Cutaneous Aspergillosis in Premature Baby: A Case Report

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ABSTRACT
Aspergillosis is a rare fungal infection in premature infants that may cause extensive tissue destruction, sepsis and subsequent multi-organ failure. 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 described a preterm neonate, who developed excessive skin lesions due to primary cutaneous aspergillosis. This paper provides the clinical presentation, diagnostics and discusses the latest for the treatment of primary cutaneous aspergillosis.

Key words: Aspergillosis, Liposomal amphotericin B, Premature.

Introduction
Neonates, especially those who are premature, are at high risk to infections with various organisms including fungi.\(^1\) Probably due to defects in phagocytic and T cell host defenses.\(^2\)

The prevalence of invasive fungal infections is increasing in very low birth weight (VLBW) infants (< 1500g), as more infants born at the youngest gestational ages survive past the immediate postnatal period.\(^3\) Although aspergillosis is rare in neonates, it poses a major threat due to high morbidity and mortality rates and ineffective or untested antifungal therapies in this population.\(^4-6\)

The usual portal of entry for Aspergillus is respiratory, however, in hospitalized patients; invasive catheters provide routes of entry leading to cutaneous or invasive aspergillosis.\(^7\) Mechanical disruption of the epidermal integrity of the infant either by local trauma or maceration by heat appears to be a prerequisite for primary cutaneous aspergillosis (PCA).\(^8\)

Case Report
A 24 week gestation male, weighing 680 gms, was born to a 20 year-old female G2P1. Prenatal screening for Chlamydia and hepatitis B was negative and group B Strep (GBS) was unknown. Mother arrived in emergency room in preterm labor with spontaneous rupture of membrane (SROM). One dose of Betamethasone was given to the mother 1.5 hours prior to delivery. Also she was given one dose of Ampicillin prior to delivery. At delivery, infant had Apgar scores of 1, 5 and 6 at 1, 5 and 10 minutes, respectively.

Infant was transported to neonatal intensive care unit (NICU). He was placed on mechanical ventilation. Curosurf was given via endotracheal tube (ETT). Umbilical artery catheter (UAC) was placed and also a peripheral inserted central catheter (PICC) was placed. Ampicillin and Gentamicin was started. Result of blood culture was negative.

Infant was transferred on day 3 of life to level 3 NICU due to unilateral grade IV intraventricular hemorrhage (IVH), Spontaneous intestinal perforation (SIP) and PDA ligation. On day of life (DOL) 4, Gentamicin was discontinued due to renal insufficiency and Cefotaxime was started. On DOL 6 kidneys, ureters and bladder (KUB) radiograph showed free air, Penrose drain
placed at bedside. Later that day, left scapular abrasion appeared cultured and growing gram-positive cocci. There was no history of probe placement or tape removal at this site. Antibiotics switched to Vancomycin/ Azithromycin for leukocytosis. Fluconazole was added for SIP- as SIP is frequently associated with systemic candidacies.

On day 15 of life, lesion increased in size 1x1cm, now with pink central portion with raised black borders, had deeply infiltrated the tissue and progressed to necrotic lesions in few days (Fig. 1). Punch biopsy was performed and it was positive for Aspergillus fumigates. Liposomal Amphotericin B was initiated. Fungal urine culture, fungal culture of abdominal drainage and fungal culture around umbilicus done, all were negative. Abdominal US was done searching for fungal balls - abscess? .On day 20 of life Azithromycin and Vancomycin was discontinued (d/c). Tracheal fungal culture due to blood ET secretions was negative.

DOL 22 premature developed large air leak. Blood culture, blood sample aspirated from PICC for culture and urine culture all were negative. Meropenem/ Vancomycin were started for persistent abnormal bowel loops, antibiotics stopped after 72 hours. At one month of life, infant seen by ophthalmologist, no fungal eye involvement was noted.

On DOL 33 fungal lesion was decreased in size - currently 1x1cm. Because the risk of CNS infection was low, no antifungal coverage for potential CNS infection was required, and also the risks of additional antifungal outweigh the benefits. On day 36 of life septic work-up was done due to metabolic acidosis, oliguria, and hypotension. Antibiotics (Vancomycin and Cefotaxime) were started. The result of blood culture (PICC and peripheral) was negative so antibiotics stopped. We were unable to obtain suprapubic or catheter sample for the urine.

At age of 38 days of life, new skin lesion appeared but no fungal elements seen by punch biopsy.

At age 44 days of life, Vancomycin/Gentamicin was started for septic evaluation. WBC was 6.7 with 0 bands, CRP was 1.1. BCx/sputum and urine culture showed no growth.

