

Case Report

Cerebral embolism through hematogenous dissemination of pulmonary mucormycosis complicating relapsed leukemia

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Abstract: Invasive mucormycosis in patients with hematological diseases mostly occurs in the lungs. Invasive mucormycosis of other anatomical sites is relatively infrequent and its pathogenesis has not so far been well elucidated. Here, we describe an autopsy case of pulmonary invasive mucormycosis complicated by cerebral embolism with infarct. A 77-year-old Japanese woman with relapsed acute myeloid leukemia complained of left visual disturbance and weakness of the lower limbs. The diagnosis of leukemic infiltration to the central nervous system was made. Repeated intrathecal injection of methotrexate plus cytarabine resulted in partial amelioration of the neurologic symptoms. However, the patient then developed fever, dyspnea, and subsequent right hemiparesis. A computed tomography (CT) scan showed a consolidative shadow with halo sign in the left lung field, which was compatible with either invasive pulmonary aspergillosis or mucormycosis. These findings accounted for fever and dyspnea, but not hemiparesis. Despite antifungal therapy, the patient succumbed to death after two weeks. Autopsy revealed pulmonary invasive mucormycosis with a fungal ball in the lumina of the adjacent ascending aorta. Intriguingly, autopsy and postmortem CT scan identified left cerebral infarct due to mucormycosis, which accounted for the right hemiparesis. It is likely that the fungal ball caused the cerebral embolism through hematogenous dissemination. We should suspect hematogenous dissemination when we see a patient with pulmonary invasive mucormycosis developing neurologic symptoms.

Keywords: Cerebral embolism, hematogenous dissemination, invasive mucormycosis, relapsed acute myeloid leukemia

Introduction

Mucormycosis, formerly referred to as zygomycosis, is a fungal disease caused by various members of the class Zygomycetes, order Mucorales, which is subdivided into the genera *Mucor*, *Rhizopus*, *Absidia*, *Apophysomyces*, *Cunninghamella*, and *Saksena* [1]. Invasive mucormycosis is an increasing complication for immunocompromised patients with hematologic malignancies undergoing intensive chemotherapy or hematopoietic stem cell transplant (HSCT) [2]. Major risk factors for invasive mucormycosis include prolonged and severe neutropenia, iron overload, high risk HSCT, severe graft-versus-host disease (GVHD) treated with corticosteroids, and relapsed leukemia

[3]. The lungs account for approximately 70% of the affected sites of mucormycosis in patients with hematologic diseases [4]. Invasive mucormycosis of the other anatomical sites is infrequent and remains to be characterized. Autopsy cases of invasive mucormycosis still plays an important role to this end because histopathological evaluation is usually required to identify the disease [5]. Here, we describe an autopsy case of invasive mucormycosis complicated by cerebral embolism with infarct.

Case report

A 77-year-old Japanese woman was referred to our institution because of leukocytosis and was diagnosed as acute myeloid leukemia (AML)

