Case Report

Iran J Pediatr
Dec 2010; Vol 20 (No 4), Pp: 487-490

Successful Treatment of Fungal Osteomyelitis with Voriconazole in a Patient with Chronic Granulomatous Disease

Masoud Mohammadpour[1,2], MD; Setareh Mamishi*[1,3], MD; Mahsa Oaji[2]; Zahra Pourpak[4]; MD, PhD, and Nima Parvaneh[1,2,3], MD

1. Department of Pediatrics, Tehran University of Medical Sciences, Tehran, IR Iran
2. Children's Medical Center, Pediatrics Center of Excellence, Tehran University of Medical Sciences, Tehran, IR Iran
3. Infectious Disease Research Center, Tehran University of Medical Sciences, Tehran, IR Iran
4. Immunology, Asthma and Allergy Research Institute, Tehran University of Medical Sciences, Tehran, IR Iran

Received: *Sep 05, 2009*; Final Revision: *Dec 25, 2009*; Accepted: *Apr 02, 2010*

Abstract

Background: Chronic granulomatous disease (CGD) is an immunodeficiency affecting phagocytic leukocytes. Defective respiratory burst mechanism renders the affected patients to be susceptible to catalase positive microorganisms. With the great successes in antibacterial prophylaxis and therapy, fungal infections are a persistent problem. Invasive aspergillosis is the most important cause of mortality in CGD.

Case Presentation: We describe a nine year-old boy with CGD who presented with aspergillus induced skull osteomyelitis. He was successfully treated with voriconazole after initial failure of amphotericin B therapy.

Conclusion: Currently, newer triazoles are recommended as initial therapy for invasive aspergillosis in immunodeficiency states such as CGD.

Iranian Journal of Pediatrics, Volume 20 (Number 4), December 2010, Pages: 487-490

Key Words: Granulomatous disease; Invasive Pulmonary Aspergillosis; Voriconazole; Osteomyelitis; Fungal Infections

Introduction

Chronic granulomatous disease (CGD) is a primary immunodeficiency of the NADPH oxidase complex characterized by recurrent bacterial and fungal infections. The underlying defect is an inability of phagocytes to make reactive oxygen intermediates and activate their intracellular proteases[1].

*** Corresponding Author;**
Address: Children's Medical Center, Dr Gharib St, 14194 Tehran, Iran
E-mail: smamishi@tums.ac.ir

© 2010 by Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, All rights reserved.

With the great success in antibacterial prophylaxis, fungal infections are a persistent problem in these patients. The incidence of fungal infections in CGD has been reported to be 20%[2]. The *Aspergillus* species affecting CGD patients are *A. fumigatus*, *A. nidulans* and rarely *A. flavus* and *A. niger*[2-5].

In some CGD series, invasive aspergillosis was the most common cause of death, accounting for over one-third of all deaths[6]. However, the arrival of highly active antifungal therapy with the azole antifungals has changed the face of fungal infections in CGD and reduced the overall mortality. Posaconazole and voriconazole are safely and effectively used in salvage therapy of refractory pulmonary aspergillosis in CGD patients[8,9]; however, their effectiveness is less documented for treatment of osteomyelitis. Here we describe a case of skull osteomyelitis due to *Aspergillus fumigatus* infection in a patient with CGD who showed a favorable response to voriconazole after initial failure with amphotericin B therapy.

Case Presentation

The patient is a 9-year-old boy diagnosed with CGD after fever and generalized lymphadenopathy at the age of 2 years. He was found to have a non-sense mutation (c.810G>A) in exon 8 of *CYBB* that introduces a premature stop codon at position 270 (p.Trp270X) of *GP91 PHOX*[10]. His past history was typical for recurrent pneumonias and adenopathies. He has received daily prophylactic treatment with 5mg/kg trimethoprim sulfamethoxazole (TMP-SMZ) and occasional interferon-γ and itraconazole. He presented with fever, vomiting and progressive headache for 3 weeks. Physical examination was remarkable for mild fever and a non-tender bulging over the supero-lateral aspect of left orbit. Funduscopy showed no papilledema. Complete blood count revealed a mild hypochromic anemia. The erythrocyte sedimentation rate (ESR) was elevated at 117 and the C-reactive protein (CRP) was +3 positive.

Chest x-ray showed ill-defined opacities over the right middle and lower lung lobes. ^{99m}Tc bone scan revealed increased uptake at the involved area indicating an inflammatory process (Fig. 1).

The excisional biopsy of the skull mass revealed septated hyphae. Culture was positive for *A. fumigatus.* Initial antimicrobial therapy consisted of ceftriaxone (70mg/kg) and vancomycin (60mg/kg), but cultures remained positive for *A. fumigates.* Thereon he received Deoxycholate amphotericin B (1 mg/kg/day), itraconazole (100 mg/day), and interferon-γ (50μg/kg).

Despite 3 weeks of this combination therapy, the fever and headache were not resolved. So, the amphotericin B and itraconazole were discontinued and intravenous voriconazole (8mg/kg/each 12 hours) started. Five days after onset of voriconazole he became afebrile, and the headache resolved over the next 2 weeks. With the suspicion of pyloric stenosis, oral prednisolone (1mg/kg/day) started as the fever abated. After 2 weeks of intravenous therapy, he left to home receiving oral voriconazole and prophylactic TMPSMZ and interferon-γ. The last follow-up visit performed 12 months after the first presentation showed no residual neurologic problems.