At age 46 days of life, lumbar puncture was performed due to tachycardia of uncertain etiology, result of CSF showed: glucose 66, protein 157, WBC 1, CSF gram stain was negative, CSF Bacterial/Fungal cultures also was negative and antibiotics were stopped. At age of 47 days of life, sepsis evaluation was done again due to concerns for tachycardia, blood, urine and tracheal culture were taken and CBC, CRP was done. Vancomycin and Tobramycin were started. CRP result was 0.9, WBC was 6 and all cultures were negative after 48 hrs, so antibiotics were stopped.

At age of 51 days of life Aspergillus lesion were resolved with no scarring or pigmentation. The neonate continued to receive Amphotericin x2 until day 66 of life. He was discharged at age of 122 days with good general condition.

Discussion

Aspergillus fumigates accounts for more than 90% of all invasive aspergillosis cases(9). Cutaneous aspergillosis can be either primary or secondary as a part of a disseminated aspergillosis. Secondary cutaneous aspergillosis can be seen in 5–10% of all cases of disseminated aspergillosis.(10)

Primary cutaneous aspergillosis increased in frequency, due to increased frequency of delivery.
of very low-birth-weight infants with impaired immunity. The most important factor predisposing towards infection in the case we presented was prematurity.

Primary cutaneous aspergillosis (PCA) is characterized by a lack of involvement of other organs, except the skin, at the time of diagnosis. In contrast to other fungal infections such as candidiasis, fungal blood cultures for Aspergillus are negative in 75% of the cases.(11)

Our patient was presented with primary cutaneous aspergillosis, which was confirmed by biopsy. Cultures of blood, cerebrospinal fluid, sputum as well as the trachea failed to grow any fungus, so there was no evidence of systemic aspergillosis in this case.

Although skin involvement can occur in neonates and older immunocompromised patients with invasive aspergillosis, air containing an increased number of Aspergillus conidia is probably the source of infection in most cases of PCA. Walmsley reviewed 39 cases of PCA, most of the patients were immunocompromised, PCA was predominantly associated with skin breaks caused by medical aids (arm boards and adhesive tape) or intravascular catheters.(12)

Stock reported severe cutaneous aspergillosis in a premature neonate linked to non sterile disposable glove contamination.(13)

In one study(14) primary cutaneous aspergillosis was associated with Hickman intravenous catheters contrast.

In our case, skin lesions were confined predominantly to the back, and were not located at sites of skin trauma or where occlusive dressings or tapes were in place. Singer(15) present four pre-term neonates who succumbed to cutaneous aspergillosis that subsequently developed into a systemic infection. The source of the infection proved to be contaminated latex fingerstalls.

In study of Etienne, humidity chambers of the neonates’ incubators used in the NIC was the suggestive source of aspergillosis infection.(16)

The origin of the infection in our premature patient is unknown.

Most premature infants had been exposed to steroids at some point before birth or had received these drugs after birth-as in our premature patient; treatment with steroids, as well as neutropenia, are the major risk factors for developing invasive aspergillosis.(17)

Primary cutaneous aspergillosis clinically is characterized by the presence of violaceous macules, papules, haemorrhagic bullae, ulcerations with central necrosis, and pustules or subcutaneous abscesses.(18)

The cutaneous lesions of our premature patient appeared as erythematous eruptions, had deeply infiltrated the tissue and progressed to necrotic lesions in few days. 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.(4)

Early clinical recognition of PCA infection and effective systemic antifungal agents are vital, because of the risk of dissemination. Stock presented a case of PCA complicated with invasive aspergillosis in an extremely preterm infant.(19)

Ophthalmological examinations should be performed in preterm infants with fungal infection in order to detect possible fungal endophthalmitis.(20)

At one month of life, our infant was seen by ophthalmologist, fortunately there was no fungal eye involvement.

Voriconazole has become the new standard of treatment in invasive aspergillosis.(21)

Voriconazole seems to be a safe antifungal drug that can be used in newborns. Advantages include oral route of administration with wider spectrum of coverage without the renal and platelet lowering side effects. Also there is a significant cost advantage over liposomal amphotericin B.(22)

However, the lipid formulations of amphotericin B are considered to be the choice of treatment if the diagnosis of invasive aspergillosis is established.(23-25)

Our premature patient was successfully treated with intravenous amphotericin B.

Surgical therapy may be necessary for the treatment of localized Aspergillus infection.(26)

However, infants, especially preterm infants, may not tolerate surgical resection, especially if cutaneous lesions are extensive.

In the review by Walmsley et al.(12) 39 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). Fortunately, in our premature lesion was completely healed without surgical intervention.

Conclusion
Because of the risk of dissemination, it is vital to note that PCA is a serious infection in premature neonates in NICU. The incidence of primary aspergillosis is going to increase. Early clinical recognition of Aspergillus infection and effective systemic antifungal agents are necessary to decrease the mortality due to aspergillosis.

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References
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