CASE REPORT
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Disseminated Aspergillosis as the Herald Manifestation of Chronic Granulomatous Disease in an Adult Patient

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ABSTRACT

Chronic granulomatous disease is an inherited defect in intracellular killing of ingested microorganisms characterized by recurrent life threatening bacterial and fungal infections including invasive aspergillosis in early childhood.

We report a disseminated aspergillosis as the representative of adult onset chronic granulomatous disease without previous infection, with dramatic response to combination of antifungal and interferon therapy.

Keywords: Adulthood; Anidulafungin; Aspergillosis; Chronic granulomatous disease; Dihydrorhodamine; Invasive fungal infection; Voriconazole

INTRODUCTION

Chronic granulomatous disease (CGD) is an inherited disorder of nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase and results in a defect in intracellular killing of ingested microorganisms characterized by recurrent life threatening bacterial and fungal infections. [1-3] There are one X-linked and four autosomal recessive forms of CGD. [4-7] The incidence rate is between 1/200,000 and 1/250,000 live births.[4] The organisms cultured from lesion of patients with CGD are generally catalase- producing including staphylococci, Escherichia coli (E.coli), Serratia; or fungi such as Aspergillus species.[8-10] Recurrent or serious infections usually lead to diagnosis of CGD in early childhood, and onset of disease in adulthood is not common. Adult onset cases have been reported in adults, formerly.[11] Usually, they have had clinically mild phenotypes or were treated in childhood without attention to underlying diseases and causes of recurrence and extension of infections.

We report an adult case of CGD without history of infection, diagnosed with disseminated aspergillosis; and properly was treated with combined antifungal agents and gamma interferon.

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CASE PRESENTATION

A 20 year-old girl was admitted due to low back pain and subcutaneous masses in left thigh and left temporal part of scalp.

She complained of non-productive cough, low-grade fever, anorexia, night sweats and weight loss since eight months before admission. Ambiguous abdominal pain in left upper quadrant and bulging of the left temporal part of scalp and left thigh were other remarkable complaints in recent few months. She was healthy until 8 months ago without significant past medical history.

She was an Iranian student and had two brothers. One of her brothers died with a presumptive diagnosis of acute pneumonia twenty years ago; and the other younger brother was healthy. Her parents were consanguinous and healthy.

On admission, she was ill, pale and cachectic with two non-tender soft purple subcutaneous masses in the occipital part of the scalp (2.5 x 2 cm) and lateral side of the left thigh (1.5 x 2 cm) and focal tenderness in lumbar examination. Other examinations were normal with no significant lymphadenopathy and organomegaly.

Complete blood cell count revealed 19,000 cell/ml leukocytes (80% neutrophils, 14% lymphocytes, 5% monocytes, 1% eosinophils) and normocytic hypochromic mild anemia (9 g/dl). Erythrocyte sedimentation rate at first hour was 90 mm/hr. Electrolyte profile, renal and liver function tests as well as urinalysis all were in normal range with negative virologic assays including human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen and hepatitis C antibody. Tuberculin skin test was negative as were sputum smear for mycobacteria, fungal and pathogenic bacterial agents.

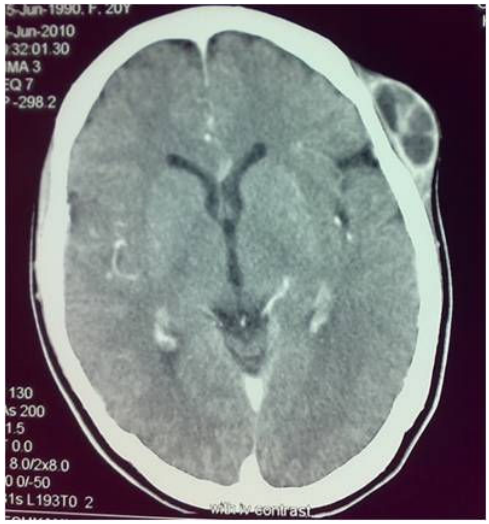

Figure 1. Brain CT scan revealed a subcutaneous soft tissue mass with septation in the left side of scalp.

