Primary Cutaneous Aspergillosis in Neonates: Case Report and Review

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A premature neonate (gestational age, 26 weeks) with multiple prematurity-related problems developed primary cutaneous aspergillosis due to Aspergillus fumigatus on the 30th day of life. The infection developed in an area that had been macerated by adhesive tape. During the infection, renovation of the hospital was in progress near the neonatal intensive care unit. The infection was cured with a short course of therapy with amphotericin B. Five cases of primary cutaneous aspergillosis in neonates have been previously reported in the English-language literature. We review these cases and discuss the risk factors and favorable outcome of the disease when treatment with amphotericin B is instituted.

Aspergillus species can cause serious invasive infections in immunocompromised patients [1]. Infections with Aspergillus species that are confined to the skin occur less frequently among such patients than do other aspergillar infections [2–4]. Neonates, especially those who are premature, are subject to infections with various organisms including fungi [5], presumably because of defects in phagocytic and T cell host defenses [6–8]. The vast majority of fungal isolates are Candida species, but Aspergillus species also cause systemic infections associated with a high mortality [9, 10]. We report a case of primary cutaneous aspergillosis (PCA) that developed in a very premature infant; the infection was cured with a short course of therapy with amphotericin B. In addition, we review the five cases previously reported in the English-language literature.

Case Report

A male neonate weighing 960 g was born after 26 weeks of gestation. Premature rupture of the membranes had occurred 4 days before his birth. He was transferred to the neonatal intensive care unit (NICU) of Hippokration Hospital (Thessaloniki, Greece), where he developed respiratory distress syndrome necessitating mechanical ventilation. On day 2 he developed pneumothorax that was treated by insertion of a chest tube, and on day 4 he developed convulsions that were treated with anticonvulsants. On day 13 he developed blood culture-negative sepsis, and on day 20 septicemia due to Staphylococcus aureus was diagnosed. Both infectious episodes were successfully treated with appropriate antibiotics. From day 16 to day 23, while being weaned from mechanical ventilation, he received dexamethasone (0.25–0.5 mg/[kg·d]).

On day 30, while he was in good condition and afebrile, he developed a red 0.5 × 0.5-cm area over his tibia, which rapidly increased in size and evolved into a dark-red plaque with slightly raised edges and pustules. His leukocyte count had been 9,000/mm³ with an absolute neutrophil count of 5,220/mm³ on day 23; these values increased to 13,500/mm³ and 8,235/mm³, respectively, on day 30. After careful disinfection of the area, the pustules were aspirated. A small quantity of purulent material was obtained; a gram stain of this material showed many neutrophils and dichotomously branched septate hyphae. No other organisms were visualized in the gram stain. Antifungal therapy with intravenous amphotericin B desoxycholate (dosage, 1 mg/[kg·d]) was initiated. Culture of the pus was subsequently negative for bacteria and yielded only Aspergillus fumigatus.

Findings on a tibial radiograph were normal, and a chest radiograph showed evidence of bronchopulmonary dysplasia without changes before, during, or after the episode of PCA. Cultures of blood and urine obtained on day 30 were negative. An ultrasonogram of the brain did not reveal any abscesses. During the preceding days, the cable of an oximeter had been fixed with adhesive tape to the area of the tibia where the lesion had appeared. Hospital-building renovation was in progress near the NICU at that time. Surveillance cultures of the oximeter, tracheal secretions from the neonate, and the tracheal-catheter tip were negative for fungi. The patient received a total of 6.7 mg/kg of amphotericin B uneventfully, and the lesion regressed and disappeared within 1 week. The involved skin remained discolored for ~3 weeks. The patient remains free of infection after 1 year.

Literature Review and Discussion

The diagnosis of PCA in this patient is strongly supported by the following findings: the presence of a typical skin lesion, similar to those that have been described previously; the appearance of dichotomously branched septate hyphae on a gram stain and growth of Aspergillus in a culture of the pus; the absence of other organisms in a stain and culture of the pus.
and the absence of clinical, radiological, and microbiological evidence of aspergillosis elsewhere. On the basis of these findings, we believe that the case does not represent colonization or another type of infection.

In our review of the English-language literature (with use of MEDLINE) and of the references in the reports that were found, we identified five cases of PCA in neonates; these cases had previously been published as isolated reports [2, 10–12]. A summary of the clinical and microbiological characteristics of these cases as well as data on treatment and outcome are shown in table 1.

Although relatively rare, PCA has been previously diagnosed in a number of adults and children [2–4]; for example, WALMSLEY et al. [2] reviewed 92 cases of PCA. Most of the patients have been immunocompromised, and PCA has been predominantly associated with skin breaks caused by medical aids (arm boards and adhesive tape) or intravascular catheters. In contrast, only five cases have been reported in neonates [2, 10–12] and of those, only one had been reported before 1992 [12]. This paucity of reports may be due not only to recent recognition of this entity but, possibly, to the increased frequency of delivery of low-birth-weight infants with impaired immunity and multiple infectious as well as noninfectious problems. Furthermore, the emergence of PCA correlates with an increased frequency of fungal infections in tertiary care hospitals where immunocompromised patients are treated [13].

While invasive aspergillosis has been well recognized as a serious infection in neonates—especially those who are premature [14]—the severity and prognosis of PCA have not been assessed, and the best treatment for the disease has not yet been defined. Although skin involvement can occur in both neonates and older immunocompromised patients with invasive aspergillosis [2], PCA is characterized by a lack of involvement of other organs, except the skin, at the time of diagnosis.

