Primary cutaneous aspergillosis in an extremely low birth weight preterm

Seyhan Erişir-Oygucu, Abdullah Barış Akcan, Nihal Oygür

Division of Neonatology, Department of Pediatrics, Akdeniz University Faculty of Medicine, Antalya, Turkey

SUMMARY: Erişir-Oygucu S, Akcan AB, Oygür N. Primary cutaneous aspergillosis in an extremely low birth weight preterm. Turk J Pediatr 2009; 51: 621-623.

Aspergillosis is an uncommon infection in neonates. However, it has been an emerging problem for preterm infants in recent years because of long-term parenteral nutrition, multiple-antibiotic therapy and immune deficiency due to prematurity. We report a preterm neonate with disseminated cutaneous lesions due to primary cutaneous aspergillosis. She died despite an early treatment with liposomal amphotericin B. Fungal infections should be remembered in preterms whose clinical conditions and laboratory tests for infection deteriorate, despite an appropriate antibiotic and supportive therapy.

Key words: infection, very low birth weight, preterm.

The survival rate of extremely low birth weight (ELBW) infants has improved due to advances in neonatal care and new invasive therapies such as central vascular catheters, endotracheal tubes, broad-spectrum antibiotics, parenteral nutrition, and postnatal steroids. Although they are very effective in increasing the survival of these very tiny and immunocompromised babies, they also place them at high risk for fungal infections. Recently, a few ELBW preterms dying from either systemic or primary cutaneous aspergillosis have been reported in the literature[1,2].

We report a preterm neonate who died with disseminated cutaneous lesions due to primary cutaneous aspergillosis despite an early treatment with liposomal amphotericin B.

Case Report

A female preterm neonate of 27 weeks' gestation was transferred to our neonatal intensive care unit (NICU) because of respiratory distress. She weighted 750 g and was treated with surfactant for hyaline membrane disease, and ampicillin and amikacin for presumed sepsis. The patient did not receive antifungal prophylaxis with fluconazole. After one week, ampicillin was discontinued and meropenem was initiated because of progressive neutropenia (white blood cell 1200/mm^3, absolute neutrophil count 750/mm^3) and thrombocytopenia (35,000/mm^3); liposomal amphotericin B (5 mg/kg/day) was added to cover fungal infections. Granulocyte colony-stimulating factor was also used to increase the neutrophil count. Blood, cerebrospinal fluid (CSF) and urine cultures were negative. No organisms were detected on Gram stain of CSF.

Protein (45 mg/dl) and glucose (CSF glucose level 50 mg/dl and simultaneous blood glucose level 83 mg/dl) concentrations and leukocyte count of CSF (30/mm^3) were also normal. On day 12, non-specific erythematous eruptions appeared on the infant's back. There was no history of probe placement or tape removal at this site. They developed into black necrotic lesions on day 14 and on the same day, superficial specimens were obtained for culture. Biopsies of the lesions were performed and the materials were stained with hematoxylin-eosin, periodic acid-Schiff and methenamine silver. Her chest X-ray was normal and fungal abscess was not detected on the abdominal ultrasound of the patient. Magnetic resonance imaging (MRI) was planned to search for abscess in the lungs or other organs but could not be performed. The preterm's condition deteriorated despite the use of broad-spectrum antibiotics, antifungal therapy, inotropic agents, bicarbonate infusions for metabolic acidosis, and repeated transfusions of fresh frozen plasma, platelets and erythrocytes. She died

due to refractory hypotension and metabolic acidosis on day 16. One day after the infant's death, multi-septated hyphae were detected on smears and Aspergillus flavus grew from the culture taken from the necrotic lesions (Figs. 1, 2).

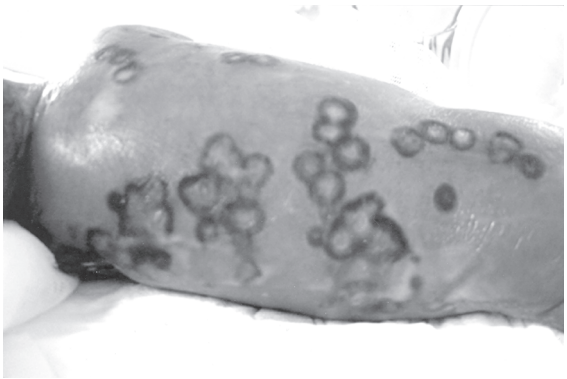

Fig. 1. General appearance of the necrotic lesions on the back of the patient.

