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Case report/Cas clinique

Voriconazole associated mucormycosis in a patient with relapsed acute lymphoblastic leukemia and hematopoietic stem cell transplant failure: A case report

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ABSTRACT

The patients with hematologic malignancies and hematopoietic stem cell transplantation (HSCT) recipients are at high risk for invasive fungal diseases (IFDs) mainly due to the severe and prolonged neutropenia related to high-dose chemotherapy. Voriconazole prophylaxis is recommended for possible IFDs. Mucormycosis is a fulminant infection, which may occur after voriconazole prophylaxis for invasive aspergillosis in immunocompromised hosts. Here, we report mucormycosis after 4 months of voriconazole prophylaxis in a young patient with relapsed acute lymphoblastic leukemia and hematopoietic stem cell transplant failure and discuss the clinical manifestation, imaging, laboratory findings and therapeutic regimens. Clinician's awareness of this entity and timely diagnosis using conventional and molecular methods are the promising approach for the management of this devastating infection.

1. Introduction

Mucormycosis is a fulminant infection, which almost always affects immunocompromised hosts. Oncology patients, solid organ transplantation (SOT) and hematopoietic stem cell transplantation (HSCT) recipients are at high risk for invasive fungal disease (IFD) mainly due to the severe and prolonged neutropenia related to high-dose chemotherapy and immunosuppressive drugs [1]. Due to increasing incidence of cancer, an increase in nosocomial mucormycosis is reported. Nosocomial mucormycosis has been linked with immunosuppressive drugs [2,3], prolonged use of intravenous catheter [4,5], antifungal prophylaxis [6,7], bandages [8] during the past two decades. Besides, there are some reports of mucormycosis after dental extraction associated with uncontrolled diabetes [9]. Recently, an increase in incidence of mucormycosis has been reported linked to the voriconazole prophylaxis in many centers for control of invasive aspergillosis [10]. Here, we report mucormycosis associated voriconazole prophylaxis in a hematopoietic stem cell transplantation recipient for acute lymphoblastic leukemia and discuss the clinical manifestation, imaging, laboratory findings and therapeutic regimens.

2. Case report

In May 2015, an 18-year-old man was admitted to Imam Khomeini Hospital in Sari with signs and symptoms of anemia, such as pallor, fatigue, dizziness and dyspnea. Investigations

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revealed anemia, thrombocytopenia and leukocytosis. On physical examination, splenomegaly was observed. Acute lymphoblastic leukemia (ALL) diagnosis was established by bone marrow biopsy. ALL was in remission after 12 sessions of chemotherapy; he underwent bone marrow transplantation and received acyclovir, oral fluconazole (200 mg/day) and ciprofloxacin as prophylaxis. The graft failure occurred by day 43 after transplantation and he received re-induction chemotherapy and prednisolone (75 mg, 5 days per month) for the relapse of ALL.

In December 2016; 2 months after graft failure; he was admitted to Imam Khomeini Hospital with the complaints of high-grade fever and profound neutropenia. The fever continued despite of broad spectrum antibiotics and he developed dyspnea and hemoptysis. Serum galactomannan assay was negative. Chest computed tomography (CT) scan revealed multiple nodules with halo signs consistent with invasive pulmonary aspergillosis (IPA). Paranasal sinuses CT was normal (the images are not shown). The patient had been treated by broad-spectrum antibiotics and amphotericin B deoxycholate according to possible IPA (CT-scan-based). The treatment response was favorable and therapy was continued for 3 weeks. The patients discharged with oral voriconazole as prophylaxis (200 mg/kg twice a day) until the last admission.

In June 2017, he admitted again with the complaints of maxillary sinus pain, necrotic ulcerations on the palate, bloody nasal discharge, fever, chills, weakness, lethargy and difficulty in swallowing. He has received the 29th session of chemotherapy for second relapse of ALL. Laboratory exam revealed neutropenia ($0.1 \times 10^3/\mu L$), thrombocytopenia ($22 \times 10^3/\mu L$) and severe anemia (HGB: 7.4 g/dL; RBC: $2.58 \times 10^6/\mu L$). In chest computed tomography (CT) scan, multiple focal area in bilateral parenchymal consolidation with surrounding ground glass opacity were seen. Another conglomerate consolidation with surrounding irregular rim of opacification (reverse halo sign), with extension to visceral pleura in anterior segment of left upper lob had suggested the diagnosis of pulmonary metastasis, Wegener's granulomatosis, mucormycosis and septic embolus. In paranasal sinus CT scan, osteomeatal complex (OMC) obstruction, diffuse mucosal, thickening with soft tissue attenuation in maxillary sinus, ethmoid air cell with nasal cavity, pterygopalatine fossa involvement and lamina papyracea destruction revealed consistent acute sinusitis (Fig. 1). In brain MRI, the cortex, white matter, brain stem, cerebellum, basal ganglia, internal capsule and corpus callosum (thalamus) showed no abnormality, just mild generalized cortical atrophy, mucosal thickening with enhancement at the all paranasal sinuses were seen (Fig. 2).

