CASE 2: 56-YEAR-OLD MAN WITH HEAD INJURY AND NEWLY DIAGNOSED AML

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Initial Presentation

A 56-year-old man weighing 165 lbs (75 kg) presented to a hospital in Austria with fatigue, intermittent fever, night sweats, weight loss, and a parietal head injury (Figure 1). Patient history reveals that the patient is a truck driver who had bumped his head due to a syncopal episode while unloading his truck a couple of days ago.

Case Work-up

His laboratory test results revealed 30% blasts in a blood differential. A Jamshidi biopsy was performed due to a suspicion of acute leukemia and confirmed the diagnosis of acute myeloid leukemia (AML).

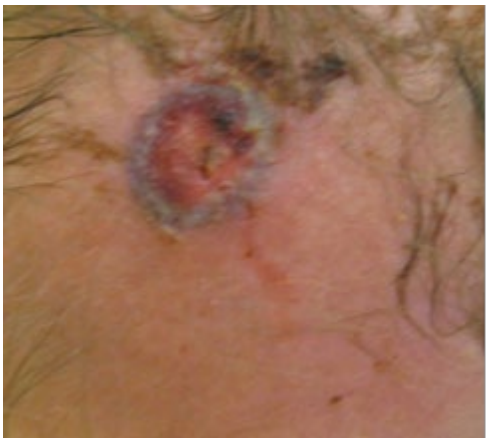

Figure 1. The parietal head injury. Image courtesy of Thomas Valentin.

Case Continued

AML induction chemotherapy with idarubicin and cytarabine (IA I) was initiated, during which the patient developed neutropenic fever despite broad-spectrum antibiotics, resulting in the initiation of caspofungin empirical therapy.

A few days later the lesion on the patient's forehead turned black (Figure 2), and a computed tomography (CT) scan of the neurocranium was ordered.

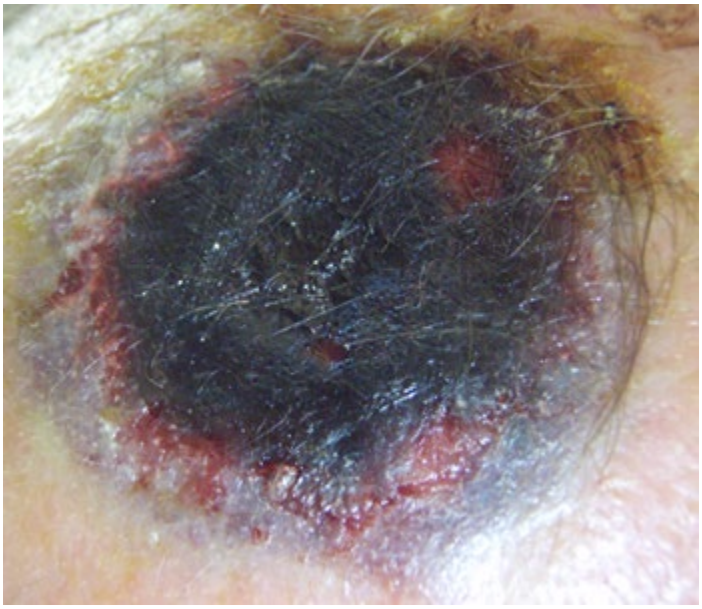

Figure 2. The parietal head injury several days later. Image courtesy of Thomas Valentin.

The CT of the cranium (Figure 3) revealed destruction of the bone but no signs of brain involvement and was followed with a magnetic resonance image (MRI) of the neurocranium.

