

## Case Report

# Isolated cutaneous aspergillosis in an acute lymphoblastic leukemia patient after allogeneic stem cell transplantation

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### Abstract

Cutaneous aspergillosis is very rare and occurs predominantly in immunocompromised patients including transplant recipients. We report a 26-year-old male with acute lymphoblastic leukemia who developed cutaneous aspergillosis after undergoing combined immunosuppressive treatment including corticosteroid, cyclosporine A, mycophenolate mofetil and mesenchymal stem cells for steroid refractory skin acute graft versus host disease after myeloablative haematopoietic stem cell transplantation. The patient was treated with oral voriconazole therapy and recovered partially.

**Key words:** haematopoietic stem cell transplantation; graft versus host disease; mesenchymal stem cells; cutaneous aspergillosis

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### Introduction

Invasive fungal infections (IFI), most frequently caused by *Aspergillus* spp. and *Candida* spp., are significant causes of morbidity and mortality in haematopoietic stem cell transplantation (HSCT) recipients [1]. IFI have two peaks after HSCT; the first high-risk interval is between conditioning and engraftment, and the second period is during the late post-transplantation period when patients are on immunosuppressive therapy or suffer from graft-versus-host disease (GVHD) [2]. Although invasive aspergillosis (IA) is a well-defined infection in lung and sinuses, cutaneous aspergillosis is a rare form of a locally invasive disease [3-4]. Cutaneous aspergillosis has been described as either a primary or a secondary infection in immunocompromised patients, including neonates, individuals with cancer, stem cell and solid organ transplant recipients, and burn victims [5- 10]. We report a patient with acute lymphoblastic leukemia (ALL) who had undergone allogeneic HSCT and developed primary cutaneous aspergillosis (PCA) on day +143, during cyclosporine A and corticosteroid treatment for acute graft versus host disease (aGVHD).

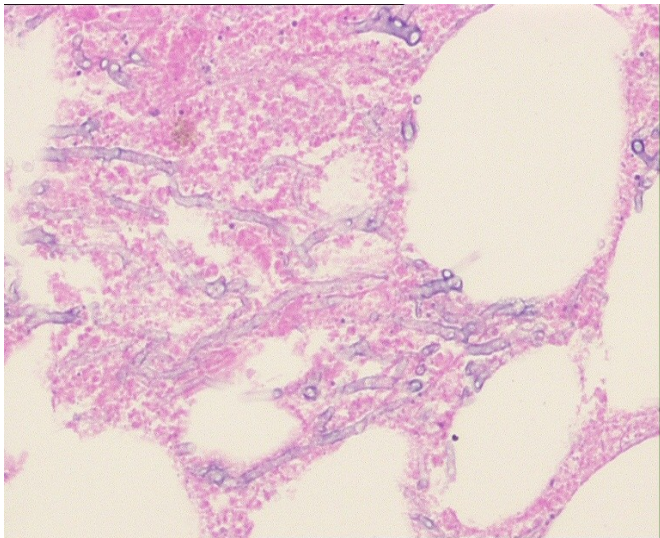
### Case history

A 26-year-old man with the diagnosis of T cell ALL underwent myeloablative allogeneic HSCT from an HLA-matched related donor in second complete remission. The conditioning regimen consisted of total body irradiation (TBI) with a total dose of 12 Gy and cyclophosphamide 120 mg/kg. He received cyclosporin A and long-term methotrexate as GVHD prophylaxis. He developed acute overall grade II skin GVHD on day +28 after HSCT, which was refractory to combined immunosuppressive treatment with cyclosporine A (CsA), mycophenolate mofetil (MMF) and corticosteroids. He received mesenchymal stem cells from the original donor on day +94 for corticosteroid refractory skin GVHD and achieved complete response with this protocol. He received intravenous immunoglobulin monthly after HSCT due to hypogammaglobulinemia. On day +128 he developed his second cytomegalovirus (CMV) reactivation and received valgancyclovir treatment. MMF and corticosteroid were gradually discontinued on days +90 and +142 respectively. Shortly after discontinuation of corticosteroids, on day +143 he developed fever with positive peripheral blood culture for *Escherichia coli*. He remained febrile under Ertapenem despite negative control blood

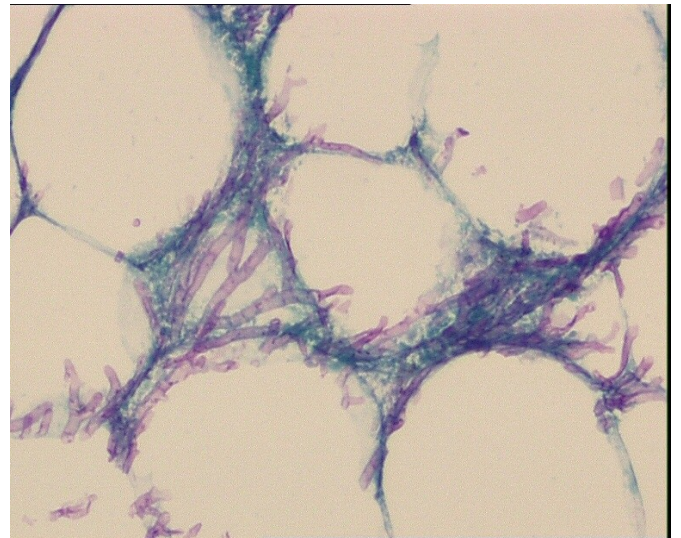
**Figure 1.** Skin lesion with the dimension of 3x2 cm



