Coexistence of Fatal Disseminated Invasive Aspergillosis and Pyoderma Gangrenosum: A Case Report

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Key Words

Aspergillosis • Pyoderma gangrenosum • Ulcerative skin

Abstract

Objective: To report an unusual case of disseminated aspergillosis involving the lymph nodes, lungs, and skin in a patient with pyoderma gangrenosum (PG) and myelodysplastic syndrome (MDS). **Case Presentation and Intervention:** A 46-year-old man presented with productive cough of 2 weeks' duration. Besides, several painless, fixed lymph nodes were palpated at his left neck. He had PG and MDS diagnosed in June 2004 with regular use of oral dapsone and prednisolone. His skin lesions healed with scar formation and no purulent discharge. A computed tomography scan of the head, neck and chest showed bilateral lung consolidation and abscesses at the left neck, right upper lung and right pleura. The neck abscess culture grew *Aspergillus* species. Dark reddish macules developed over the right arm, chest and abdominal wall, and the left lower limb 2 weeks after initiation of amphotericin B. The histology of the right arm skin biopsy showed invasive aspergillosis. Caspofungin was started then for suspicion of poor response to amphotericin B. He expired despite 35 days of antifungal therapy. **Conclusion:** This report highlights the rarity of coexistence of disseminated aspergillosis and PG, and should alert physicians to the possibility of invasive fungal infection superimposed on a chronic skin lesion.

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Introduction

Invasive aspergillosis is a rapidly progressive, often fatal infection in immunocompromised patients, including those who have a malignancy, received bone marrow or solid organ transplants, and patients with long-term steroid use or profound neutropenia [1–3]. Cutaneous aspergillosis may be a cutaneous manifestation of disseminated or deep tissue infection with presentation as an area of rapidly increasing erythema with a necrotic, often ulcerated center. The diagnosis needs to be confirmed by a skin lesion biopsy for both microbiologic culture and histopathology [4, 5]. Pyoderma gangrenosum (PG) is a rare cutaneous disease and often begins as an inflammatory nodule or pustule with gradual peripheral enlargement. Myelodysplastic syndrome (MDS) is a heterogeneous group of closely related clonal hematopoietic disorders characterized by ineffective blood cell production or dysplasia and risk of transformation to acute myelogenous leukemia. The coexistence of PG and disseminated aspergillosis is very rare, and it is difficult to differentiate the skin lesions unless the histology is known [5, 6]. Herein, we report a rare case of disseminated aspergillosis involving the lymph nodes, lungs, and skin in a patient with PG and MDS.

Fig. 1. **a** Initial presentation of facial skin lesions: PG. **b** The neck was swollen with erythematous plaque-like lesions. **c, d** Nodular cutaneous aspergillosis over the chest wall and right upper arm. A lesion had been excised during biopsy, and residual sutures were present.

Case Report

A 46-year-old man was diagnosed to have MDS (refractory anemia with excess blasts-2) and PG in June 2004. The diagnosis of MDS was confirmed by bone marrow biopsy, and the initial presentations were thrombocytopenia and anemia. The hematologist did not suggest any treatment for MDS at this stage. The patient initially presented with left facial ulcerating and necrotizing lesions in March 2004, which subsequently progressed to skin defects and necrosis in the left cheek and inferior eyelid. Extensive necrotizing fasciitis was impressed first and he received 4 times debridement for his facial lesions. However, his wounds failed to heal and additional necrosis and pustules began to overlie the surface even after several reconstruction and skin graft surgeries. In addition, the original donor skin site on his left inguinal area began to show necrosis that mimicked his facial lesions. The pathology of his facial skin biopsy revealed massive, nonspecific neutrophilic infiltration, hemorrhage and necrosis of the overlying epidermis. PG was diagnosed based on his histopathological findings, clinical presentation, and poor response to antimicrobial therapy and repeated surgical debridement. Oral prednisolone (60 mg per day) was initiated in May with gradual tapering to 10 mg a day over 6 months. Oral dapsone (100 mg per day) was then coadministered. His skin lesions began to heal gradually with scar formation and no purulent discharge (fig. 1a).

