The Pediatric Infectious Disease Journal Publish Ahead of Print

DOI: 10.1097/INF.0000000000001136

Primary Cutaneous Aspergillosis in a Preterm Infant

Marie Antoinette Frick [1], MD, Hector Boix[2], MD, Fátima Camba Longueira[2], MD, M. Teresa Martin-Gomez[3], MD, PhD, José Ángel Rodrigo-Pendás[4], MD, and Pere Soler-Palacin[1], MD, PhD

[1]Pediatric Infectious Diseases and Immunodeficiencies Unit. Vall d´Hebron University Hospital, Barcelona, Spain.

[2]Neonatology Department. Vall d´Hebron University Hospital, Barcelona, Spain.

[3]Microbiology Department. Vall d´Hebron University Hospital, Barcelona, Spain.

[4]Preventive Medicine and Epidemiology Department. Vall d´Hebron University Hospital, Barcelona, Spain.

CORRESPONDING AUTHOR: Pere Soler-Palacín, MD, PhD. Pediatric Infectious Diseases and Immunodeficiencies Unit. Hospital Universitari Vall d'Hebron. Pg. de la Vall d'Hebron, 119-129. 08035 Barcelona. Spain. Telephone number: 0034934893140. Fax number: 0034934893039. Email address: psoler@vhebron.net

FUNDING: No sources of support to declare.

KEY WORDS: Aspergillosis, premature infant, voriconazole, drug toxicity.

ABBREVIATED TITLE: Neonatal Primary Cutaneous Aspergillosis

RUNNING HEAD: Cutaneous Aspergillosis.

DISCLOSURES: The authors have no conflicts of interest or funding to disclose.

ABSTRACT

Primary cutaneous aspergillosis (PCA) is rare in premature infants. It requires combined medical and surgical strategies. Amphotericin B is recommended as first line therapy, but salvage regimens with others antifungal agents, such as voriconazole, have been reported. Voriconazole´s pharmacodynamics is unknown in this population. We report a case of severe toxicity to voriconazole in a preterm patient with PCA.

INTRODUCTION

Premature infants have an increased risk of developing invasive fungal infection. In contrast to candidiasis, invasive aspergillosis (IA) and primary cutaneous aspergillosis (PCA) are rare in this population. In PCA, a prompt diagnosis and effective systemic antifungal treatment are essential to prevent invasive disease and decrease related mortality.[1] Use of voriconazole in neonates is limited to case reports where it has been used successfully as salvage therapy with no significant side effects, [2-3,4] but its precise role and appropriate dosage in this age group remain uncertain, and it should be used with caution as a second or third line agent with a strict control of the serum concentrations.[2,5] We report a case of PCA in a preterm infant, who developed severe voriconazole toxicity.

CASE REPORT

A male newborn was delivered at a tertiary-care hospital by caesarean section at 24 6/7 weeks' gestational age because of partial placental abruption. Birth weight was 550g. After neonatal intensive care unit (NICU) admission, the infant received surfactant for hyaline membrane disease, and conventional mechanical ventilation was established. Umbilical catheters were placed, and antibiotic therapy (ampicillin and gentamicin) and parenteral nutrition were started. On the following days, the patient´s condition worsened due to a patent ductus arteriosus and pulmonary hemorrhage, requiring ibuprofen and high-frequency oscillatory ventilation. Hyperglycemia, thrombocytopenia, neutropenia and anemia developed. Cultures were sterile, but antibiotics were continued because of the patient´s clinical situation. From birth, the infant's skin was noted to be very thin and vulnerable, and had several abrasions.

On day 4, two erythematous skin lesions with elevated edges, central ulceration and white-greyish exudate were observed at the cervical region (Figure 1). There was no history of probe placement or tape removal at this site. Superficial culture samples were collected, and vancomycin was added. The skin lesions extended, and on day 7 the patient´s respiratory condition worsened with hypoxemia and bibasal infiltrates on chest radiograph. A second dose of surfactant and a trial of inhaled nitric oxide were started to improve hypoxemia. *Aspergillus fumigatus* and *A. nidulans* were isolated on skin smear cultures. Serum galactomannan antigen was >10. A presumptive diagnosis of IA was established, and liposomal amphotericin B was initiated at 5mg/kg/day, with no clinical response. Fungal abscesses were not detected on abdominal or cerebral ultrasound imaging. Bronchoalveolar lavage and chest computed tomography were not performed because of the patient´s critical condition. Blood cultures were negative, but tracheal aspirate yielded *Klebsiella pneumoniae*. Cefotaxime was then started. Due to clinical worsening, intravenous voriconazole 3mg/kg/12h was added to the antifungal regimen on day 12, with previous normal renal and hepatic functions.

