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Case report

Invasive sinus aspergillosis with acute myeloid leukemia: A case report

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ABSTRACT

Invasive fungal sinusitis is still a life-threatening infection in immunocompromised patients. Its onset is rapid and leads to severe complications. We describe a neutropenic patient with acute myeloid leukemia who developed invasive sinus aspergillosis despite receiving prophylactic itraconazole and empirical micafungin. The patient demonstrated apparent clinical findings such as nasal discharge, nasal congestion, and skin and mucosal necrosis. Computer tomography scans strongly demonstrated invasive maxillary sinusitis. Serological examinations for (1-3)-β-D-glucan and *Aspergillus* galactomannan antigen were positive, suggesting *Aspergillus* infection. The diagnosis of invasive sinus aspergillosis was confirmed by *in situ* hybridization using *Aspergillus*-specific probe in formalin-fixed, paraffin-embedded tissue samples. The causative organism was identified as *Aspergillus fumigatus* by fungal culture. Despite surgical treatment with drainage and intensive antifungal administration of voriconazole and liposomal amphotericin B, the infection rapidly disseminated to the lungs, resulting in a fatal progression of the condition.

1. Introduction

There is now growing evidence that invasive and systemic fungal infections are becoming major causes of morbidity and mortality among immunocompromised patients, such as patients with hematological malignancies and transplant recipients [1,2]. Furthermore, despite prophylactic and empirical antifungal treatment, the emergence of breakthrough invasive fungal infections caused by theoretically sensitive organisms as well as resistant organisms has raised serious concern in immunocompromised patients, who show a poor prognosis [3–5].

Invasive fungal sinusitis has increasingly been recognized as a life-threatening fungal infection in patients with hematological malignancies [6–10]. Although there is a wide range of causative pathogens, *Aspergillus* species account for most cases of invasive fungal sinusitis [6–10]. Cases of invasive sinus aspergillosis (ISA) in both adult and pediatric patients have been reported in the literature (Table 1) [7–9]. The prognosis of patients with ISA depends on the underlying disease, the stage of infection, and anti-fungal management, with the fatality rate ranging from 28.6% to 88.1% [9–11]. Early diagnosis and aggressive therapy are critical to achieve optimal therapeutic results [6–11]. In general, the early signs and symptoms of ISA are subtle, and the disease must be distinguished from bacterial infection [6–9]. Although the definitive diagnosis of invasive aspergillosis is based on histological and cultural evidence of *Aspergillus* infection, fungal culture runs the risk of growth failure and is time-consuming [9,10]. Serological tests for the detection of (1-3)-β-D-glucan and *Aspergillus* galactomannan antigen have been developed for the early diagnosis of invasive aspergillosis [12,13]. In addition, a preliminary molecular diagnostic method based on *in situ* hybridization in tissue sections has been found to be more useful than culture-based diagnosis for the rapid and accurate diagnosis of invasive aspergillosis [14]. Treatment should include resection of the infected tissue in conjunction with intensive treatment with systemic antifungal agents [6–11]. However, even with such aggressive therapy, patients with ISA may not be curable when the infection is diagnosed at the advanced and late stages.

We describe a patient with acute myeloid leukemia (AML) who developed breakthrough ISA due to *A. fumigatus* at the advanced stage and disseminated pulmonary aspergillosis, underscoring the importance of early diagnosis in combination with surgical management and systemic antifungal therapy.

2. Case report

On February 17, 2009, a 69-year-old man with relapse of AML was admitted for reinduction chemotherapy (enocitabine, idaru-

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Table 1
Summary of data for previously reported cases of ISA.

Reference (number of cases)	Signs and symptoms	Serological examinations	X-ray examination	Biopsy	Anti-fungal treatments Surgical treatments
7 (5)	Nasal congestion Facial swelling Sinus pain Nasal necrosis	Negative *Aspergillus* galactomannan antigen	Positive findings including CT and MRI	Positive histology Positive culture	VRCZ and AMPH-B Surgery and drainage
8 (3)	Nasal congestion Nasal discharge Eyelid edema Headache	N.D.	Positive findings including CT	Positive histology Positive culture	AMPH-B Surgery
9 (12)[a]	Nasal congestion Sinus pain Periorbital swelling Nose ulceration	N.D.	Positive findings including CT	Positive histology Positive culture	AMPH-B Surgery (9 of 12 cases)

