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Letter to the editor

Rhino-orbital Mucormycosis presenting as facial cellulitis in a patient with high-risk acute myeloid leukemia in relapse

In 2014, a 45-year-old man with no prior medical history was diagnosed with high-risk acute myeloid leukemia with a normal karyotype, mutated NPM1, and an FLT3 internal tandem duplication (equal ratio of mutated over wild-type). He achieved complete response (CR) after one cycle of induction chemotherapy containing idarubicin and cytarabine, with negative NPM1 molecular residual disease (MRD), which was followed by two consolidation cycles of cytarabine and ponatinib (NCT 02428543). Faced with a high risk of molecular relapse, he underwent allogeneic stem cell transplantation (allo-SCT) in February 2015 with reduced intensity conditioning (thiotepa 5 mg/kg one day, busulfan 6.4 mg/kg two days and fludarabine 30 mg/m^2/d for 5 days) from a haploidentical donor, followed by an infusion of donor-derived natural killer lymphocytes on day 10 (NCT 01947322).

Early post-transplantation follow-up was uneventful. Four months after allo-SCT, molecular relapse occurred, followed by cytologic relapse despite the withdrawal of immunosuppressive drugs and the introduction of sorafenib. Salvage chemotherapy with gemtuzumab ozogamicin (GO), mitoxantrone, and cytarabine was administered, resulting in CR and negative MRD after one cycle. Due to the predicted length of aplasia, antifungal prophylaxis with oral posaconazole at 300 mg/day was started during each period of aplasia.

At 7 months post-transplantation, consolidation chemotherapy with GO and cytarabine was administered. He was started on piperacillin-tazobactam for febrile neutropenia on day 5 of consolidation therapy. Bacterial maxillary sinusitis was suspected based on computerized tomography (CT) scan showing unilateral filling of the maxillary sinus, and metronidazole and intravenous vancomycin were added to the antibiotic regimen. Fever and neutropenia persisted at 72 h of introduction of broad-spectrum antibiotics, and filgrastim 10 μg/kg/day was started. Three days later extensive necrosis of the palate was noted together with facial skin lesions. Due to suspicion of breakthrough invasive fungal infection despite optimal blood dosages of posaconazole (>700 mg/mL) and cerebral infection, a combined antifungal therapy was started, consisting of liposomal amphotericin B (L-AMB) at 3 mg/kg/day and intravenous voriconazole at 4 mg/kg/day (after 6 mg/kg at day 1). A facial CT-scan at day 7 of fever showed unilateral maxillary sinusitis and extensive cellulitis of the maxillary and peri-orbital regions (Fig. 1).

The patient's clinical status rapidly deteriorated, and repeat imaging showed large maxillary and peri-orbital soft-tissue necrosis (Fig. 2). Based on the rapid progression of symptoms, rhino-maxillary mucormycosis was suspected given positive specific mucormycosis PCR on a blood sample. The patient received L-AMB whose dose was increased up to 10 mg/kg/day due to suspicion of cerebral infection.

Despite neutropenia, salvage surgery was performed, consisting in hemimaxillectomy and enucleation of the left eye. Mycological cultures of bone biopsy specimens confirmed the diagnosis of Rhizomucor sp, specimen in a family of mucormycosis associated this antifungal susceptibility (S for amphotericin B, I for posaconazole, R for voriconazole and echinocandin). High-dose amphotericin B therapy was then continued alone despite tubulopathy toxicity which required daily potassium infusions. Granulocyte transfusions from volunteer donors stimulated by dexamethasone were administered for 10 consecutive days at a distance of L-AMB perfusion.

Despite one month of high-dose antifungal therapy, follow-up biopsies showed persistent mucormycosis, and the patient required repeat surgical curettage. Three weeks after the second surgery and after specific mucormycosis PCR was negative, LAM-B was tapered to 7.5 mg/kg/day due to tubulopathy toxicity. In December 2015, three months after diagnosis of mucormycosis, LAM-B was switched to oral posaconazole at 300 mg daily. A boost of donor-CD34+ cells was performed in January 2016 due to persistent cytopenia. In February 2016, a second molecular relapse was successfully managed with sorafenib at 200 mg daily and donor-derived lymphocyte infusions. Sorafenib was continued with no significant side effect in association with posaconazole. At one-year post-mucormycosis diagnosis, the patient underwent facial reconstructive surgery, and after more than three years of follow-up, the patient remains in good health, having achieved molecular CR, and showing no evidence of graft-versus-host disease under posaconazole and sorafenib.

