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Diagnosis and Treatment of Cutaneous Aspergillosis

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Aspergillosis is an opportunistic mycosis caused by fungi in the genus *Aspergillus*, mostly *A. fumigatus* and *A. flavus*. Typical entry portals in primary cutaneous aspergillosis include burns, trauma sites, surgical wounds, intravenous catheters, and macerated skin in underlying occlusive dressings. In individuals who are immunocompromised, the dissemination risk is significant. Skin findings range from firm papules and necrotic papulonodules to hemorrhagic bullae and ulcers. The prognosis is poor but improves when the patient is no longer neutropenic or when corticosteroids are discontinued. Localized primary cutaneous aspergillosis can be excised surgically, followed by oral antifungal administration. For the first-line treatment of pulmonary invasive aspergillosis, isavuconazole and voriconazole are the preferred agents, whereas liposomal amphotericin B is supported moderately.

Key Words: Aspergillosis, Cutaneous aspergillosis

INTRODUCTION

Several studies have been conducted to elucidate the multiple aspects of pulmonary and invasive aspergillosis in patients who are immunocompromised; however, only a few reports are available on primary cutaneous aspergillosis. Aspergillosis is an opportunistic infection that is caused by fungi in the genus *Aspergillus*, mostly *A. fumigatus* and *A. flavus*. Several host factors and clinical conditions are associated with aspergillosis, including (1) neutropenia, immunosuppression, immunodeficiency, or structural lung disease for invasive pulmonary aspergillosis and (2) burns, sites of trauma, surgical wounds, intravenous catheters, and macerated skin in underlying occlusive dressings as entry portals in primary cutaneous aspergillosis. The prognosis could be poor; thus, clinicians should be aware of this disease. This study aimed to briefly describe the definition, skin findings, histologic examination, prophylaxis, and treatment of cutaneous aspergillosis.

DEFINITION

Cutaneous aspergillosis is defined as a skin infection caused by fungi in the genus *Aspergillus*[1] and is categorized into primary and secondary cutaneous aspergillosis. Primary cutaneous aspergillosis presents skin lesions without visceral involvement, whereas in secondary cutaneous aspergillosis, the conidia are inhaled, resulting in a primary lung infection followed by dissemination to the skin. Most aspergillosis cases are *Aspergillus* infection of the lungs, and cutaneous aspergillosis is considered an opportunistic infection[2,3]. Therefore, disseminated secondary cutaneous aspergillosis accounts for most cutaneous aspergillosis, and cutaneous aspergillosis cases are rarely reported in patients who are immunocompetent[4,5]. Patterson et al. and D'Antonio et al. reported cutaneous involvement of invasive aspergillosis in 5% and 4% of cases, respectively[6,7].

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SKIN FINDINGS

As previously explained, cutaneous aspergillosis is considered an opportunistic infection. Thus, secondary cutaneous lesions are well documented, which result from contiguous extension of infected underlying structures to the skin or widespread blood-borne skin embolism[4,8]. Host factors, such as neutropenia, allogeneic hematopoietic stem-cell transplantation, long-term use of immunosuppressants, and immunodeficiency are important in secondary cutaneous lesion development. Skin lesions appear as scattered erythematous macules or papules that evolve to hemorrhagic bullae or ulcerative nodules because of the infected internal organs' dissemination[9], which often develop as an eschar in time[10]. Hematogenously disseminated embolic lesions may occur because of the *Aspergillus* organism's angiotropic nature[10]. Primary cutaneous aspergillosis arises from either direct physical inoculation, such as a penetrating wound or occlusive dressing site of a wounded skin[11]. Primary cutaneous lesions usually develop in patients with burns, trauma sites, surgical wounds, intravenous catheters, and macerated skin[12]. Some patients are immunocompetent, but patients with underlying risk factors, such as malignancies, organ transplantation, and congenital or acquired immunodeficiency syndrome, were also reported[13,14]. Some cases were reported in infants who were premature[15,16]. Additionally, onychomycosis caused by *Aspergillus* was also reported[17]. According to this article, the clinical presentation of onychomycosis was nonspecific, but a distal-lateral pattern was commonly observed[17]. The reports show that skin manifestations of primary cutaneous aspergillosis vary from macules, papules, nodules, or plaques to pustules[10]. Among neonates, lesions occurred with purulent discharge[16,18]. Infection of the paranasal sinuses was also reported as another clinical presentation[19,20]. This study states that in the inoculated type, the primary lesion develops from macule or papule to nodule or granulated tissue, whereas in the wounded skin type, superficial spreading natured macerated and ulcerative lesion. Additionally, host factors are also important because dissemination occurs easily in patients who are immunocompromised.

HISTOLOGIC EXAMINATION

Histologic examination of lesions of cutaneous aspergillosis includes the following: (1) 45° dichotomous branching of hyaline hyphae; (2) septate hyphae best demonstrated with methenamine silver or PAS staining; (3) suppurative and granulomatous inflammation and/or necrosis; and (4) striking tendency of the fungal hyphae to invade large and small arteries and veins, causing inflammation, thrombosis, and infarction. Inflammation is dominant in the superficial dermis with or without subcutaneous fat layer sparing in primary cutaneous aspergillosis cases. Contrarily, the epicenter of inflammation in the secondary cutaneous aspergillosis tends to be solely in the deep dermis or subcutaneous fat layer[13].

PROPHYLAXIS

For aspergillosis prevention, prophylactic antifungals are commonly administered to patients undergoing chemotherapy and hematopoietic stem-cell transplantation, both before and during neutropenic periods. Additionally, a patient with febrile neutropenia who is unresponsive to broad-spectrum antibiotic therapy might empirically receive voriconazole, posaconazole, or one of the echinocandins[21].

TREATMENT

Nowadays, isavuconazole and voriconazole are the preferred agents for the first-line treatment of invasive aspergillosis[21,22], whereas liposomal amphotericin B is moderately supported[21]. However, the cutaneous aspergillosis treatment guideline is currently unavailable. Localized primary cutaneous aspergillosis can be excised surgically, followed by oral antifungal administration. In this study, disseminated cutaneous aspergillosis was treated appropriately according to invasive aspergillosis. Voriconazole or isavuconazole treatments for severe primary cutaneous aspergillosis were reported[15,16]. Until recently, itraconazole treatment case reports of patients with primary cutaneous aspergillosis who are immunocompetent are reported[5,23].

CONCLUSION

In patients with this disease, invasive aspergillosis is the major cause of death; thus, dermatologists should be aware of its cutaneous findings. There is limited information on the prevalence, diagnosis, and treatment of primary cutaneous aspergillosis and onychomycosis caused by *Aspergillus*, only case reports or small case series in the literature. This study therefore suggests a preliminary classification as presented in Table 1. Further studies are needed to find the optimal treatment for invasive and primary cutaneous aspergillosis.

Table 1. The study's preliminary suggestion of cutaneous aspergillosis classification

Type	Risk factors	Skin findings	Treatment
Primary (Inoculated)	Injury Catheter	Macule Papule Nodule Granulation tissue	Amphotericin B Itraconazole
Primary (Wounded)	Burn Trauma Surgical wound Neonate	Superficial spreading erosive patch Ecthyma gangrenosum Hemorrhagic bulla	
Secondary (Disseminated)	Neutropenia Allo-HSCT Immunosuppressants Malignancy Congenital immunodeficiency Structural lung disease	Sporotrichoid nodules Embolic Ulceration Necrosis Eschar	Isavuconazole Voriconazole

CONFLICT OF INTEREST

In relation to this article, I declare that there is no conflict of interest.

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