Note: AMPH-B, amphotericin B; VORZ, voriconazole; N.D., not done.
[a] Twelve of 17 patients with invasive mold sinusitis developed ISA.

bicin, and etoposide). On day 13 after admission, the patient was placed on itraconazole (ITCZ; 200 mg po q.d.) for antifungal prophylaxis because of a dramatically decreased leukocyte count (100 cells/μl: 0% neutrophil). On day 23, the patient was febrile and unresponsive to antimicrobial treatment with panipenem and amikacin. Due to persistent fever and marked neutropenia, empirical antifungal treatment of micafungin (MCFG; 150 mg iv q.d.) was started combined with ITCZ. On day 29, the patient was referred

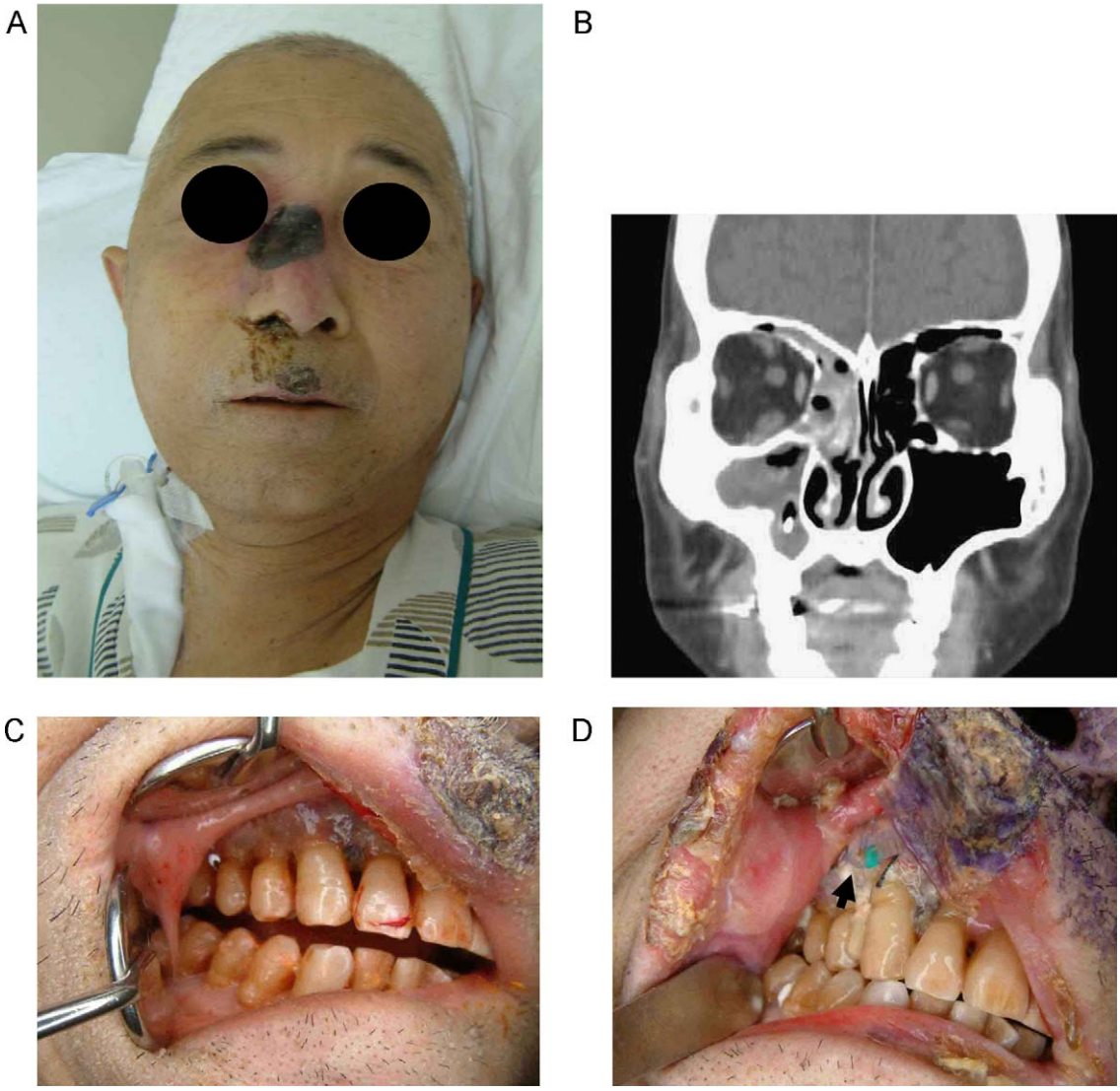

Fig. 1. Oro-facial and CT findings. (A) Photograph showing a black necrotic crust on the right root of the nose, facial swelling and nasal discharge. (B) CT scan of the face demonstrated a dense area within the right maxillary sinus and invasion of the ethmoidal sinus, eroding the bone. (C) Photograph of the right upper gingiva covered with a gray, necrotic pseudomembrane. (D) Post-surgical photograph showing the Penrose drain (arrowhead) in the surgical wound and some necrotic alveolar bone.

to the Department of Dermatology because he complained of right nasal pain and facial erythema. The skin lesion was biopsied and histopathological examination of HE-stained tissue sections demonstrated inclusion bodies in epidermal cells suggesting a viral infection of the skin. The serum level of (1-3)-β-D-glucan was slightly elevated (12.8 pg/ml; normal value <11 pg/ml).

On day 39, the patient was referred to the Department of Oral Surgery because a black necrotic crust rapidly developed at the right root of the nose and caused facial swelling; in addition, he complained of severe right buccal pain, nasal congestion, and nasal discharge (Fig. 1A). Computer tomography (CT) scans demonstrated a destructive lesion in the maxillary sinus that invaded the ethmoidal sinus, but there was no intracranial involvement (Fig. 1B). Oral examination demonstrated a wide destructive ulcer in the right maxillary mucogingiva, which was covered by a gray, necrotic pseudomembrane (Fig. 1C). His serum had a high concentration of (1-3)-β-D-glucan (54.2 pg/ml) and