

Chronic granulomatous disease presenting with invasive aspergillosis and hypogammaglobulinemia

İnvaziv aspergilloz infeksiyonu ve hipogamaglobulinemi ile başvuran kronik granülomatözlü bir olgu

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ABSTRACT

Chronic granulomatous disease (CGD) is a rare disorder with the unifying characteristics of severe predisposition to bacterial and fungal infections, impaired ability of phagocytic leukocytes to produce microbicidal oxygen metabolites and failure of these cells to kill certain microorganisms. *Aspergillus* spp. are the most common fungal pathogens in these patients. Cranial aspergillosis is a rare presentation with a high mortality rate. Immunoglobulin levels of CGD patients are usually normal or elevated. We herein describe a five-year-old boy with CGD presenting with disseminated aspergillosis and hypogammaglobulinemia (low IgA and IgG).

(*Asthma Allergy Immunol* 2009;7:189-193)

Key words: Granulomatous disease, chronic, child, hypogammaglobulinemia, invasive pulmonary aspergillosis, aspergillosis

Received: 30/07/2009 • Accepted: 24/09/2009

ÖZET

Kronik granülomatöz hastalık lökositlerin bakteri ve mantarları öldürmesinde önemli rolü olan mikrobisit oksijen metabolitlerini üretme yeteneklerinin bozulması sonucu ortaya çıkan, bakteriyel ve mantar infeksiyonlarına yatkınlık oluşturan klinik bir sendromdur. *Aspergillus* spp. bu hastalarda en sık karşılaşılan mantar infeksiyonu etkenidir. Kranial aspergillozis ise nadiren görülür ve mortalitesi yüksektir. Kronik granülomatözlü hastalarda immunoglobulin düzeyleri ise genellikle normal veya yüksektir. Burada, dissemine aspergillozu olup, hipogamaglobulinemi ile seyreden beş yaşında erkek olgu sunulmaktadır.

(*Asthma Allergy Immunol* 2009;7:189-193)

Anahtar kelimeler: Granülomatöz hastalık, kronik, çocuk, hipogamaglobulinemi, invaziv pulmoner aspergillozis, aspergillozis

Geliş Tarihi: 30/07/2009 • Kabul Ediliş Tarihi: 24/09/2009

INTRODUCTION

Chronic granulomatous disease (CGD) is a rare disorder of phagocytes that predisposes patients to bacterial and fungal infections. In these patients, fungal infections are most commonly caused by *Aspergillus* species^[1]. Invasive aspergillosis is an important life-threatening condition, and when it involves the central nervous system (CNS), may cause a high mortality rate of 88-99%^[2]. In patients with CGD, immunoglobulin levels are usually within normal ranges or elevated, which might be due to continuous immune stimulus caused by active or uncontrolled infection^[3]. The association of CGD with immunoglobulin deficiency is very rare^[4,5]. Herein, we describe a case of CGD presenting with invasive aspergillosis and hypogammaglobulinemia.

CASE REPORT

A five-years-old boy was referred to our hospital with loss of vision, fever and somnolence. He was the first child of consanguineous parents. His family history was unremarkable, except for a maternal uncle who died at 20 days of age from an unknown cause. Apart from cervical and axillary lymphadenitis in his 2nd and 3rd years of life, his past medical history was unremarkable. He had a history of hospital admission two months earlier with complaints of fever, weakness and cough, which was unresponsive to antibacterial therapy. His chest X-ray revealed an upper alveolar opacity and his thorax computerized tomography (CT) scan revealed perivascular and peritracheal lymphadenopathies, diffuse small nodular interstitial pattern and consolidation at the right apex and inferior lingula (Figure 1). Biopsies taken from mediastinal lymph nodes during mediastinotomy revealed trabecular granulomatous inflammation with epithelioid histiocytes and Langerhans' giant cells. He was diagnosed as tuberculosis (TB), and anti-TB treatment (isoniazid, rifampicin, and pyrazinamide) was initiated. During follow-up, due to progressive vomiting, headache and somnolence, a lumbar

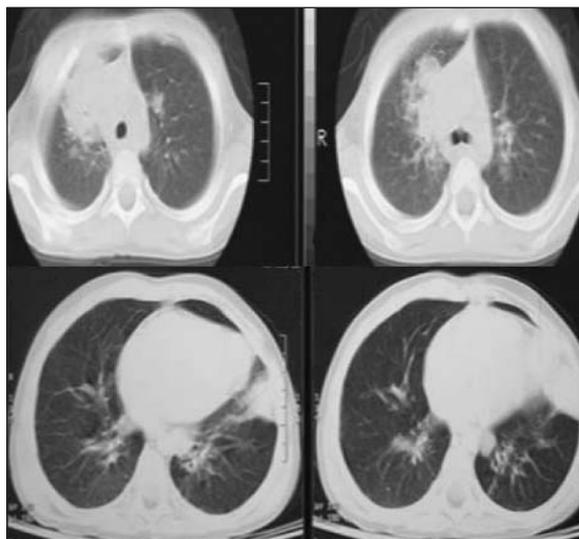


Figure 1. Thorax computerized tomography scan of the patient.

puncture was performed, and cerebrospinal fluid (CSF) examination revealed no leukocytes, glucose level of 35 mg/dL, protein level of 19 mg/dL, negative acid fast smear, and culture for *Mycobacterium tuberculosis*. Although CSF findings were not consistent with TB, streptomycin (SM) and prednisolone were added to his therapy. His cranial magnetic resonance imaging (MRI) showed lesions appearing bilaterally on the frontoparietal and temporal epidural regions consistent with empyema or soft tissue (Figure 2A). Vancomycin and metronidazole were added to his treatment with no improvement. He developed loss of vision. The patient was then referred to our hospital for further evaluation.