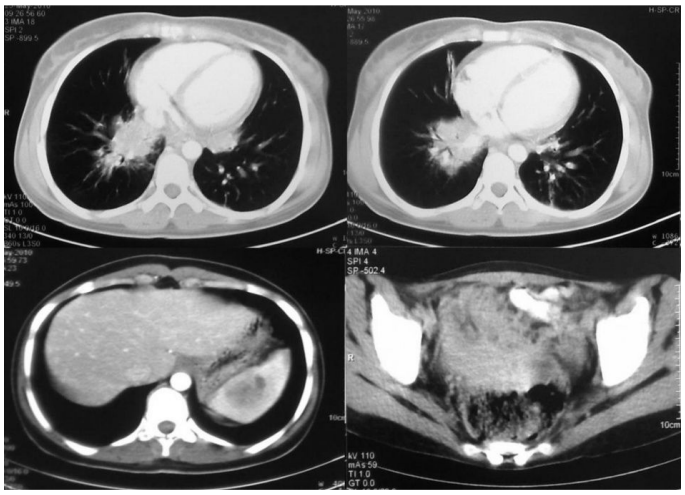

Figure 2. Chest and abdominopelvic CT scan with contrast revealed perihilar mass in right lung (above), hypodense lesion in spleen (left below) and heterogeneous infiltrative soft tissue density in pelvic fossa (right below).

Brain, chest and abdominopelvic computed tomography (CT) scans were performed (Figure 1 and 2). She underwent bronchoscopy with bronchoalveolar lavage and transbronchial biopsy according to the findings of chest CT scan and normal sputum analysis. All of them were unremarkable.

DISCUSSION

CGD is an inherited defect in intracellular killing of ingested microorganisms characterized by recurrent life threatening bacterial and fungal infections including invasive aspergillosis in early childhood. [1,2,12] Patients usually are diagnosed in early childhood.[13,14] with infective involvements of skin and lung more commonly including suppurative adenitis, abscesses and pneumonia[15] followed by osteomyelitis, sepsis, urinary infection, severe gastroenteritis, oral aphthae and Crohn-like inflammatory bowel disease.[16] According to the reports from Iran, the median diagnostic age is 8 years, with a diagnostic delay of 4.5 years [17,18] compared to the median age of onset at four months of age and the median diagnostic age of 5.5 years in other national reports.[19,20] Recently, adult cases of CGD have been reported due to novel mutations or mosaic patterns.[21,22] In the latter, the patient showed a somatic mosaic for the cytochrome b (-245) beta CYBB mutation, which probably originated during her lifetime in her bone marrow.[22]

Furthermore, it seems that patients with X-linked recessive form of the disease have a more serious clinical phenotype than patients with the autosomal recessive forms, based on the fact that they are diagnosed significantly earlier (mean, 3.01 years of age versus 7.81 years of age, respectively).[4] Moreover, the diagnosis may be delayed due to potent antimicrobial agents that inadvertently treated many CGD-associated infections, postponing diagnosis until more severe infections indicate CGD as the underlying cause.[23]

The frequency and mortality rate of fungal infections have been reduced markedly since the advent of itraconazole prophylaxis and the use of voriconazole for treatment of filamentous fungal infections (e.g., Aspergillus). Combination therapy including antibacterial and antifungal and gamma interferon, dramatically reduce the rate of severe infections from one per patient-year to almost one every year per 10 patient.[10,24-30] Successful hematopoietic cell transplantation (HCT) may be a definitive cure for CGD.[31]

The interesting findings in this patient, were firstly, delay in presentation of CGD until twenty years of age without any previous infections and secondly the high burden of aspergillus infection as multiple involved organs particularly the isolation of this germ from spleen and bone marrow. Usually Aspergillus infection in phagocytic disorders particularly CGD presents as local slowly progressing infection but as observed in this patient, multiple organs were affected (skin, lung, pelvic cavity, spleen, vertebrae and bone marrow).