was positive for *Aspergillus* galactomannan antigen (4.9 ng/ml; normal value <0.5 ng/ml), strongly suggesting ISA. His leukocyte count was 200 cells/μl (10% neutrophils) and his platelet count was 22,000 cells/μl. On day 41, antrotomy of the maxillary sinus and debridement of the necrotic gingiva were performed under local anesthesia with platelet infusion. The lateral portion of the sinus wall and soft tissue was necrotic. After the necrotic tissues were removed, a Penrose drain was placed for washing and instilling antifungal drugs into the surgical wound area (Fig. 1D). Fungal hyphae were found in a 10% KOH preparation of the tissue sample, supporting the diagnosis of ISA. Both MCFG and ITCZ were discontinued and the patient was started on voriconazole (VRCZ; 200 mg po b.i.d.) combined with liposomal amphotericin B (L-AMPH-B; 150 mg iv q.d.) for ISA. The patient was also subjected to sinus rinses with AMPH-B (1 mg/ml diluted in distilled water) once a day as part of his post-surgical care. On day 43, histopathologically, Grocott-stained tissue sections showed organisms with dichotomously branched septate hyphae at acute angles, supporting the diagnosis of ISA (Fig. 2A). On day 45, the hyphae in tissue sections were identified as *Aspergillus* species by *in situ* hybridization [14] using a highly specific DNA probe for *Aspergillus* species, thereby confirming the ISA (Fig. 2B). Tissue culture on Sabouraud's dextrose agar yielded fungi that were morphologically identified as *A. fumigatus* on day 53.

On day 55, the patient was still febrile and complained of persistent cough. The level of (1-3)-β-D-glucan dramatically increased to 364.1 pg/ml, and the serum was positive for *Aspergillus* galactomannan antigen. Thoracic high-resolution CT scans demonstrated several nodules (Fig. 3A) and a dense, cavitating infiltrate with halo sign in the lower lobes of both lungs (Fig. 3B), suggesting invasive pulmonary aspergillosis. On day 65, the oro-facial necrotic area showed gradual improvement due to daily systemic administration of VRCZ and L-AMPH-B in addition to sinus rinses with AMPH-B. There were no symptoms suggestive of intracranial invasion. In addition, the level of (1-3)-β-D-glucan decreased to 254.6 pg/ml.