On 1st December 2004, he was admitted to the Infectious Diseases Ward for cough with purulent sputum of 2 weeks' duration when he was still on prednisolone (10 mg per day) and dapsone (100 mg per day) therapy. On admission, he appeared fair with a respiratory rate of 22 breaths/min. Other vital signs and physical examination had no remarkable findings. The white blood cell count was $17.7 \times 10^9/l$ with a differential of 78% neutrophils, 3%

lymphocytes, 4% metamyelocytes, and 15% monocytes. Platelets were $35 \times 10^9/l$ and serum C-reactive protein level was 141 mg/dl (normal, <5 mg/dl). The wounds on the left side of his face and inguinal areas had no pustules and were clean grossly. The chest X-ray disclosed several consolidations at the left lung. He initially received intravenous cefuroxime 0.75 g every 8 h a day. Generalized bone pain, dyspnea, fever up to 38.3°C and progressive enlargement of left neck lymph nodes developed 3 days after admission. The left neck lymph nodes were painless and fixed, and the largest one was about 3 cm in diameter with 6 overlying erythematous to violaceous plaques (fig. 1b). Mild tenderness of the largest lymph node developed 2 days after onset of fever. A computed tomography (CT) scan of the head, neck and chest showed bilateral lung consolidation and abscesses on the left side of the neck, the right upper lung and right pleura. Ultrasound-guided left neck abscess aspirate on the 8th hospital day grew *Aspergillus* species, and amphotericin B (50 mg per day) was started 2 weeks after admission. The neck abscess enlarged progressively to 4 cm in diameter and an ultrasound-guided drainage was done on the 17th hospital day. After 2 weeks of amphotericin B treatment, dark reddish macular rash with progressive swelling appeared over the right arm (two sites, largest one about 3×5 cm²), anterior chest wall (five sites, largest 2×2 cm²), abdomen and left lower limb (several sites, sizes varying from 2×2 to 3×5 cm²) (fig. 1c, d).

The pathology of the right arm skin biopsy on the 41st hospital day revealed cutaneous ulceration with many branching, septate hyphae invading blood vessels, which was confirmed to be invasive aspergillosis with involvement of the vessels, deeper skin and connective tissue (fig. 2), and later the tissue culture from the same site yielded *Aspergillus* species. Amphotericin B was discontinued on the 44th hospital day, with an accumulated dosage of 1.5 g totally. Intravenous ceftriaxone 2 g per day and caspofungin

Fig. 2. Hematoxylin and eosin staining of a biopsy taken from the right forearm showing many branched, septate hyphae invading blood vessels.

50 mg per day were started on the 45th hospital day for suspicion of superimposed bacterial infection and poor response to amphotericin B due to his progressive downhill, malaise and progressive exacerbation of thrombocytopenia. He did not survive the disseminated invasive aspergillosis and finally expired after 35 days of antifungal therapy.

Discussion

We have described a rare case of PG and MDS coexisting with disseminated aspergillosis involving the lungs, lymph nodes and skin. The long-term steroid use in such a case with MDS and PG might be a predisposing factor of deep fungal infection. The culture of the neck abscess and the skin pathology afforded the microbiological and histopathological clues for diagnosis of disseminated aspergillosis. Notably, the patient's first clinical sign of pulmonary aspergillosis was seen on a CT scan after the onset of his skin manifestations. Cutaneous aspergillosis is

relatively rare and poorly characterized [1, 3, 7] and it is hard to differentiate from PG while presenting with areas of rapidly expanding erythema with necrotic and ulcerated skin centers [5, 6]. The erythematous maculae might become purpuric and rapidly progress in size, with subsequent development to hemorrhagic, necrotizing ulcers. The skin pathology was the mainstay to make a definite clinical diagnosis [5, 8, 9].

PG is a rare, inflammatory, noninfective and non-neoplastic skin disorder that is often associated with systemic diseases, such as inflammatory bowel disease, rheumatoid arthritis or hematological malignancy. Up to 50% of patients have some variants [8, 10]. The cause of PG remains obscure, although bacterial infection is believed not to be related to it, which makes the term pyoderma redundant [8]. Our patient had a stable course of PG under maintenance therapy with oral dapsone and prednisolone. The hospitalization course and the skin biopsy pathology did not favor the recurrence of PG.

The efficacy of antifungal therapy for invasive aspergillosis has been extremely poor. As reported by Patterson et al. [3], a favorable response was seen in fewer than 40% of patients, and the overall mortality rate was nearly 60% [9]. Our patient had an indolent, progressively fatal course despite prompt amphotericin B therapy. Alternative options to traditional amphotericin B treatment may be considered if clinical response is not satisfactory. The alternatives include high-dose liposomal amphotericin B, echinocandins, or the newer azole drugs, such as itraconazole or voriconazole [11]. Caspofungin has been shown to be efficacious during empirical antifungal therapy for

neutropenic patients or severely ill patients with refractory invasive *Aspergillus* infections and invasive candidiasis [12].

Conclusion

This report highlights the rarity of coexistence of disseminated aspergillosis and PG, and should alert physicians to the possibility of invasive fungal infection superimposed on a chronic skin lesion. Early skin biopsy is advised for early diagnosis.

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