart ultrasonography and the ophthalmic examination were normal. Based on the typical radiological pattern, antituberculous treatment was initiated (rifampicin 600mg, isoniazid 300mg, ethamboutol 1250mg and pyrazinamide 1500mg).

A week after admission fever and leukocytosis persisted. The sputum and gastric fluid sample were Ziehl-Nielsen and AMTD (Amplified Mycobacterium *Tuberculosis* Direct) test negative and cultures of blood, urine and stool specimens for common pathogens were also negative. In addition serological tests for CMV, EBV, HSV1 and 2, VZV, Widal, Wright, *Ricketsia mooseri*, RSV, *Coxiella burnetti, Chlamydophila psittachi, Chlamydiphilla pneumonia, Mycoplasma pneumonia*, Adenoviruses were negative for recent infection. The patient was also submitted to bronchoscopy for bronchoalveolar lavage

(BAL) which was negative for Aspergillus fumigatus complex antigen (galactomannan), Nocardia and Pneumonocystis. Meropenem and vancomycin was added to his treatment for a possible hospital-acquired pneumonia. After one week amphotericin was also added to his regimen.

At that time, investigation of immune parameters, focused on T-lymphocytes was conducted in peripheral blood and BAL samples (Table 1). The percentage and total number of T and B lymphocytes were normal, while NK lymphocytes were at reduced levels (64/μL). An inversed ratio of CD4+/CD8+ lymphocytes was observed but absolute number of each subpopulation was within normal limits. The patient was also submitted to bone marrow biopsy which revieled increased number of eosinophils, sea blue mast cells and plasmocytes 5%.

The adequacy of polymorphonuclear cells (PMNs) NADPH oxidative burst mechanisms was measured by the Dihydrorhodamine (DHR) assay. The DHR reducing activity of the patient's PMA (Phorbol-myristrate-acetate) primed PMNs, was non detectable. On the contrary the patient's mother demonstrated a lower than normal activity with a single curve pattern, which was not compatible with X-linked defect. Indeed, the patient's PMNs showed a normal gp91phox expression whereas the p47phox subunit was not detected by Western Blot analysis (Figure 2). This result was confirmed by DNA sequence analysis (c.75_76delGT in NCF1 gene).

Due to the patient's deterioration, second-line antituberculous agents were empirically added (amikacin 900mg, levofloxacin 750mg, and cycloserin 750mg), while amphotericin, meropenem and vancomycin were discontinued. Five days later fever was resolved and WBC decreased. The patient was discharged after 65 days, afebrile, clinically stable with an improving chest x-ray (Figure 3) and WBC count. He was referred to the National Immunological Department Center for Primary Immunodeficiencies for further management of his CGD. Cultures for *M. tuberculosis* were repeatedly negative. Five months after discharge a significant improvement in his chest CT scan was observed. The patient was treated for 18 months (6 months of amikacin) and remained clinically and radiologically stable.

Discussion

Chronic granulomatous disease (CGD) is a primary immunodeficiency that affects phagocytes and leads to recurrent or persistent intracellular bacterial and fungal infections and to granuloma formation [12]. The diagnosis of CGD is usually established during the first years of life with a mean age for the autosomal recessive form of 8.8 years for Europe [2]. There are indeed a few reports about cases with first diagnosis of CGD in adulthood [13,14,15]. The delayed diagnosis in our patient at the age of 27 could be attributed to his autosomal disorder due to which he had a milder course, even though he had been at high risk for infections because of his drug abuse.

The diagnosis of infection by *M. tuberculosis* is challenging, especially in patients with underlying immunodeficiency. Our patient had a history with TB meningitis in childhood which could support the aspect of Mycobacterium infection. His chests X-ray as well as the computer tomography scan were highly diagnostic for miliary TB. Moreover, a miliary pattern has not been described in patients with CGD diagnosed with other severe bacterial or fungal pulmonary infection [16,17]. In addition, it is quite interesting that even though a positive culture for *M. tuberculosis* was never obtained, our patient had undoubtable clinical and imaging improvement with second-line anti-TB treatment. Thus, even though

the diagnosis of TB was not clearly established, continuation of treatment for MDR-TB for 18 months was decided, based on the patient's medical history and clinical outcome. The reported incidence of tuberculosis in 2013 Greece was 5 cases per 100 000 people (WHO report). MDR cases represented the 1.5% of new cases and 9.1% of retreatment cases [18].