On day 14 the patient developed signs of shock, with kidney (urea 120mg/dL, creatinine 3.9mg/dL) and liver failure (up to AST 548UI/L, ALT 56UI/L). Cefotaxime was replaced by meropenem, inotropic agents were initiated, parenteral nutrition was discontinued and drug plasma levels were measured. Drug trough values were 30mcg/mL for voriconazole and 18mcg/mL for vancomycin. Because of these highly toxic serum concentrations, both drugs were discontinued. At this time, the skin lesions had considerably reduced in size.

From day 15 onwards the patient´s situation progressively deteriorated, with persistent renal impairment, elevated C-reactive protein (up to 26mg/dL), thrombocytopenia and anemia.

However, liver function normalized on day 18. Coagulase-negative *Staphylococcus* and *Enterococcus faecalis* were isolated from umbilical catheter tips.

On day 22, the infant´s condition worsened to multiorgan failure and death. At that time the fungal skin lesions had almost healed. There was no evidence of primary immunodeficiency. The postmortem study found intestinal perforation and hepatomegaly, but no evidence of IA. Coagulase-negative *Staphylococcus* and *E. faecalis* were isolated in liver and spleen biopsies, peritoneal, pleural and ascitic fluids, and blood culture.

Environmental samples obtained on day 8 from the NICU were negative. There had been no recent construction sites near the NICU. The air within the NICU was not HEPA filtered. No further cases of *Aspergillus* spp. infection were detected.

DISCUSSION

Premature infants have an increased risk of developing invasive fungal infection because of immunological immaturity as well as vulnerable epidermal layer. Other predisposing factors are hyperglycemia, systemic steroids, broad-spectrum antibiotherapy, long-term parenteral nutrition, neutropenia, underlying immunodeficiencies, prolonged hospitalization and construction sites near the NICU.[1,6-7] *Aspergillus* spp. are ubiquitous molds that can cause invasive infection in immunosuppressed patients, with the respiratory tract being the usual portal of entry. In long-term hospitalized patients, invasive catheters, venous arm boards, points of contact of adhesive tapes, abraded skin, and bedsores due to prolonged supine position provide cutaneous routes of entry.[1] *A. fumigatus*, *A. flavus* and *A. niger* are the most common species described in PCA.[6] Our patient had many of the reported predisposing factors for the development of PCA: prematurity,

vulnerable and abraded skin, neutropenia, broad-spectrum antibiotics, parenteral nutrition, central venous catheters, and endotracheal tube.

To date, about 20 cases of neonatal PCA have been reported (minimum gestational age 23 1/7 weeks, lowest birth weight 510g and age at onset, 5-35 days of life).[1,6-7] Surprisingly, our patient´s skin lesions were first noticed on day 4 of life, although they may have initiated earlier, as they were located on the back and the patient was in supine position. Thus, this is likely the earliest age of presentation described in the literature.

Management of PCA includes medical treatment and surgical interventions.[1] Amphotericin B is the drug of choice in neonates, although some resistant strains have been reported.[1,3] The lack of pharmacokinetic, pharmacodynamic, and safety data on newer antifungal agents in preterm infants reduces treatment options. Use of voriconazole in neonates is limited to case reports of PCA, IA and refractory fungal infections in preterm infants where it has been used as salvage therapy at doses ranging from 2mg/kg/12h to 4mg/kg/12h, with a favorable outcome and no significant side effects.[2-4,8] To date, there are no validated therapeutic ranges for voriconazole in neonates and premature infants. Given the lack of studies on appropriate dosage in this age group, voriconazole should be used with caution and be reserved as second or third line agent in this age group.[5] Dosage should be managed according to the clinical response and strict plasma levels monitoring, primarily to limit toxicity.[2,5-6,9]

In our patient intravenous liposomal amphotericin B was initiated after the diagnosis of PCA. But given the development of respiratory insufficiency, IA was then suspected. Chest computed tomography could not be performed, hence the diagnosis of probable IA based on the EORTC criteria could not be established.[10] Nevertheless, intravenous voriconazole was added to the

antifungal regimen at 3mg/kg/12h. As would be expected, both *Aspergillus* species isolated in our patient were susceptible to the two antifungal agents used.