On admission, he had nerve palsy of bilateral abducent and left 3rd, 4th and 7th cranial nerves and optic atrophy. Laboratory findings were as follows: erythrocyte sedimentation rate 113 mm/hour, C-reactive protein 234 mg/dL, leukocyte count 15.400/mm³ (74% neutrophils, 20% lymphocytes), hemoglobin 11.3 g/dL, and platelet count 865.000/mm³. Tuberculin skin test was 0 mm. *Salmonella*, *brucella*, and viral serologies including human immunodeficiency virus were negative. His repe-

ated cranial MRI revealed millimetric round destructing areas at sphenoidal, ethmoidal, occipital, clivus, tuberculum sella and dorsum sella regions and opacities at the nasopharynx and cavernous sinuses, suggestive of TB meningitis (Figure 2b). In the differential diagnosis, histiocytosis X was considered and bone marrow examination was performed, which revealed normocellular findings without any infiltration. Bronchoscopic examination revealed normal anatomical structures. Bronchoalveolar lavage cytology was normal, and cultures were negative for bacteria, mycobacteria and fungi. A nasopharyngeal biopsy revealed chronic granulomatous inflammation but failed to show a microorganism. On the 20th day of admission, the patient developed left focal convulsion and hemiparesis. Unresponsiveness to broad spectrum antibiotics and anti-TB treatment led us to consider fungal infections in the differential diagnosis, and liposomal amphotericin B was added to his treatment.

Cranial MRI showed progressive lesions, and intracranial biopsy was performed revealing fungal hyphae on pathologic examination. Anti-TB therapy was discontinued and voriconazole was added to the amphotericin B treatment. On the 48th day of admission, he developed purulent discharge from the mediastinotomy scar and from his ear, in which *Aspergillus* spp. was isolated. In his immunologic work-up, serum IgA and IgG levels were found to be below the normal range (Table 1). His lymphocyte subset analysis and pneumococcal antibody titer (9.1 mg/L) were also normal. The phagocytic cell functions of the patient and his mother were tested with dihydro rhodamine flow cytometry assay and results were consistent with autosomal recessive CGD (Stimulation index (SI) for patient: 1.3, for mother: 100, for control: 101) (Figure 3). Despite voriconazole, amphotericin B and intravenous immunoglobulin treatment, the patient expired on the 63rd day of his admission.

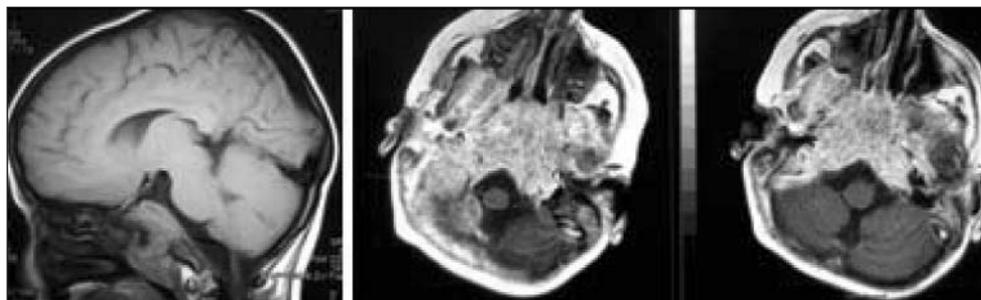


Figure 2A. Initial cranial magnetic resonance imaging of the patient.



Figure 2B. Follow-up cranial magnetic resonance imaging.

Table 1. Immunoglobulin levels of the patient

	Result (%)	Normal range (%)
IgG (mg/dL)	447	745-1804
IgA (mg/dL)	< 14	57-282
IgM (mg/dL)	77	78-261

DISCUSSION

Chronic granulomatous disease is a hereditary disorder of phagocytes in which affected patients suffer from recurrent bacterial and fungal infections. Classically, this disease is described as a pure disorder of intracellular killing, with preservation of other aspects of phagocytic functions such as migration and phagocytosis^[6]. The immunoglobulins of patients with CGD are usually high, an alert for diagnostic suspicion when associated with the clinical manifestations described earlier^[3]. Recent studies have shown that patients with CGD had diminished T-cell numbers and reduced peripheral blood memory B-cell compartment. It is not known whether diminished T-or memory B-cell numbers influence the immunoglobulin production and secondary antibody responses in CGD patients^[6,7]. However, hypogammaglobulinemia is very rare in CGD, with only two reports of CGD and selective IgA deficiency^[4,5].

