Primary cutaneous aspergillosis at the site of cyanoacrylate skin adhesive in a neonate

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Abstract
Primary cutaneous aspergillosis is a rare but potentially life-threatening disease. We present the case of a premature infant who developed primary cutaneous aspergillosis with Aspergillus niger at the site of a skin abrasion that had been treated with a purple-colored cyanoacrylate product. The infection was treated successfully with gentle debridement of the cyanoacrylate product, followed by intravenous voriconazole and topical fluconazole. To our knowledge, this is the first reported case of primary cutaneous aspergillosis occurring at the site of cyanoacrylate-based skin adhesive.

KEYWORDS
infection, neonatal, skin barrier, therapy

1 | INTRODUCTION

Skin infections caused by Aspergillus species can be primary or secondary. In primary cutaneous aspergillosis, spores from the air directly infect skin that has been weakened or damaged in some way. This form of cutaneous aspergillosis is most commonly seen at intravenous catheter insertion sites, burns, and surgical wounds and has been reported at sites covered by tape or occlusive dressings. In secondary cutaneous aspergillosis, the fungus enters the skin through hematogenous dissemination, usually from a primary organ or soft tissue source. The appearance of Aspergillus skin lesions varies widely and can present as inflamed erythematous macules; necrotic papules or nodules; and less commonly, hemorrhagic bullae, ulcers, and thrombosis.1,2

2 | CASE REPORT

A premature boy, born at 35 weeks and 2 days (birth weight 2800 g) via cesarian section for intrahepatic cholestasis of pregnancy, was admitted to the neonatal intensive care unit (NICU) because of respiratory difficulty and low Apgar scores. The NICU was situated in a newly opened hospital building, although no obvious construction activity was noted during the patient’s hospitalization. At birth, he was noted to have a large, erythematous abrasion involving the right upper back related to birth trauma. A cyanoacrylate liquid skin protectant was applied to the abraded area.
cyanoacrylate glue, which resulted in purple discoloration, limited assessment of color and detail. The examining dermatologist felt that it was unlikely that the plaque was due to birth or resuscitation-related trauma and raised concern about vascular malformation, kaposiform hemangioendothelioma, fat necrosis of the newborn, or deep fungal infection. The NICU team was instructed to cease application of the cyanoacrylate skin protectant and perform serial photography of the lesion. Magnetic resonance imaging and magnetic resonance angiography showed no evidence of a high-flow vascular lesion.

Over the next week, the patient’s abrasion initially appeared to improve, with a decrease in erythema and areas of sloughing, but he developed a new black, necrotic, circular lesion measuring 1 by 1 cm within the affected area (Figure 2). Dermatology was reconsulted, and the decision was made to proceed with a punch biopsy, given suspicion of fungal infection. Tissue culture of the punch biopsy sample showed 2+ colonies of *Aspergillus niger*. Blood cultures and serum galactomannan assay were negative. Bacterial cultures and Gram stain were negative. The patient was started on intravenous voriconazole and topical ketoconazole cream for 6 days and then transitioned to oral voriconazole. Plastic surgery gently debrided the eschar and remaining glue. The skin lesion demonstrated consistent improvement (Figure 3), with a decrease in erythema and resolution of necrosis, and the patient was discharged on oral voriconazole with close outpatient follow-up.

3 | DISCUSSION

For serious cutaneous infections by *Aspergillus* species to occur, at least 3 conditions must be met: disruption of skin integrity, immune dysfunction, and exposure to *Aspergillus* spores. The overwhelming majority of infants who develop primary cutaneous aspergillosis were born prematurely, which is the chief cause of immune dysfunction in this group. In utero, the stratum corneum does not fully develop until approximately 34 weeks of gestation. As a result, the epidermal barrier of infants born at <34 weeks of gestation is particularly weak and susceptible to disruptions in integrity.

At any age, there is a known association between foreign bodies—usually occlusive dressings, bandages, or tape at catheter sites—and cutaneous aspergillosis. Skin maceration, the deterioration of skin with prolonged exposure to moisture, such as the sweat that gathers beneath occlusive dressings, may explain this association.