Cerebral mucormycosis with embolism

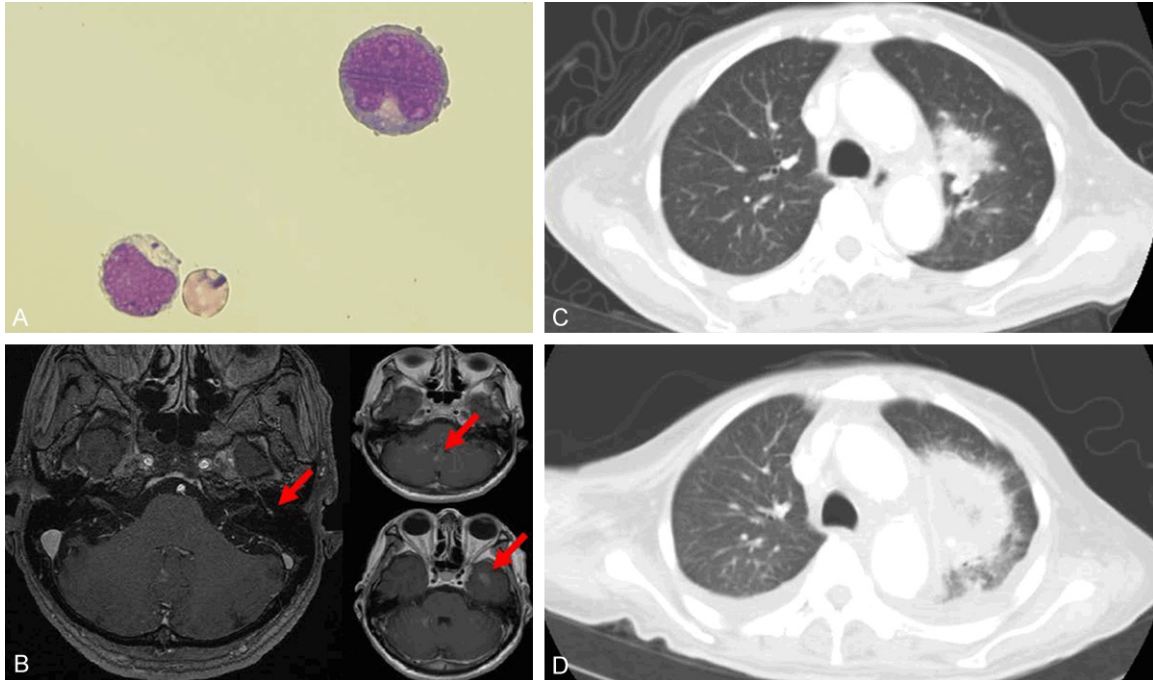


Figure 1. Relapse of acute myeloid leukemia (A, B) and pulmonary mucormycosis visualized by computed tomography (CT) (C, D). (A) Leukemic blasts in the cerebrospinal fluid (Wright-Giemsa stain, $\times 400$). (B) High contrast lesions with gadolinium enhancement in the left facial nerve (left panel) and cerebrum (upper and lower right panels). Arrows indicate the enhanced lesions. (C) A consolidative shadow with halo sign at the onset of pneumonia. (D) Exacerbation of the lesion in **Figure 2C** after one week of treatment with micafungin followed by voriconazole.

with *MLL-AF6*. She achieved complete remission after two cycles of induction therapy with idarubicin plus cytarabine, and subsequently received three cycles of consolidation therapy. Oral itraconazole was administered as antifungal prophylaxis during the treatment, and there were no episodes of documented infections. She felt lightheadedness and dizziness on completion of consolidation therapy. Two weeks later, the patient presented with left facial nerve palsy which was followed by left visual disturbance and weakness of the lower limbs. On admission, laboratory data showed white blood cell (WBC) count of $1.9 \times 10^9/L$ with 6% blasts, hemoglobin level of 9.1 g/L, and platelet count of $76 \times 10^9/L$. WBC count in the cerebrospinal fluid (CSF) was increased to $568 \times 10^6/L$. Microscopic examination of the CSF revealed that the cells were composed of leukemic blasts (**Figure 1A**). Magnetic resonance imaging (MRI) revealed a high contrast lesion with gadolinium in the cerebrum, accounting for the left facial nerve palsy (**Figure 1B**). The diagnosis of relapsed AML with central nervous system (CNS) involvement was made. Intrathecal injection of methotrexate plus cytarabine was repeatedly performed for the treat-

ment of CNS leukemia, which led to a salient decrease in CSF cell count and partial amelioration of neurologic symptoms. On the other hand, systemic chemotherapy for AML relapse was not exerted because her general condition was poor and the intrathecal injection induced severe neutropenia. The patient then developed fever and dyspnea. Empiric antifungal treatment with micafungin was initiated. Computed tomography (CT) scan disclosed a consolidative shadow with halo sign in the left lung (**Figure 1C**). Blood cultures and serum fungal markers such as galactomannan antigen and (1-3)- β -D glucan repeatedly gave negative results. Taken together, she was clinically diagnosed as invasive pulmonary aspergillosis or mucormycosis. Empiric micafungin was switched to liposomal amphotericin B, but her fever and dyspnea did not improve. Five days after the onset of pneumonia, she suddenly developed weakness of right upper and lower limbs, shooting pain of the right upper limb, and visual disturbance. Although we strongly suspected recurrent CNS involvement of AML as a cause of the neurologic symptoms, further scrutiny by lumbar puncture was not available due to her poor general condition and severe thrombocy-