In the largest cohort of European CGD patients to date [2], susceptibility to *M. tuberculosis* or atypical mycobacteria was not reported. However, the investigators [2] referred to a number of recent reports, some of which had at that time not been published and claimed there is indeed an increased susceptibility for mycobacterial infection in CGD [19,20]. In addition, in a brief report Lau et al observed that *M. tuberculosis* caused persistent infection and chronic exaggerated inflammation in the lung but not in other organs, such as the spleen, in six patients with CGD [21]. The investigators also suggested that patients with CGD are susceptible to TB and BCG complications and that oxidative burst is probably important in host defense against mycobacterial infections. Moreover, according to a recent report, CGD patients are sensitive to infection with the vaccinal BCG strain which based on the literature is by far the most common mycobacterial disease in these patients [22]. The latest review on pulmonary manifestations, a retrospective study from France in adults with CGD, refers to cases typical and atypical mycobacteria as the identified pathogen [17]. Thus, the older view that the phagocyte NADPH oxidase does not interfere with the defense against mycobacteria, the *in vivo* participation of neutrophils in the mycobacterial host defense and the susceptibility of CGD patients to mycobacterial infections are still questioned [23].

The present case is noteworthy firstly because the age of CGD diagnosis was above the expected and secondly due to the impressive improvement with second-line antituberculous agents, which supports the diagnosis of TB infection despite lack of laboratory confirmation. The diagnosis of CGD should be considered in the investigation of an underlying immunodeficiency even for adult patients. In addition, TB should be included in the differential diagnosis in patients with CGD.

Figures

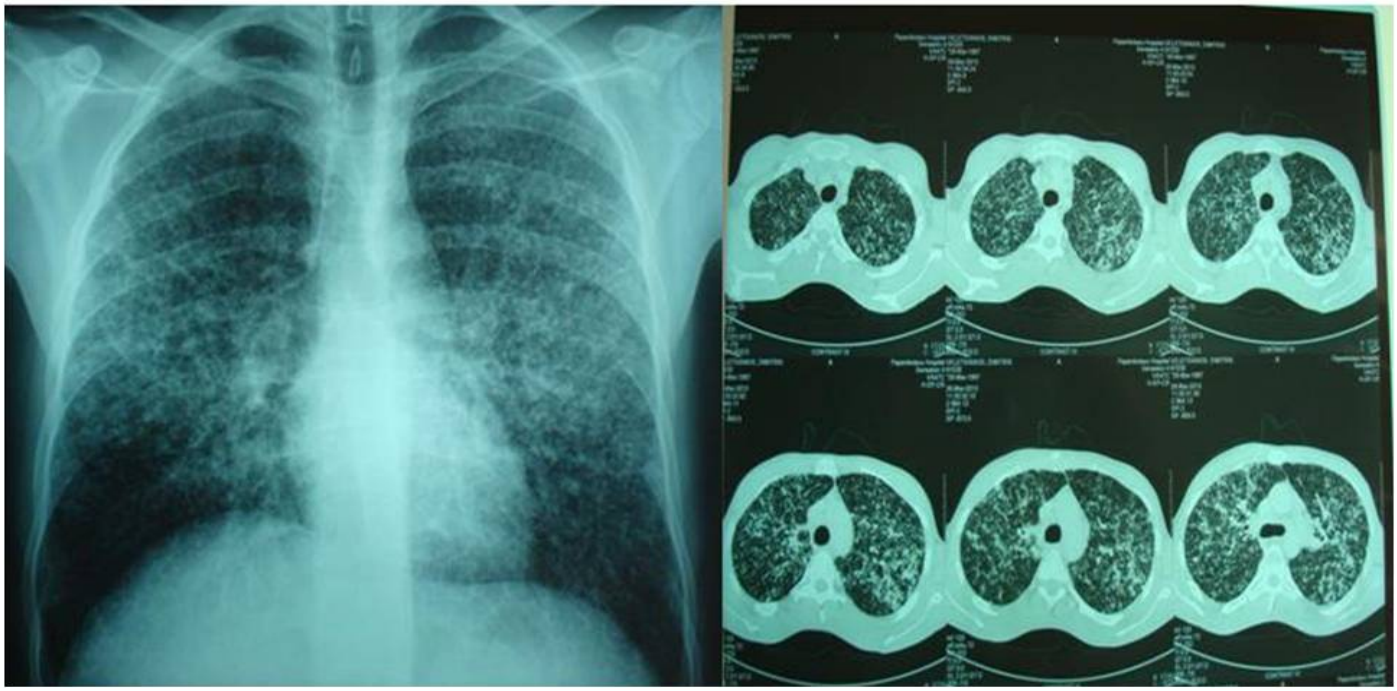

Figure 1: Patient's chest x-ray and CT scan on admission.

