RESIDENT’S FORUM

Multiple erythematous nodules with a necrotic center in a patient with acute lymphoblastic leukemia

Case report

A Taiwanese man 20 years of age presented with neutropenic fever, dyspnea, and generalized skin eruptions after receiving chemotherapy for the management of acute lymphoblastic leukemia (Figure 1A). The chemotherapy regimen was given for 6 months but discontinued due to the profound pancytopenia, in which the absolute neutrophil count (ANC) was below 100/mm³. Multiple discrete painful skin eruptions started to develop 2 months later. The initial presentation of skin lesions was multiple tender erythematous papules to subcutaneous nodules carrying a necrotic center (Figure 1B), in which bullae and crusted ulceration developed progressively (Figures 1C and D). Skin biopsy showed numerous acute angle branching septate hyphae within dermal blood vessels resulting in vascular occlusion (Figures 2A and B). Concurrently, chest radiography revealed reticulonodular opacities in the bilateral lung. The patient was treated with oral voriconazole 200 mg twice a day and intravenous micafungin 100 mg once a day for 3 weeks according to the results from micro-organic culture of both sputum and skin specimen. However, the general condition including neutropenia and dyspnea were not reversed. He eventually died due to sepsis with respiratory failure.

Figure 1 (A) Generalized skin eruptions over the trunk and extremities; (B) red patches in the early stage and erythematous nodules with a necrotic center in the late stage; (C, D) progression to bullae and eschars in the end stage.
Diagnosis

Disseminated fusariosis.

Discussion

Both skin-tissue and sputum culture revealed the growth of *Fusarium* spp. (Figure 2C), whereas the blood culture showed negative finding. *Fusarium* is a filamentous fungus found naturally on plants and in the soil. The most common *Fusarium* species associated with human infection are *F. solani*, *F. oxysporum*, and *F. moniliforme*. In immunocompeptent patients, infections may develop over the skin defect resulting from trauma, burns, insect bites, or foreign body implantations. Disseminated fusariosis mainly occurs in severely immunocompromised hosts and manifests cutaneous involvement in up to 70% of cases. Nasal sinuses are the other source for disseminated *Fusarium* infection. Fusariosis is one of the leading fungal infections in victims with hematologic malignancies, preceded by candidiasis and aspergillosis.

Localized cutaneous infections shown in immunocompetent patients may display various clinical manifestations including nonspecific papules, plaques, pustules, ulcers, or cellulitis in addition to onychomycosis. The presentation of generalized erythematous papulonodular lesions in a neutropenic and febrile patient not responding to extensive antibiotic treatment is highly suggestive of disseminated fungal infections, such as the fusariosis found in our case. Typically, the cutaneous lesions of disseminated fusariosis are concurrently shown at different stages of development, such as multiple papules, subcutaneous nodules, target-like lesions, and ecchyma gangrenosum-like lesions, where the associated necrotic centers are related to the vascular invasion by fungi. Hemorrhagic bullae or subcutaneous abscess may also occur.

The histopathologic examination of skin lesions revealed acutangle branching and septated hyaline fungal hyphae, which invaded dermal blood vessels and resulted in thrombosis. The aforementioned pathologic findings are corresponding to the clinical feature of necrotic centers shown in cutaneous lesions. The histopathologic features of angioinvasion shown by *Fusarium* resemble to those of aspergillus and *Scedosporium*, among others. The definitive diagnosis is dependent on the isolation of organism from skin biopsy specimen or blood culture. Different from aspergillosis, disseminated fusariosis can be diagnosed by blood culture in 40% patients. Although our case revealed a negative result from the blood culture, the reported rate of positive blood culture is nearly 60% in the presence of disseminated cutaneous fusariosis.

*Fusarium* species are resistant to many antifungal agents such as itraconazole, ketoconazole, fluconazole, caspofungin, and micafungin. Therefore, the standard treatment is not well documented. Liposomal amphotericin is usually the treatment of choice and the combination with voriconazole has been reported as a successful treatment for the resistant strain. Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor may exhibit clinical benefits by reducing the duration of neutropenia. However, the mortality rate in refractory neutropenic patients is nearly 100%.

Prolonged neutropenia, acute graft-versus-host disease, glucocorticoid administration, and bone marrow transplantation from an human leukocyte antigen (HLA)-mismatched donor are the risk factors for disseminated fusariosis. Disseminated fusariosis is a life-threatening disease whose prognosis is mostly dependent on the immunity of patients. Unfortunately, the outcome of neutropenic patients with fungemia is still poor despite the availability of new antifungal agents. Cutaneous lesions usually precede fungemia and may serve as clues for the early detection of disseminated fusariosis in most patients. Therefore, dermatologists should be aware of these characteristic clinical features and provide adequate management in the early stage for patients who are immunocompromised.

References