Cerebral mucormycosis with embolism

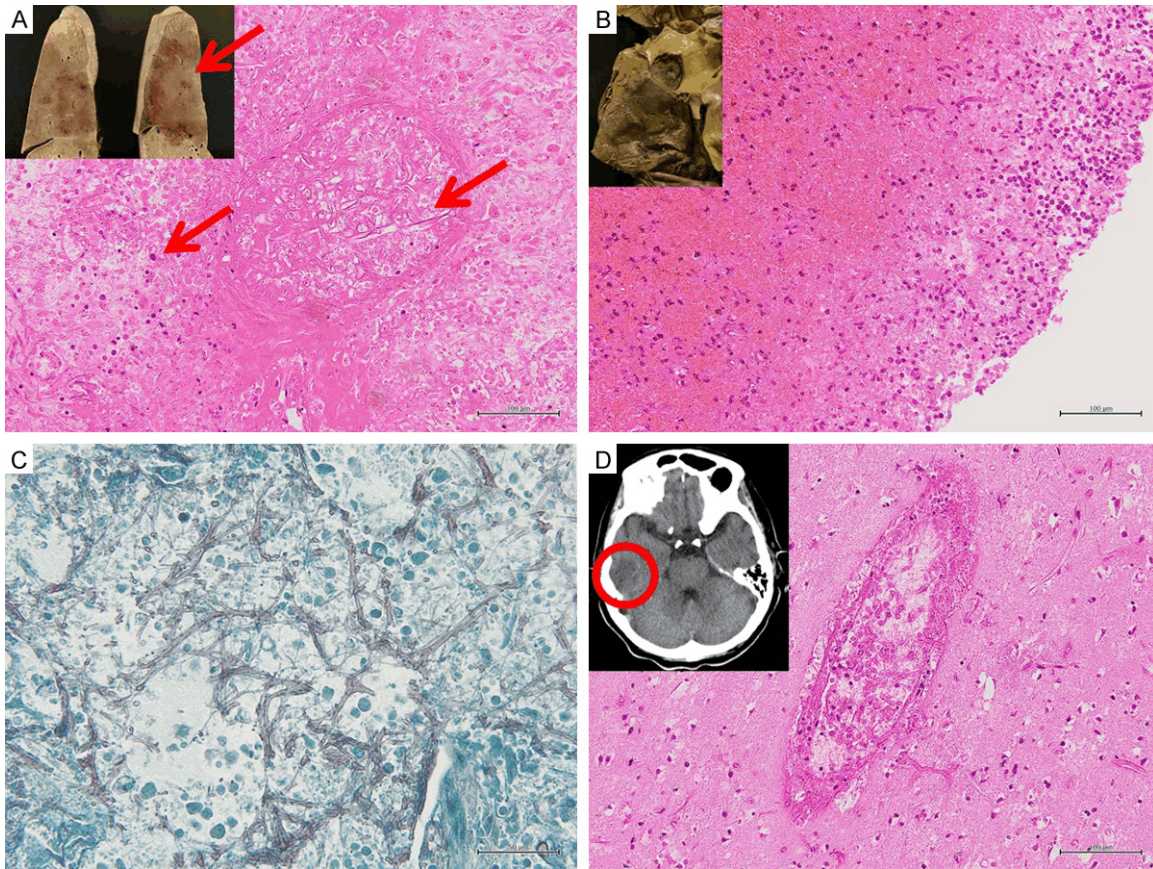


Figure 2. Autopsy findings. (A) Hemorrhagic infarct was found in the left lung (left upper panel). Microscopic examination of pulmonary parenchyma identified filamentous fungi occupying a blood vessel (H-E stain, $\times 400$). (B) A huge thrombus was detected in the ascending aorta (left panel) which was composed of filamentous fungi and leukemic blasts (right panel, H-E stain, $\times 400$). (C) The fungi were morphologically featured by obtuse divergent angle and lack of a partition wall (Grocott stain, $\times 800$). (D) Invasive mucormycosis in the left temporal lobe of the cerebrum. The blackened infarct was macroscopically found in the right temporal lobe visualized as a low density area by a postmortem CT scan (left upper panel). An embolus comprising filamentous fungi and leukemic blasts occupied a cerebral blood vessel on microscopy (right panel, H-E stain, $\times 400$).

topenia. A follow-up CT scan showed a salient aggravation of pneumonia and pleural effusion (Figure 1D). The patient eventually succumbed to death in two weeks after the onset of pneumonia.

Autopsy and postmortem CT were performed with written informed consent from the patient's family. The autopsy findings were remarkable for leukemic infiltration and fungal infection. As for the former, leukemic blasts infiltrated extensive organs and tissues including the bone marrow, cerebrum, spine, liver, spleen, kidney, and pericardium. Microscopic examination indicated diffuse proliferation of myeloblasts in the cerebrum although there was no apparent formation of a myeloid sarcoma. As for the latter, there were large nodules with hemorrhagic infarct in the upper lobes of

the lungs (Figure 2A). The lesions infiltrated into the adjacent mediastinum and caused ascending aortitis. There was a fungal ball in the lumina of the ascending aorta (Figure 2B). Microscopic examination revealed that the fungi were irregular in width and lacked septa (Figure 2C). The divergent angle was approximately 90° , leading to the diagnosis of mucormycosis. Autopsy and postmortem CT also identified a fungal embolism with infarct in the left temporal lobe of the cerebrum (Figure 2D).

Discussion