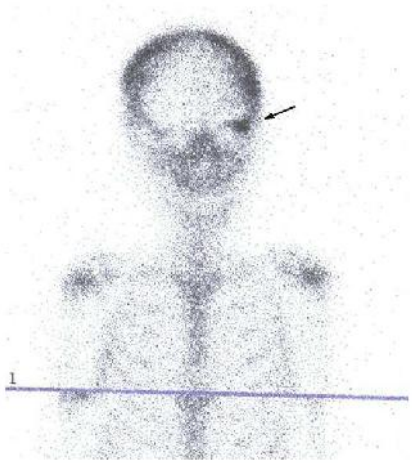

Fig. 1: ^{99m}Tc imaging showing increased radiotracer localization (arrow) in the superolateral aspect of the left orbit.

Discussion

The NADPH oxidase in phagocytes is essential in host defense against aspergillosis. The activation of NADPH oxidase results in the generation of reactive oxygen metabolites with antimicrobial activity[11]. In neutrophils, this process is coupled with activation of intracellular proteases[1].

The overall incidence of fungal infections has been reported to be 20% in CGD patients, with *Aspergillus spp.* being responsible for 78% of all fungal infections in these patients[2]. Indeed, *Aspergillus* is one of the major causes of morbidity and mortality in CGD. In a series of 368 patients, *Aspergillus spp.* were the most commonly isolated organisms from CGD patients with pneumonia and the second most commonly isolated organism from those with osteomyelitis[7].

The lung is the most common site of invasive aspergillosis from which infection may extend to near-by structures or disseminated hemato-genously to other organs[11]. Here, we presented a patient who came with both pulmonary infiltrates in the chest x-ray and skull bone involvement caused by *A. fumigatus.* It has been shown that *A. nidulans* mainly produces osteomyelitis after contiguous extension from the primary lung inoculum, but *A. fumigatus* is mostly accounts for osteomyelitis in distant organs after hematogenous spread[12].

Our patient showed poor clinical response to Deoxycholate amphotericin B and itraconazole experienced persisting of fever and headache, so we changed to voriconazole. This resulted in a long lasting “Complete response” considering the newly established criteria for response to antifungal therapy[13]. Amphotericin produces suboptimal results against invasive aspergillosis in immunodeficient patients[3,4]. Recent studies of patients with invasive aspergillosis have shown that treatment with voriconazole is more effective than treatment with amphotericin B[14,15].

Conclusion

As a conclusion, newer triazoles (voriconazole, posaconazole) are recommended as initial therapy for invasive aspergillosis in immunodeficiency states such as CGD[3,14]. In the cases of osteomyelitis or aggressive pulmonary involvement, surgical debridement is also advised [5,12].

Acknowledgment

Voriconazole (Vfend) was a compassionate release from Pfizer Pharmatceuticals.
The authors would like to thank Haran T. Schlamm, Pfizer Global Research and Development, who kindly provided us with voriconazole. We also thank Rosemarie Rymer, The CGD Research Trust, for her valuable contribution.

References

1. Reeves EP, Lu H, Jacobs HL, et al. Killing activity of neutrophils is mediated through activation of proteases by K+ flux. Nature. 2002; 416(6878):291-7.
2. Cohen MS, Isturiz RE, Malech HL, et al. Fungal infection in chronic granulomatous disease. The importance of the phagocyte in defense against fungi. Am J Med. 1981;71(1):59-66.
3. Almyroudis NG, Holland SM, Segal BH. Invasive aspergillosis in primary immunodeficiencies. Med Mycol. 2005; 43 (Suppl 1):S247-S259.
4. Mamishi S, Parvaneh N, Salavati A, et al. Invasive aspergillosis in chronic granulomatous disease: report of 7 cases. Eur J Pediatr. 2007;166(1):83-4.
5. Segal BH, DeCarlo ES, Kwon-Chung KJ, et al. Aspergillus nidulans infection in chronic granulomatous disease. Medicine (Baltimore). 1998;77(5):345-54.

6. Mouy R, Fischer A, Vilmer E, Seger R, et al. Incidence, severity, and prevention of infections in chronic granulomatous disease. J Pediatr. 1989;114(4 Pt 1):555-60.
7. Winkelstein JA, Marino MC, Johnston RB, et al. Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine (Baltimore). 2000; 79(3): 155-69.
8. Segal BH, Barnhart LA, Anderson VL, et al. Posaconazole as salvage therapy in patients with chronic granulomatous disease and invasive filamentous fungal infection. Clin Infect Dis. 2005; 40(11):1684-8.
9. van't Hek LG, Verweij PE, Weemaes CM, et al. Successful treatment with voriconazole of invasive aspergillosis in chronic granulomatous disease. Am J Respir Crit Care Med. 1998; 157(5 Pt 1):1694-6.
10. Teimourian S, Rezvani Z, Badalzadeh M, et al. Molecular diagnosis of X-linked chronic granulomatous disease in Iran. Int J Hematol. 2008; 87(4):398-404.
11. Segal BH. Aspergillosis. N Engl J Med. 2009; 360(18):1870-84.
12. Dotis J, Roilides E. Osteomyelitis due to Aspergillus spp. in patients with chronic granulomatous disease: comparison of Aspergillus nidulans and Aspergillus fumigatus. Int J Infect Dis. 2004;8(2):103-10.
13. Segal BH, Herbrecht R, Stevens DA, et al. Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: Mycoses Study Group and European Organization for Research and Treatment of Cancer consensus criteria. Clin Infect Dis. 2008; 47(5):674-83.
14. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med. 2002;347(6):408-15.
15. Walsh TJ, Lutsar I, Driscoll T, et al. Voriconazole in the treatment of aspergillosis, scedosporiosis and other invasive fungal infections in children. Pediatr Infect Dis J. 2002;21(3):240-8.