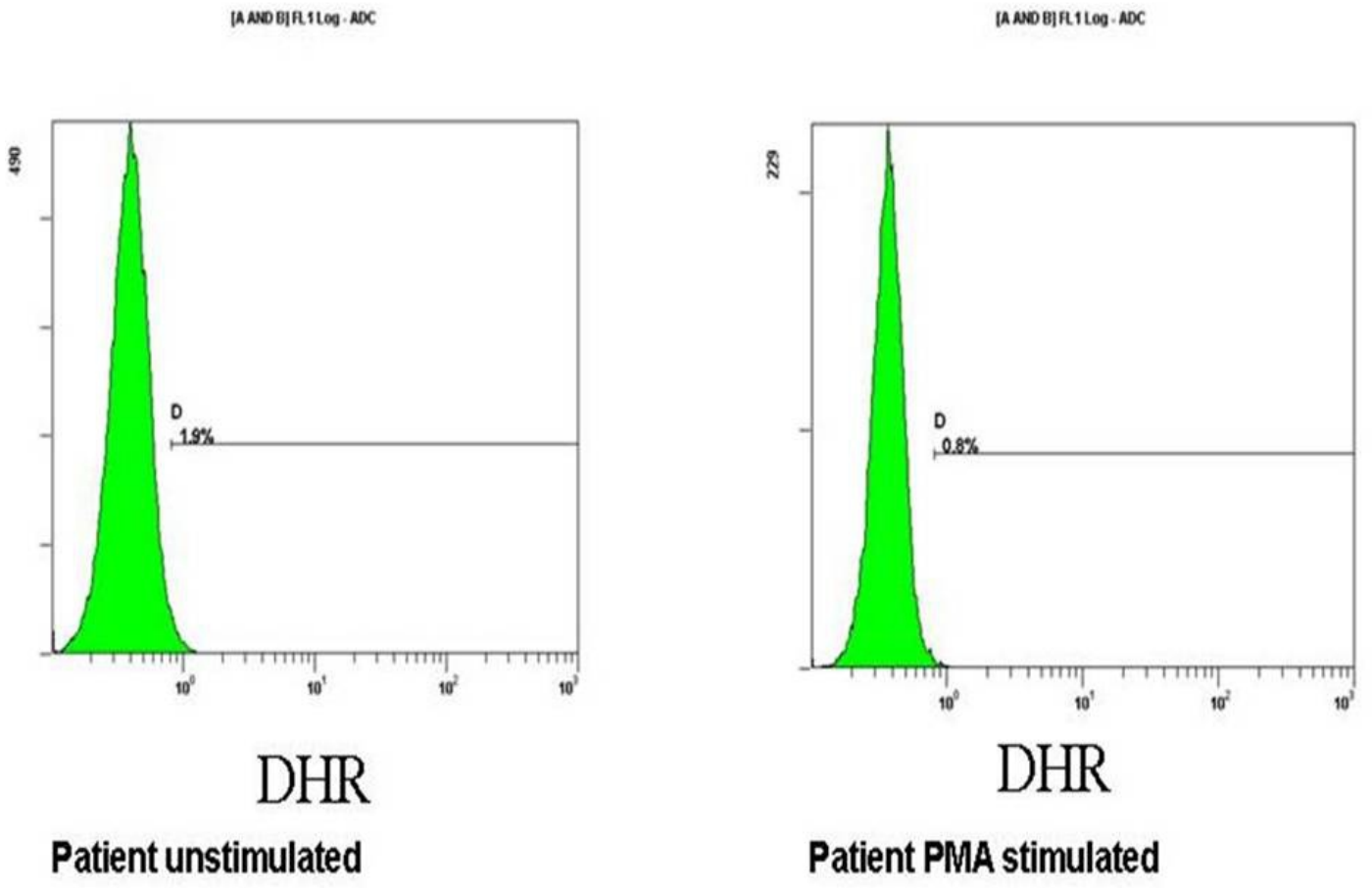

Figure 2: No increase in fluorescence intensity was observed post PMA stimulation, a finding indicating deficiency of the oxidative burst mechanisms

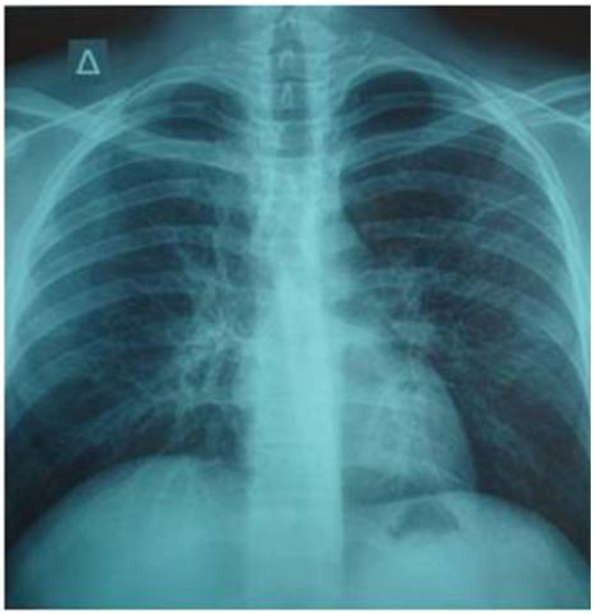

Figure 3: Patient's chest x-ray on discharge.

Table

Cells	Blood	Bal
Cd3+	75.40%	97%
Cd19+	18.83%	1%
CD3-CD16+56+	3.09%	2%
CD3+CD4+	24.43%	40%
CD3+CD8+	46.71%	60%
CD4+/CD8+	0.52	0.67
CD3+CD16+56+	17,00%	7%

Table 1: T-lymphocytes population in patient peripheral blood and BAL samples

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