The main side effects of voriconazole are elevated transaminases, visual disturbances, retinopathy in preterm infants, skin reactions due to photosensitization, and renal dysfunction resulting from accumulation of a solubilizing excipient, sulfobutylether-cyclodextrin, which is only present in the intravenous formulation.[2] Our patient developed severe renal impairment that did not improve even after stopping the nephrotoxic drugs and hepatotoxicity that reverted after discontinuing the drug and the parenteral nutrition. No other hepatotoxic drugs had been used. There were no drug interactions that could raise voriconazole plasma levels.

Our patient´s skin lesions healed without surgical resection. Other authors have reported successful nonsurgical treatment of PCA in neonates.[3,4] Preterm infants may not tolerate surgical debridement, especially if the lesions are extensive, and often they are too ill to undergo surgery.[1] In our patient, PCA lesions had almost completely resolved at the time of death; thus the antifungal therapy likely cured PCA and may have prevented its dissemination.

The role of galactomannan antigen testing in neonates is controversial. Our patient´s galactomannan value was high, which led to a suspicion of IA. However, post-mortem study showed no evidence of IA. The patient's death was presumably multifactorial (extreme prematurity, bacterial sepsis, severe renal dysfunction and intestinal perforation). Interpretation of galactomannan antigen findings in the neonatal population can be confusing, since false-positive results occur frequently due to *Bifidobacterium* spp. gut colonization, formula-milk feeding and use of beta-lactam antibiotics. In one study, galactomannan antigen monitoring was reported to be useful in a term newborn affected by bilateral renal aspergilloma, showing decreases as the patient improved and ultimate normalisation.[8] Serum PCR assays for

Aspergillus spp. may be more specific for IA detection in neonates than galactomannan antigen testing.

PCA usually occurs in isolated cases, although clusters due to contamination of incubator humidity chambers, non-sterile disposable latex gloves, or adhesive tapes have been reported.[9] Prompt source recognition and implementation of isolation precautions prevent its spread throughout the NICU. No contaminated specimens were detected in the NICU and no other cases occurred in our case.

In conclusion, PCA can occur in preterm infants, and it is important to rule out IA to decide the optimal antifungal regimen. Further studies are needed to establish the appropriate dosage and duration of voriconazole therapy and to determine the safety profile of the drug in neonates and particularly, in preterm infants. In situations where voriconazole is needed its serum concentrations should be closely monitored to avoid toxicity.

REFERENCES

1. Herron MD, Vanderhooft SL, Byington C, et al. Aspergillosis in a 24-week newborn: a case report. *J Perinatol*. 2003;23:256-259.
2. Watt K, Manzoni P, Cohen-Wolkowiez M, et al. Triazole use in the nursery: fluconazole, voriconazole, posaconazole and ravuconazole. *Curr Drug Metab*. 2013; 14:193-202.
3. Santos RP, Sánchez PJ, Mejías 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.
4. Frankenbusch K, Eifinger F, Kribs A, et al. 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.
5. Testoni D, Smith PB, Benjamin DK. The Use of Antifungal Therapy in Neonatal Intensive Care. *Clin Perinatol*. 2012;39:83-98.
6. Groll AH, Jaeger G, Allendorf A, et al. Invasive pulmonary aspergillosis in a critically ill neonate: case report and review of invasive aspergillosis during the first 3 months of life. *Clin Infect Dis*. 1998;27:437-52.
7. Papouli M, Roilides E, Bibashi E, et al. Primary cutaneous aspergillosis in neonates: case report and review. *Clin Infect Dis*. 1996;22:1102-1104.
8. Martinez-Pajares JD, Martinez-Ferriz MC, Moreno-Perez D, et al. Management of obstructive renal failure caused by bilateral renal aspergilloma in an immunocompetent newborn. *J Med Microbiol.* 2010;59:367-369.

9. James MJ, Lasker BA, McNeil MM, et al. Use of a repetitive DNA probe to type clinical and environmental isolates of *Aspergillus flavus* from a cluster of cutaneous infections in a neonatal intensive care unit. *J Clin Microbiol.* 2000;38:3612-3618.
10. De Pauw B, Walsh TJ, Donnelly IP et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis*. 2008;46:1813-21.

FIGURE LEGEND

Figure 1. Two erythematous skin lesions in the cervical region, with elevated edges, central ulceration, and white-greyish exudate.

Figure 1.