Mucormycosis of the cerebrum is a rare complication. It usually manifests as rhino-cerebral mucormycosis where lesions of the nasal cavity and para-nasal sinuses extend to the adjacent central nervous system (CNS). The pathogene-

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sis of our case was different. There was no evidence of mucormycosis in the nasal cavity and para-nasal sinuses. Instead, pulmonary mucormycosis with ascending aortitis was followed by cerebral fungal embolism. It is therefore likely that a fungal ball in the ascending aorta caused the cerebral embolism through hematogenous dissemination. With a literature review, we found that hematogenous dissemination is a rare but recurrent cause of cerebral mucormycosis [6, 7].

In our case, the diagnosis of invasive mucormycosis was difficult while the patient was alive. The pulmonary consolidative shadow with halo sign was compatible with both aspergillosis and mucormycosis. Histological evaluation of the fungal infection was not available due to her poor general conditions. When her neurologic symptoms deteriorated after the onset of pulmonary mucormycosis, we considered recurrence of AML in the CNS as the most plausible cause.

Rhino-cerebral mucormycosis can be readily visualized by MRI and CT scan. Trans-nasal biopsy is available for patients under poor conditions. In contrast, autopsy of the CNS is usually required for the diagnosis of cerebral mucormycosis through hematogenous dissemination. Given that only a fraction of patients are subject to autopsy of the CNS, it is plausible that invasive cerebral mucormycosis with infarct has so far been underestimated.

In conclusion, we should suspect cerebral mucormycosis through hematogenous dissemination when we see a patient with pulmonary invasive mucormycosis developing neurologic symptoms.

Disclosure of conflict of interest

This is not a sponsored study, but we declare the potential conflict of interest with the pharmaceutical companies that deal with the drugs described in this study. FN received speaking fee from Astellas Pharma Inc. and Pfizer Japan Inc.; MK received grant from Astellas Pharma Inc., MSD K.K., Sumitomo Dainippon Pharma Co., Ltd., and Pfizer Japan Inc.. MK also reports speaking fee from MSD K.K. and Pfizer Japan Inc..

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