Finally, dramatic response to combined antifungal regimen was another intriguing finding in this patient, which may help us in treatment of other patients with disseminated aspergillosis. After 6 months, the patient was in healthy condition. She was afebrile and gained 6 kg weight while all paraclinic abnormalities resolved consisting of 20 mm/hr ESR, 11 mg/dl hemoglobin and significant reduction in size of pulmonary, splenic and pelvic masses while she was taking itraconazole 400 mg per day and she was supposed to continue for further six months of this treatment and then received antibacterial and antifungal prophylaxis.

We conclude that CGD should be considering in all patients with recurrent catalase positive microorganisms as well as fungal infections regardless of the age, although it usually manifests in children.

REFERENCES

1. Denning, D.W. Invasive aspergillosis. Clin Infect Dis 1998; 26(4):781-803.
2. Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. Clin Infect Dis 2001; 32(3):358-66.
3. Curntte JT. Chronic granulomatous disease, The solving of a clinical riddle at the molecular level. Clin Immunol Immunopathol 1993; 67(3 Pt 2):2–15.
4. Winkelstein JA, Marino MC, Johnston RB Jr, Boyle J, Curnutte J, Gallin JI, et al. Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine (Baltimore) 2000; 79(3):155-69.
5. Roos D, de Boer M, Kuribayashi F. Mutations in the X-linked and autosomal recessive forms of chronic granulomatous disease. Blood 1996; 87(5):1663-81.
6. Rae J, Newburger PE, Dinauer MC, Noack D, Hopkins PJ, Kuruto R, et al. X-Linked chronic granulomatous disease: mutations in the CYBB gene encoding the gp91-phox component of respiratory-burst oxidase. Am J Hum Genet 1998; 62(6):1320-31.