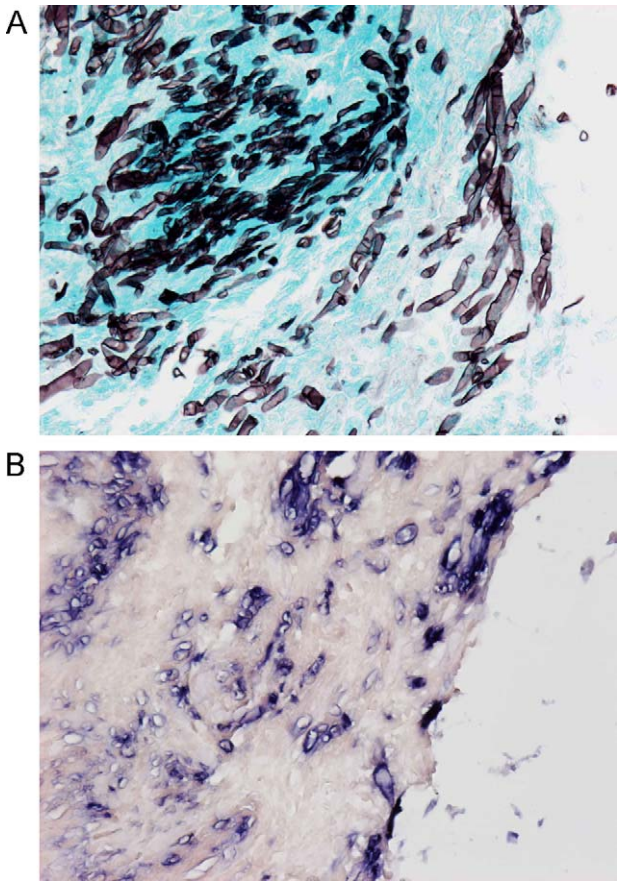

Fig. 2. Histopathological findings of necrotic sinus tissue. (A) Grocott staining showing the branching septate hyphae (magnification 100×). (B) *In situ* hybridization using an *Aspergillus*-specific DNA probe revealed *Aspergillus* hyphae in the same area (magnification 100×).

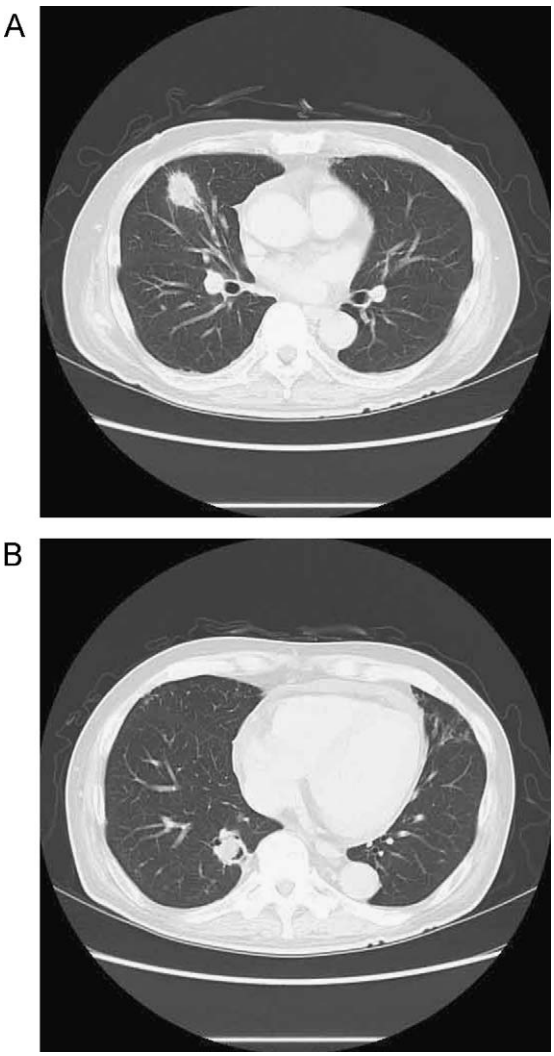

Fig. 3. Pulmonary CT. CT scans of the chest demonstrated multiple nodules (A) and cavitating infiltrate (B) in the lower lobes of the lungs.