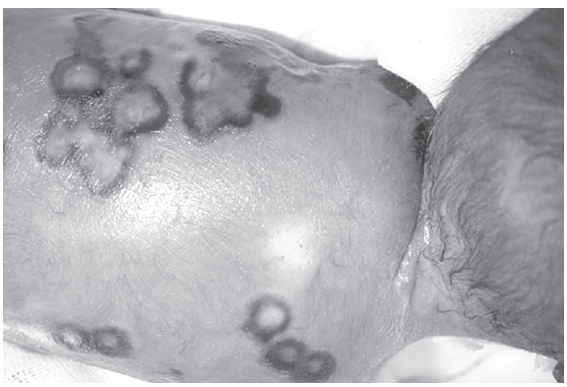

Fig. 2. Closer appearance of the necrotic lesions on the back of the patient.

Discussion

Aspergillus spp. are present everywhere in nature and are not accepted as a severe source of infection in immunocompetent hosts, but can cause a life-threatening sepsis in immunocompromised patients. In recent years, aspergillosis has emerged as a problem for preterm infants because of long-term parenteral nutrition, multiple-antibiotic therapy and immune deficiency due to prematurity. In hospitalized preterm babies, even adhesive tapes used to secure catheters or endotracheal tubes can lead to cutaneous infection with Aspergillus spp.

Aspergillosis has been classified by Groll et al.[3] as primary cutaneous aspergillosis and invasive aspergillosis. Different types of cutaneous aspergillosis have been described: the solitary necrotizing dermal plaque; subcutaneous granuloma; papular eruption with suppurative vegetating or necrobiotic tendencies; and progressive confluent granulomas[4]. In primary cutaneous aspergillosis, the typical skin lesion, which commonly begins on the back, is an erythematous or violaceous papule that progresses to a central ulceration. The cutaneous lesions of our patient appeared as erythematous eruptions and progressed to necrotic lesions in two days. Unfortunately, it was not possible to follow the progress of the lesions as the baby died four days after their appearance on her back.

There have been various studies investigating the efficacy of new antifungal agents against aspergillosis, such as voriconazole, caspofungin and itraconazole. However, voriconazole or the lipid formulations of amphotericin B are considered to be the choice of treatment if the diagnosis of invasive aspergillosis is established[5-9]. Some studies recommend using voriconazole for initial therapy and accept it as a cost-effective option despite its being an expensive agent, because the clinical outcomes with this agent seem to be better than the initial therapy with conventional amphotericin B[10-13]. However, cases have been immunocompromised adult or child patients in almost all of these studies. Aspergillosis in preterms has generally been represented as a few case reports in the literature, but it seems it will increase in number as the survival of more immature preterms increases[14-18].

Diagnosis of cutaneous aspergillosis requires biopsy from the lesions for culture and for histopathological examination. In our patient, hyphae were detected in tissue samples and definitive diagnosis was made by positive tissue culture for *Aspergillus flavus*.

In general, the clinical presentation seems to be better and the mortality lower with primary cutaneous aspergillosis. Our patient died despite the early treatment with liposomal amphotericin B, and the species was found to be sensitive to this agent. However, she may still have had invasive aspergillosis since fungal blood, urine and CSF cultures for Aspergillus

are negative in most of the patients with invasive aspergillosis. In addition, we could not obtain autopsy permission from her parents to search for fungal abscesses in other organs.

It is not clear whether we would have been successful or not, but we could have tried to add a second antifungal agent such as voriconazole as soon as the lesions appeared. However, there was not enough time to obtain a response to treatment with voriconazole and amphotericin B together since the baby died four days after the lesions developed. To our knowledge, there has been only one preterm case report in the literature treated with combined therapy[14].

Based on a cohort study done recently, prophylaxis with fluconazole seems to reduce the incidence of fungal colonization and systemic infection with Candida spp. in preterm neonates. However, Aspergillus spp. and other molds are not affected by this drug, so it is not clear whether or not preterm infants colonized with Aspergillus spp. would also benefit from antifungal prophylaxis[19,20].