We report here a case of rhino-orbital mucormycosis, the third-most-frequent invasive fungal infection in allo-SCT recipients after invasive candidosis and aspergillosis. Mucormycosis usually presents as rapidly progressive necrotic sinus or pulmonary infection and is associated with high mortality rates. Prompt recognition is critical, and its management requires close cooperation between hematologists, surgeons, infectious disease specialists, and microbiologists. Guidelines for the management of mucormycosis have recently been updated and recommend the use of high-dose (>5 mg/kg) amphotericin B as a first-line antifungal agent [1]. In this case, mucormycosis has developed under optimal posaconazole prophylaxis, likely explained by the intermediate sensibility of this strain. Lionakis et al. published a review about emerging fungal under antifungal drugs [2]. For breakthrough of fungal infection under posaconazole, they proposed a high dose of L-AMB and switched to different triazole. In the first intention, LAM- B and voriconazole were used empirically (isavuconazole was not available in our center in 2015). Surgical debridement was accomplished urgently in our

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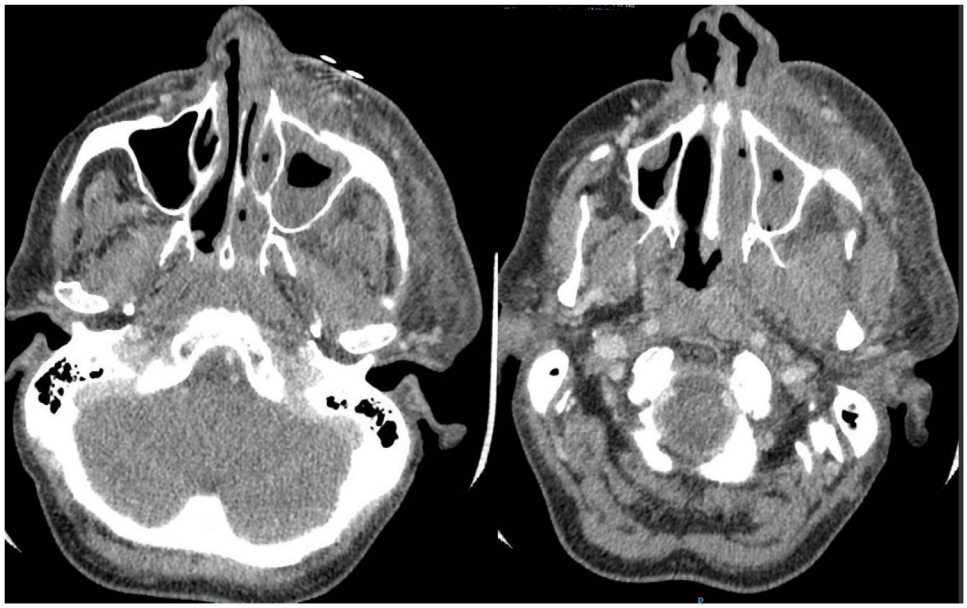

Fig. 1. Facial CT-scan on 08/09/2015 showing unilateral maxillary sinusitis wih adjacent cellulitis.

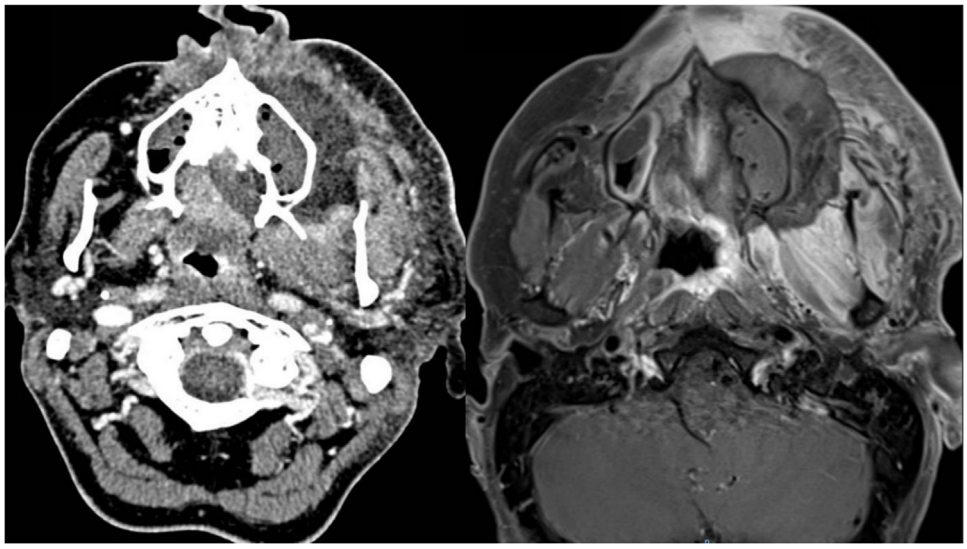

Fig. 2. CT scan end MRI on 11/09/2015 showing extensive soft-tissue necrosis of the maxillary region.

patient. Surgical debridement has to be extensive, involving all necrotic areas for rhino-oculo-cerebral infection, and repeated surgical procedures are recommended to achieve local control and improve outcome [3]. Indeed, Necrosis in mucormycosis is a limiting factor for the penetration of antifungal, and his removal is urgently needed to improve survival.

In the setting of prolonged neutropenia and fungal infection, filgrastim and leucocyte transfusions as adjunct salvage treatment options have shown controversial results. On 15 patients who received granulocyte transfusion (stimulation by dexamethasone and G-CSF) during fungal infection in prolonged neutropenia, 11 had favorable outcomes [4]. However, a recent randomized phase III study did not show the benefit of adding granulocyte transfusions for infections (bacterial and proven fungal infections represents respectively 40% and 25%) during prolonged neutropenia [5]. In our case, a combination of high-dose antifungal therapy, extensive surgery, and leukocyte transfusions allowed for controlling an often fatal infection and achieving the long-term survival of the patient.

Conflicts of interest

None.

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