On the first day of clinical diagnosis of rhinocerebral mucormycosis, treatment was started with liposomal amphotericin B, vancomycin and meropenem. Surgical debridement of the necrotic tissues of hard palate was postponed to the 3rd day of the last admission because of sever thrombocytopenia. Microscopic examination of the debrided tissues demonstrated right angle branching and broad aseptate and sparsely septate hyphae (Fig. 3), consistent with mucormycosis, although cultures showed no growth. For accurate identification of the causative fungi, DNA extracted from the infected tissues and aspirates and then

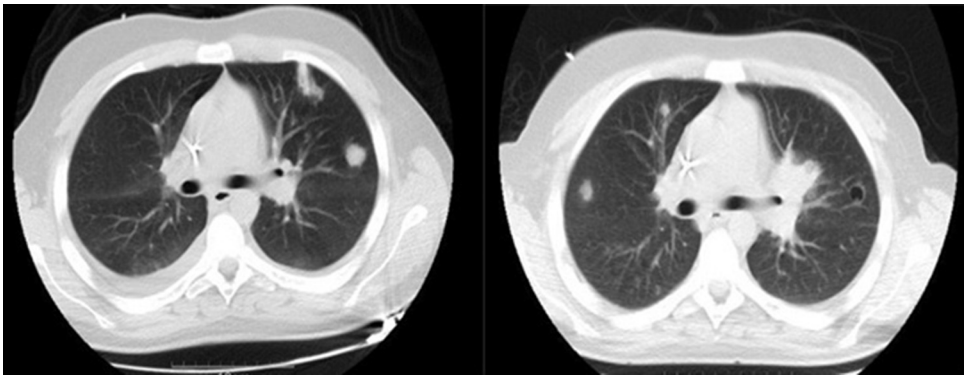

Fig. 1. chest computed tomography (CT) scans showing multiple pulmonary speculate nodules (MPN) in upper right lobe, well-defined 10 mm cysts contain air (air cyst) and hilar opacified acinar nodule 48mm × 46 mm diameter in the left upper lobe accompanying pleural effusion.

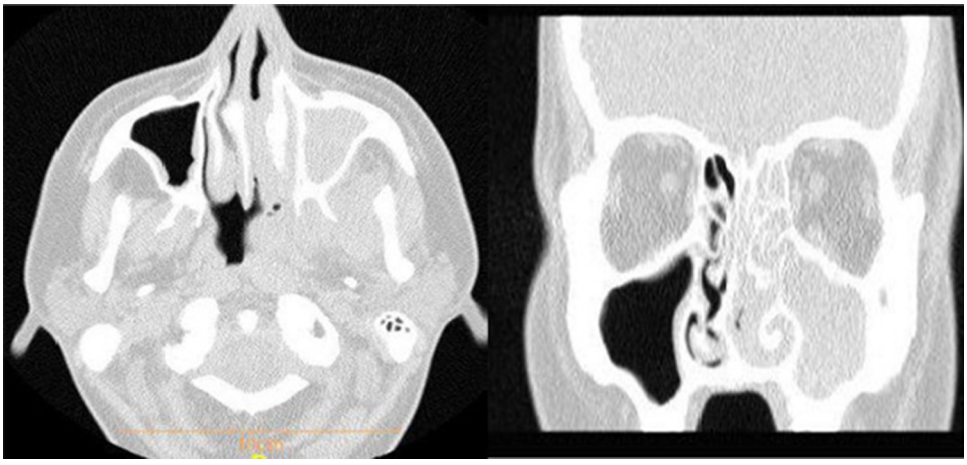

Fig. 2. In sinus CT scan, osteomeatal complex (OMC) obstruction and diffuse opacification of the left paranasal sinuses and mild mucosal thickness of right maxillary and sphenoid sinuses were revealed that consistent acute sinusitis.

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