7. Ariga T, Furuta H, Cho K, Sakiyama Y. Genetic analysis of 13 families with X-linked chronic granulomatous disease reveals a low proportion of sporadic patients and a high proportion of sporadic carriers. Pediatr Res 1998; 44(1):85-92.
8. Dennis CG, Greco WR, Brun Y, Youn R, Slocum HK, Bernacki RJ, et al. Effect of amphotericin B and micafungin combination on survival, histopathology, and fungal burden in experimental aspergillosis in the p47phox-/- mouse model of chronic granulomatous disease. Antimicrob Agents Chemother 2006; 50(2):422-7.
9. O'Neil KM, Herman JH, Modlin JF, Moxon ER, Winkelstein JA. Pseudomonas cepacia: an emerging pathogen in chronic granulomatous disease. J Pediatr 1986; 108(6):940-2.
10. Speert DP, Bond M, Woodman RC, Curnutte JT. Infection with Pseudomonas cepacia in chronic granulomatous disease: role of nonoxidative killing by neutrophils in host defense. J Infect Dis 1994; 170(6):1524-31.
11. Liese J, Jansson A, Petropoulou Th, Kloos S, Belohradsky BH, Jendrossek V, et al. Chronic granulomatous disease in adults. The Lancet 1996; 347(8996):220-3.
12. Curntte JT. Chronic granulomatous disease: The solving of a clinical riddle at the molecular level. Clin Immunol Immunopathol 1993; 67(3 Pt 2):S2–15.
13. Kobayashi S, Murayama S, Takanashi S, Takahashi K, Miyatsuka S, Fujita T, et al. Clinical features and prognoses of 23 patients with chronic granulomatous disease followed for 21 years by a single hospital in Japan. Eur J Pediatr 2008; 167(12):1389-94.
14. Martire B, Rondelli R, Soresina A, Pignata C, Broccoletti T, Finocchi A, et al. Clinical features, long-term follow-up and outcome of a large cohort of patients with Chronic Granulomatous Disease: an Italian multicenter study. Clin Immunol 2008; 126(2):155-64.
15. Jones LB, McGrogan P, Flood TJ, Gennery AR, Morton L, Thrasher A, et al. Chronic granulomatous disease in the United Kingdom and Ireland: a comprehensive national patient-based registry. Clin Exp Immunol 2008; 152(2):211-8.
16. Soler-Palacin P, Margareto C, Llobet P, Asensio O, Hernandez M, Caragol I, et al. Chronic granulomatous disease in pediatric patients: 25 years of experience. Allergol Immunopathol (Madr) 2007; 35(3):83-9.
17. Khalilzadeh S, Bloorsaz MR, Mansouri D, Baghaie N, Hakimi S, Velayati AA. Clinical and Radiological Aspects of Chronic Granulomatous Disease in Children: A case Series from Iran. Iran J Allergy Asthma Immunol 2006; 5(2):85-8.
18. Tafti SF, Tabarsi P, Mansouri N, Mirsaeidi M, Motazedi Ghajar MA, Karimi S, et al. Chronic granulomatous disease with unusual clinical manifestation, outcome, and pattern of inheritance in an Iranian family. J Clin Immunol 2006; 26(3):291-6.
19. Movahedi M, Aghamohammadi A, Rezaei N, Shahnavaz N, Jandaghi AB, Farhoudi A, et al. Chronic granulomatous disease: a clinical survey of 41 patients from the Iranian primary immunodeficiency registry. Int Arch Allergy Immunol 2004; 134(3):253-9.
20. Aghamohammadi A, Moein M, Farhoudi A, Pourpak Z, Rezaei N, Abolmaali K, et al. Primary immunodeficiency in Iran: first report of the National Registry of PID in Children and Adults. J Clin Immunol 2002; 22(6):375-80.
21. Lun A, Roesler J, Renz H. Unusual late onset of X-linked chronic granulomatous disease in an adult woman after unsuspicious childhood. Clin Chem 2002; 48(5):780-1.
22. Wolach B, Scharf Y, Gavrieli R, de Boer M, Roos D. Unusual late presentation of X-linked chronic granulomatous disease in an adult female with a somatic mosaic for a novel mutation in CYBB. Blood 2005; 105(1):61-6.
23. Schapiro BL, Newburger PE, Klempner MS, Dinauer MC. Chronic granulomatous disease presenting in a 69-year-old man. N Engl J Med. 1991;325:1786-1790.Pfaller MA, Messer SA, Hollis RJ, Jones RN; SENTRY Participants Group. Antifungal activities of posaconazole, ravuconazole, and voriconazole compared to those of itraconazole and amphotericin B against 239 clinical isolates of Aspergillus spp. and other filamentous fungi: report from SENTRY Antimicrobial Surveillance Program, 2000. Antimicrob Agents Chemother 2002; 46(4):1032-7.
24. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002; 347(6):408-15.
25. Denning DW, Ribaud P, Milpied N, Caillot D, Herbrecht R, Thiel E. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. Clin Infect Dis 2002; 34(5):563-71.

26. Anaissie, EJ. Trial design for mold-active agents: time to break the mold--aspergillosis in neutropenic adults. Clin Infect Dis 2007; 44(10):1298-306.
27. Patterson TF, Kirkpatrick WR, White M, Hiemenz JW, Wingard JR, Dupont B, et al. Invasive aspergillosis: Disease spectrum, treatment practices, and outcomes. Medicine (Baltimore) 2000; 79(4):250-60.
28. Singh N. Invasive aspergillosis in organ transplant recipients: new issues in epidemiologic characteristics, diagnosis, and management. Med Mycol 2005; 43(Suppl 1):S267-70.
29. Roilides E, Uhlig K, Venson D, Pizzo PA, Walsh TJ. Enhancement of oxidative response and damage caused by human neutrophils to Aspergillus fumigatus hyphae by granulocyte colony-stimulating factor and gamma interferon. Infect Immun 1993; 61(4):1185-93.
30. Soncini E, Slatter MA, Jones LB, Hughes S, Hodges S, Flood TJ, et al. Unrelated donor and HLA-identical sibling haematopoietic stem cell transplantation cure chronic granulomatous disease with good long-term outcome and growth. Br J Haematol 2009; 145(1):73-83.