Air containing an increased number of Aspergillus conidia is probably the source of infection in most cases of PCA. This notion is supported by the fact that construction was in progress close to involved NICUs when PCA occurred in cases 4 and 6 (table 1), although surveillance cultures of air were not performed (or were not reported to be positive). Construction in hospital areas that are close to wards housing immunocompromised patients is a well-described risk factor for the acquisition of airborne Aspergillus conidia and infection among these patients [1]. In addition, invasion of skin by Aspergillus species following trauma induced by adhesive tape or bed sores was reported in all cases except for case 5 (table 1).

Prematurity was a universal feature of these neonates. Phagocytic host defenses are impaired during early infancy, particularly in preterm infants [6–8], and this may have been an additional risk factor for the development of aspergillosis in these patients. Most patients had been exposed to steroids at some point before birth or had received these drugs after birth; treatment with steroids, as well as neutropenia, are the major risk factors for developing invasive aspergillosis [1]. However, none of these patients were neutropenic, and only one patient, who had myocarditis, was receiving steroid therapy during the

| Table 1. Characteristics of neonates with primary cutaneous aspergillosis. |
|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| Patient no. [reference] | Gestational age (w/y/ sex) | Birth weight (g) | Age at onset of infection (d) | Prior antibiotics | Exposure to steroids | Other risk factors | Clinical presentation | Mode of diagnosis | Aspergillus species recovered | Treatment (total dose) | Outcome |
| 1 [12] | 26/F | 800 | 21 | Yes | NR | Maceration of skin by adhesive tape, bed sores | Slightly erythematous nodule with pustules | Stain, culture | A. fumigatus | AmB (60 mg/kg) | Cured |
| 2 [10] | 25/F | 785 | 6 | Yes | Antepartum | None | Large, dark crust with slightly raised, erythematous borders | KOH preparation, culture | A. fumigatus | None | Died |
| 3 [10] | NR/M | 670 | 7 | Yes | None | Before infection | Necrotic, edematous borders | Stain, culture | A. fumigatus | None | Died |
| 4 [11] | 27/M | 1,500 | 8 | Yes | Before infection | Presence of oximetry, plugging | Posture with erythematous margins | Stain, culture | A. fumigatus | AmB (16 mg/kg) | Cured |
| 5 [2] | NR/F | NR | 22 | NR | During infection | Necrotic, edematous borders | Culture | A. fumigatus | AmB (6 mg/kg) | Died |
| 6 [PR] | 26/M | 960 | 30 | Yes | Before infection | Maceration of skin by adhesive tape, construction near NICU | Dark red plaque with pustules | Stain, culture | A. fumigatus | AmB (6.7 mg/kg) | Cured |

NOTE. AmB = amphotericin B; NICU = neonatal intensive care unit; NR = not reported; PR = present report.

* Unrelated to aspergillosis.

† Patient had concomitant myocarditis.
course of the infection. Thus, the combination of prematurity-related immunodeficiency and direct (or indirect) exposure to air with an increased number of *Aspergillus* conidia appears to be the most likely cause of PCA in these neonates.

The clinical presentation of PCA has been reported for four cases. A necrotic plaque with pustules or pustules alone characterized PCA in three neonates. In one neonate the lesion was a fluctuant nodule with pustules on it. It has been suggested that a necrotic area on the skin (a plaque with an eschar and/or pustules) is characteristic of PCA, whereas a maculopapular eruption caused by thrombosis of small vessels is more characteristic of hematogenous dissemination to the skin [10]. It is noteworthy that all patients presented with some degree of cutaneous inflammation and subsequent necrosis.

On the basis of the cases reported so far, it is difficult to draw a definitive conclusion regarding appropriate therapy and the likely outcome of PCA. All three infants who survived had been treated with intravenous amphotericin B in total dosages that ranged from 6.7 mg/kg (present case) to 60 mg/kg (case 2, table 1); our patient, who was cured, received the lowest dose of amphotericin B. Among the three patients who died, one had not received any therapy (case 3), one had received 6 mg/kg of amphotericin B (case 5), and the third (case 1) had been treated only with resection of the lesion. The two patients who received treatment presumably died of unrelated causes including cardiac arrest during cardiac catheterization (case 1) and myocarditis (case 5). An autopsy was not performed on the patient who did not receive any therapy; thus, whether he developed disseminated aspergillosis is unknown [10]. It is unclear that resection of the involved skin is helpful, but it appears that this procedure was not required in most of the reported cases.

In the review by Walmsley et al. [2], 41 children were reported to have PCA. Among 39 of the patients who received treatment, 35 received a regimen containing amphotericin B. Only three of these patients were treated surgically, and one patient received nystatin. The cure rate was 59% (23 of 39 patients). For these patients, as for the neonates, it is hard to draw any conclusions or offer any recommendations regarding the treatment of PCA. Amphotericin B has been used to treat PCA in four of six infants as well as the majority of older children. Amphotericin B, alone or in combination with fluconazole, constitutes the mainstay of antifungal therapy for aspergillosis [3]. The therapeutic roles of the newer azoles such as itraconazole and of lipid formulations of amphotericin B have not been evaluated; however, in view of the nephrotoxicity of amphotericin B and the frequent renal impairment in premature neonates, it is important to determine the efficacy of these agents.

PCA has emerged as a potentially serious infection in premature neonates in NICUs. Because of the risk of dissemination, PCA should be treated vigorously with active systemic antifungal agents. With appropriate treatment, the outcome of PCA appears to be favorable.

References