In a 2016 review of primary cutaneous aspergillosis in all age groups, 49.2% of all cases reported in the literature were associated with a foreign body. In this analysis, approximately half of cases of primary cutaneous aspergillosis in neonates were also associated with a foreign body. None of the 130 cases were associated with cyanoacrylate skin adhesive at the site of infection, and to our knowledge, there has never been a report of cutaneous aspergillosis occurring at the site of cyanoacrylate application.

Cyanoacrylates are a large class of chemical adhesives originally developed in the United States during World War II and include the active agents in super strength, instant adhesives and in new products that have been developed as skin adhesives. Cyanoacrylate-based skin adhesives are believed to protect against maceration and subsequent wound infection by bonding tightly to the stratum corneum. Most cyanoacrylate glues dissolve in...
acetone (nail polish remover), but results vary from product to product. There are many cyanoacrylate-based skin adhesives available in the United States (eg, DermaBond, SurgiSeal, 3M Cavilon, and Medline Marathon Liquid Skin Protectant), and most contain n-2-butyl-cyanoacrylate or 2-octyl-cyanoacrylate. Although aimed at health care providers, most skin adhesives in this class can be easily purchased online, and use by caregivers and patients has become more common.

At least one study has shown 2-octyl cyanoacrylate skin adhesive to have antimicrobial properties against gram-positive bacteria, and multiple studies have shown lower rates of surgical site infection with superficial cyanoacrylate closures than with traditional closure techniques such as staples and sutures. Cyanoacrylate tissue adhesives should not be used in tension-bearing wounds, hairy areas, crush wounds, areas of high moisture, or wounds at high risk of infection. They should be used with great caution in individuals at high risk of wound infection such as those with diabetes, vascular disease, and prolonged steroid use. Logically, premature infants would fall into this category given their poor skin integrity and immature immune system, even though there are no specific manufacturer- or regulatory body-issued contraindications to use in premature infants. Cyanoacrylates have been successfully used for surgical wound closure in extremely low-birthweight preterm infants, but outside of small trials and unusual cases, use of cyanoacrylate tissue adhesive in neonates and infants has been poorly studied, and further study is needed to determine its appropriate role in wound management in this population.

The clinical presentation of primary cutaneous aspergillosis is known to vary widely, and in infants, a diverse array of lesion types and body sites have been described. The most commonly involved body areas are the back, thighs, and upper extremities. Much as in other age groups, many of the reported cases of primary cutaneous aspergillosis in infants presented as erythematous papules or plaques with central necrosis. The illusion of violaceous color that the cyanoacrylate product created, which was overlaid on the abraded skin and obscured the true diagnosis before the development of a necrotic eschar, is a novel aspect of our case. The cyanoacrylate product, whose use has not been well studied in neonates, impaired visualization of the underlying skin and may have promoted fungal growth in a manner similar to occlusive dressings. Further clinical experience with such products is needed to determine whether this was the case.

One trend that this case illustrates is that real-world management of primary cutaneous aspergillosis has changed from amphotericin B to voriconazole in recent years. The Food and Drug Administration approved voriconazole for the treatment of invasive fungal infections in May 2002. Voriconazole has a favorable adverse effect profile, with mostly reversible adverse effect, including visual disturbance, transaminitis, and cholestasis, as opposed to amphotericin B, which is associated with fevers, chills, hypotension, arrhythmias, intravenous phlebitis, anemia, and nephrotoxicity. In the Global Comparative Aspergillus Study, a trial of 277 individuals aged 12 and older with suspected or confirmed invasive aspergillosis, those randomized to voriconazole were found to have 29% mortality, compared with 42% mortality in the amphotericin group, and were more likely to have a clinical response to voriconazole.

In conclusion, primary cutaneous aspergillosis is a rare disease that premature infants may be predisposed to because of their immature skin barrier and immune system. Given wide variability in clinical presentations, diagnosis is not always straightforward. Delayed diagnosis of cutaneous aspergillosis risks death or permanent disability, so a high index of clinical suspicion in vulnerable groups can be life saving. Occlusive dressings and catheters are known to be associated with primary cutaneous aspergillosis, and given their prolonged adherence to skin, cyanoacrylates may carry a higher risk. Studies on the use of cyanoacrylate skin protectant use in premature infants are lacking. Until the risks of cyanoacrylate use in premature infants are better understood, providers should use these products cautiously, bearing in mind that they should not be used on infected skin and that any product that bonds to the skin prevents accurate visualization of what lies beneath.

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REFERENCES