In our patient, IgA and IgG levels were below normal range for age.

Fungal infections constitute up to 20% of infections in CGD, and *Aspergillus* spp. are considered the major causative fungal agents^[1]. Invasive aspergillosis may be the first manifestation of CGD. The primary lesions are usually in the lung in the form of necrotizing granulomatous pneumonia and alveolar consolidation^[8]. Initially, these patients can be misdiagnosed as TB because of nodular or granulomatous pulmonary lesions as in our patient^[9].

Disseminated aspergillosis occurs by hematogenous spread to distant sites or by contagious extension. Aspergillosis pneumonia can be disseminated to ribs, chest wall, soft tissues, and bones. Thoracic wall extension of pulmonary aspergillosis is rare and has been reported almost exclusively in patients with CGD^[10]. In our patient, the infection had probably spread through hematogenous route from pulmonary lesions to the cranium and by contagious route to the chest wall.

The incidence of cerebral aspergillosis is difficult to determine because the diagnosis is often unsuspected and difficult to confirm. The clinical presentation and laboratory findings are nonspecific, and CT findings are similar to those

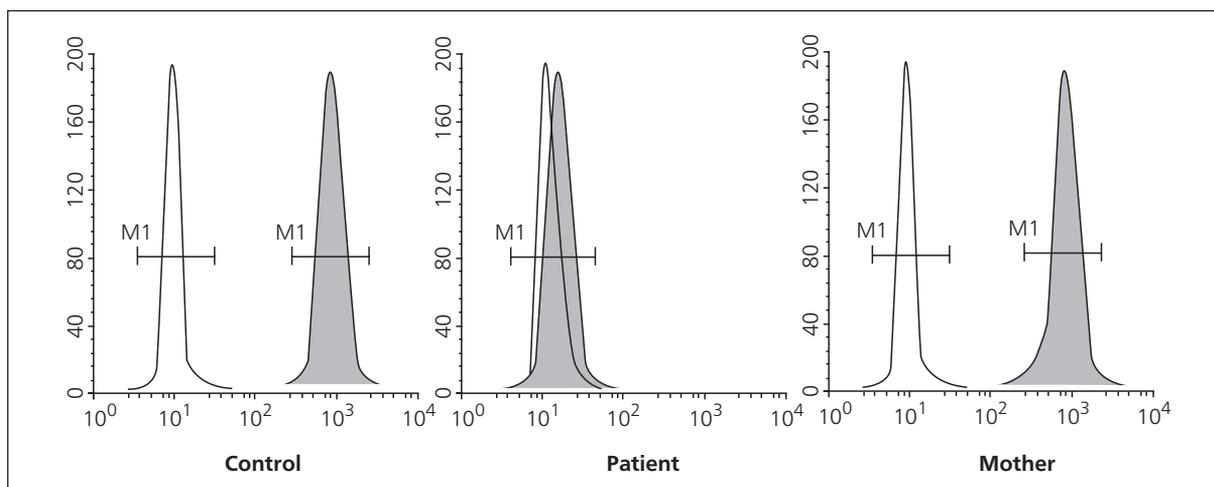


Figure 3. Dihydro rhodamine flow cytometry assay (DHR 123 test) of the patient and his mother.

of other infectious causes of brain abscess. Since differential diagnosis is extensive, including other fungal infections and opportunistic diseases, biopsy is recommended for confirmation^[11]. Our patient had abnormal neurological signs on admission and his neurological functions rapidly deteriorated. Intracranial biopsy revealed invasive fungal infection, which was later confirmed by positive culture for *Aspergillus* spp.

The treatment of infections in CGD patients is still challenging, since the underlying immunodeficiency is the most important factor with respect to the outcome of treatment. Previously, amphotericin B was the primary medical therapy for invasive aspergillosis^[10]. Recently, voriconazole has been approved for primary therapy, and has been shown to be superior to amphotericin B in some studies. Itraconazole has been shown to be effective for aspergillosis in CGD but variable resorption from the intestine is its disadvantage. In a murine model of CNS aspergillosis, amphotericin B and voriconazole combination showed significant enhanced activity. Although interferon-gamma has been used for prophylaxis and treatment of CDG since 1991^[12]. It took time to initiate it within the last few days of life in the presented case due to unavailability. Furthermore, it has been reported that transfusion of granulocytes could be useful for controlling infections in patients with severe granulocytopenia or defective granulocyte functions^[13]. However, this therapy could not be given to our patient due its unavailability in our hospital. Our patient was treated initially with amphotericin B, which was later combined with voriconazole, but no benefit could be shown since the disease course progressed rapidly.

In conclusion, chronic granulomatous disease should be considered in the differential diagnosis for all children presenting with invasive fungal infections, particularly those involving the pulmonary and central nervous systems. The approach to treatment should be more aggressive in these patients.

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