In conclusion, preterm neonates, especially ELBW infants, are prone to fungal infections, and the incidence of primary aspergillosis is going to increase. Timely diagnosis and early and effective antifungal therapy are necessary to decrease the mortality due to aspergillosis in NICUs.

REFERENCES

1. Herron MD, Vanderhooft SL, Byington C, King JD. Perinatal/neonatal case presentation. Aspergillosis in a 24-week newborn: a case report. J Perinatol 2003; 23: 256-259.
2. Fuchs H, Baum H, Meth M, Wellinghausen N, Linder W, Hummler H. CNS-manifestation of aspergillosis in an extremely low-birth-weight infant. Eur J Pediatr 2006; 165: 476-480.
3. Groll AH, Jaeger G, Allendorf A, Herrmann G, Schloesser R, von Loewenich V. Invasive pulmonary aspergillosis in a critically ill neonate. Case report and review of invasive aspergillosis during the first three months of life. Clin Infect Dis 1998; 27: 437-452.
4. Findlay GH, Roux HF, Simson IW. Skin manifestations in disseminated aspergillosis. Br J Dermatol 1971; 85: 95-97.
5. Patterson TF, Boucher HW, Herbrecht R, et al. Strategy of following voriconazole versus amphotericin B therapy with other licensed antifungal therapy for primary treatment of invasive aspergillosis: impact of other therapies on outcome. Clin Infect Dis 2005; 15: 1448-1452.
6. Rüping MJ, Vehreschild JJ, Cornely OA. Antifungal treatment strategies in high risk patients. Mycoses 2008; 51: 46-51.
7. Rüping MJ, Vehreschild JJ, Cornely OA. Patients at high risk of invasive fungal infections: when and how to treat. Drugs 2008; 68: 1941-1962.
8. Forrest GN, Walsh TJ. Approaches to management of invasive fungal infections in patients with hematologic malignancies. Support Cancer Ther 2004; 2: 21-30.
9. Wingard JR, Leather H. A new era of antifungal therapy. Biol Blood Marrow Transplant 2004; 10: 73-90.
10. Garbino J, Schnetzler G, Roberts C. Invasive aspergillosis: is the treatment with "inexpensive" amphotericin B cost saving if "expensive" voriconazole is only used on demand? Swiss Med Wkly 2006; 136: 624-630.
11. Lewis JS, Boucher HW, Lubowski TJ, Ambegaonkar AJ, Day DI, Patterson TF. Cost advantage of voriconazole over amphotericin B deoxycholate for primary treatment of invasive aspergillosis. Pharmacotherapy 2005; 25: 839-846.
12. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002; 347: 408-415.
13. Steinbach WJ, Stevens DA. Review of newer antifungal and immunomodulatory strategies for invasive aspergillosis. Clin Infect Dis 2003; 37: 157-187.
14. Santos RP, Sanchez PJ, Mejias A, et al. Successful medical treatment of cutaneous aspergillosis in a premature infant using liposomal amphotericin B, voriconazole and micafungin. Pediatr Infect Dis J 2007; 26: 364-366.
15. Frankenbuch K, Eifinger F, Kribs A, Rengelshauseu J, Roth B. Severe primary cutaneous aspergillosis refractory to amphotericin B and the successful treatment with systemic voriconazole in two premature infants with extremely low birth weight. J Perinatol 2006; 26: 511-514.
16. Muldrew KM, Maples HD, Stowe CD, Jacobs RF. Intravenous voriconazole therapy in a preterm infant. Pharmacotherapy 2005; 25: 893-898.
17. Woodruff CA, Hebert AA. Neonatal primary cutaneous aspergillosis: case report and review of the literature. Pediatr Dermatol 2002; 19: 439-444.
18. Perzigian RW, Faix RG. Primary cutaneous aspergillosis in a preterm infant. Am J Perinatol 1993; 10: 269-271.
19. Manzoni P, Arisio R, Mostert M, et al. Prophylactic fluconazole is effective in preventing fungal colonization and fungal systemic infections in preterm neonates: a single-center, 6-year, retrospective cohort study. Pediatrics 2006; 117: e22-e32.
20. De Pauw BE, Donnelly JP. Prophylaxis and aspergillosis-has the principle been proven? N Engl J Med 2007; 356: 409-411.