**Figure 2.** Histologic findings are consisting with aspergillus which branched and having septa formation. (HEx 400)



**Figure 3.** Histologic findings are consisting with aspergillus which branched and having septa formation. (LGP, x400)



cultures and CMV PCR analysis. He developed ecchymotic nonulcerated nodular skin lesions with dimensions of 1 x 2 cm on the upper third of the left leg and 3 x 2 cm on the distal third of the right tibia (Figure 1). On day +162, due to skin lesions and fever unresponsive to antibacterial treatment, the nodule on the upper leg was removed surgically for diagnosis. We refrained from surgically removing the second nodule on the distal tibia because of anatomic difficulties. Histological examination of the skin biopsy revealed cutaneous aspergillosis, which was confirmed by branched *Aspergillus* hyphae with septa formation in deep dermis and subcutaneous adipose tissue that was detected with positive light green PAS (LGP) staining (Figures 2 and 3). Unfortunately, it was not microbiologically investigated because at first sight it was considered to be the primary disease involvement. The patient was not on antifungal treatment prior to the diagnosis of PCA. Infections of sinuses and pulmonary cavities were excluded by paranasal computerised tomography (CT) and high-resolution CT of lungs. In our institution we monitor the levels of galactomannan antigen, pan fungal PCR, and *Aspergillus* PCR weekly in patients using steroids for early diagnosis of IFI. However, we found no positive results for this patient both prior to and after the diagnosis of PCA. Multiple blood cultures were negative for bacterial and fungal etiology. After the loading dose he was started on voriconazole 4 mg/kg per day orally. He is still on oral voriconazole treatment with partial response of the nodular lesion on distal tibia.

## Discussion

Invasive aspergillosis is a life-threatening infection in immunocompromised patients. PCA occurs relatively less frequently and is poorly characterized. Bone marrow transplant recipients are at risk for developing PCA [1,3]. PCA generally involves sites of skin injury, burns, surgery, intravenous access catheter sites, sites associated with occlusive dressings, or sites of traumatic inoculation [3].

Invasive aspergillosis in immunocompromised patients is a diagnostic challenge to clinicians. Clinical symptoms and signs are usually nonspecific as with most infections brewing up in an immunosuppressed host. Severe GVHD and its immunosuppressive treatment, such as high-dose steroids, also predispose patients to invasive aspergillosis. The immunosuppressive effect of mesenchymal stem cells, prolonged neutropenia, or

marked macrophage dysfunctions that occur as a result of disease and its treatment or complication might as well cause IA [11,12].

Primary cutaneous aspergillosis may manifest with papules, multiple nodules sometimes purplish in colour, plaques which may ulcerate and form a central eschar, or haemorrhagic bullae. In the case of nodular lesions, such a polymorphic clinical picture requires differential diagnosis with respect to recurrence of the primary hematological diseases [1].

Secondary lesions can resemble ecthyma gangrenosum, traditionally caused by *Pseudomonas aeruginosa*. Embolic lesions occur in approximately 11% of patients with disseminated aspergillosis, similar to the 10% to 13% incidence of skin lesions seen among patients with disseminated candidiasis [11].

The hyphae of *Aspergillus* have a relatively characteristic size (3-6  $\mu$ m) and morphology (septate with progressive arboreal and dichotomous branching). It may sometimes be difficult to distinguish from *Fusarium* and *Pseudallescheria boydii* (both of which are also septate and branch at acute angles in histological sections). Histological examination is necessary because it shows invasion of tissues and demonstrates the pathogenicity of the mycete; however, diagnosis of primary cutaneous aspergillosis must also be based on culture [1].

The treatment approach to cutaneous aspergillosis generally depends on the underlying status of the patient. Although itraconazole has been used successfully as a first-line treatment for nodular primary cutaneous aspergillosis, for secondary cutaneous aspergillosis, or extensive primary cutaneous disease, intravenous amphotericin B and surgical therapy should be considered [11]. However, itraconazole has recently been marketed in Turkey and it was not available in our hospital at that time so voriconazole was initiated based on its demonstrated efficacy over amphotericin B in the treatment of aspergillosis [13]. As the presence of secondary cutaneous lesions reflects disseminated infection, therapy with systemic voriconazole (A-I) was recommended as primary therapy. Surgical intervention, particularly for primary cutaneous infection, may be useful. Biopsy culture could be the mainstay confirmation of mycological diagnosis as it is very important to exclude other potential pathogens (*e.g.*, *Fusarium* species and Zygomycetes) [4,14,15]. It was not cultured, however, at first sight as it was

considered that the lesion was caused by the primary disease involvement of the disease itself.

Every skin lesion in immunocompromised patients should be carefully examined for the possibility of infections. Cutaneous aspergillosis should be considered in the differential diagnosis of a rapidly growing lesion with an area of central necrosis in an immunocompromised host. These skin lesions might occur as the first clinical manifestation of disseminated disease. Early diagnosis and rapid initiation of systemic effective anti-fungal treatment for cutaneous aspergillosis is important for successful outcome in immunocompromised patients.

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