After receiving human recombinant G-CSF (2400 μg/total), the leukocyte count increased to 1000 cells/μl (43% neutrophils). However, on day 71, the patient with relapse of AML suddenly developed severe respiratory failure; his condition deteriorated and he died on day 79. An autopsy was not performed. *In vitro* susceptibility testing showed that the causative *A. fumigatus* was sensitive to MCFG (MIC = 0.03125 μg/ml), ITCZ (MIC = 0.25 μg/ml), VRCZ (MIC = 0.125 μg/ml), and AMPH-B (MIC = 0.25 μg/ml).

3. Discussion

Despite advances in antifungal prophylaxis and treatment, invasive fungal infection remains the most common infectious cause of death among neutropenic patients undergoing induction chemotherapy for AML [1,2]. In particular, breakthrough invasive fungal infection including aspergillosis in patients receiving prophylactic or empirical treatment is a well-known problem and results in a high mortality rate [3–5]. In the present case, the patient developed ISA during prophylaxis with ITCZ and empirical therapy with MCFG, which have been shown to be effective against isolated *A. fumigatus in vitro*, suggesting the possibility that the plasma concentrations of these agents were ineffective for a patient with deep neutropenia [4].

In general, ISA is characterized by rapid spread of the fungus from the sinus airspace into adjacent structures such as the brain and occasional dissemination to the lungs with a very high mortality rate [9–11]. Therefore, early diagnosis and aggressive treatment of ISA are essential for patient survival [6–10]. The reported symptoms of ISA include nasal congestion, nasal discharge, abnormal findings in the nasal cavity, buccal swelling with pain or numbness, gingival and skin necrosis, and high fever, but these symptoms are not always specific to ISA [6–10]. Although radiographs and CT scans demonstrated sinus involvement and spread of the lesion, suggesting the presence of fungal or bacterial infection, a definitive diagnosis requires histological and cultural confirmation based on surgical specimens [7–9,14]. Serological assay for (1-3)-β-D-glucan is highly sensitive for fungal infections but not specific for aspergillosis, while the detection of *Aspergillus* galactomannan antigen is less sensitive but more specific [12,13]. In this patient, most of the clinical findings, such as nasal symptoms and orofacial necrosis, were apparent. In addition, CT scans demonstrated sinus involvement and destruction of the bone. Furthermore, a high level of (1-3)-β-D-glucan and positive *Aspergillus* galactomannan antigen indicated *Aspergillus* infection. Therefore, all these findings were strongly suggestive of ISA at the advanced stage. In addition to the usual histopathological examination and tissue culture, we performed *in situ* hybridization using an *Aspergillus*-specific DNA probe to confirm the diagnosis of aspergillosis [14]. Although the method is still preliminary, *in situ* hybridization is a promising technique for a more prompt diagnosis compared to culture-based methods, which are often time-consuming and carry the risk of growth failure due to incorrect handling of the tissue samples.

Aggressive systemic anti-fungal therapy is necessary to eradicate *Aspergillus* infection in immunocompromised patients [7–10]. Amphotericin B was long the standard treatment for ISA, but the current standard therapy is VRCZ, which has led to better responses and improved survival [12]. We treated our patient with VRCZ and L-AMPH-B to enhance the anti-fugal activity against aspergillosis [5]. Furthermore, to help pharmacological therapy reach the infected area, immediate surgical debridement of the necrotic tissue is necessary, as demonstrated in our patient. Published case series strongly supports the need for surgical debridement plus antifungal agents to optimize the outcome, showing a 60% survival rate for patients with ISA that would otherwise be as low as 28.6% [9]. We also adopted drainage and drug instillation of the sinus after surgical debridement to eradicate aspergillosis [7,8]. The oro-facial condition of ISA gradually improved in this patient after aggressive treatment including surgery, systemic antifungal therapy, and sinus irrigation. As ISA was thought to be the advanced stage when diagnosed, the infection resulted in fatal disseminated pulmonary aspergillosis despite treatments.

In conclusion, from our experience, fungal infection should be clinically diagnosed at an early stage and treated with surgery in combination with intensive antifungal administration to significantly reduce the mortality rate in neutropenic patients with AML.

4. Conflicts of interest

There are no conflicts of interest to be declared.

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