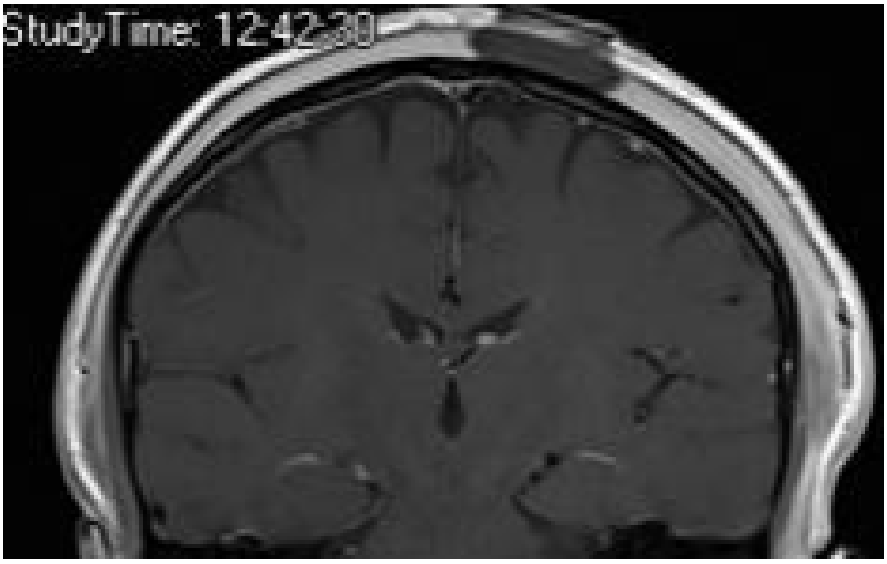

Figure 3. CT of the cranium showing bony destruction. Image courtesy of Thomas Valentin.

The MRI of the cranium revealed diffuse hypodense areas in the skull temporoparietally as well as diffuse thickening of soft tissue periorbital and temporoparietal. In addition, it showed diffuse infiltrative, primarily inflammatory, and disease of the soft tissue and skull but no sign of central nervous system (CNS) involvement.

Lumbar puncture was performed, and the cerebrospinal fluid (CSF) showed no signs of inflammation and the culture remained negative.

A wound swab was performed, and microscopy showed aseptate or pauci-septate, ribbon-like hyphae with an irregular pattern of branching.

Challenge Question 1. Which of the following fungal pathogens is the most likely cause of the infection?

- **A.** *Aspergillus* spp.
- **B.** Mucorales
- **C.** *Fusarium* spp.
- **D.** *Candida* spp.
- **E.** A and B

Discussion

A. ***Aspergillus* spp**. Aspergillus usually spreads to the CNS either by hematological dissemination from pulmonary foci or expands directly from paranasal sinus infection. Aspergillus spp. may also enter the CNS due to traumatic inoculation or during surgical procedures [1,2]. Primary cutaneous aspergillosis mostly arises around intravenous line sites, burns, bruises, or surgical wounds, which represent potential ports of entry in patients with neutropenia. The microscopic finding, however, clearly indicates another mold as a causative pathogen here. Aspergillus hyphae are typically thin with regular septa. The branching angle is typically acute.

B. **Mucorales**. Fungi in the Mucorales group typically have no or few septa and hyphae with a ribbon-like appearance and irregular branching, as was seen on the microscopy here.

C. ***Fusarium* spp**. The main routes of infection due to Fusarium are inhalation of airborne microconidia, and while rare, direct inoculation through traumatic injury may occur. Dissemination to the central nervous system (CNS) has been described[3]. Fusarium hyphae are morphologically similar to those of *Aspergillus* spp., appearing as hyaline septate filaments that typically branch in acute 45° and sometimes even 90° angles.

D. ***Candida* spp**. Candida infection can be ruled out by the microscopic findings.

E. A and B. Since **A** is not the correct answer, **E** is not correct either.

Correct answer: B.

Test Results

The wound swab showed growth of *Rhizopus oryzae*, of the order Mucorales. Minimum inhibitory concentration (MIC) testing results are shown below in Figure 4.

Figure 4. MIC testing results.

Antifungal	**MIC (mcg/mL)**
Amphotericin B	6
Fluconazole	> 256
5-Fluorocytosine	>32
Itraconazole	>32
Voriconazole	16
Caspofungin	>32
Posaconazole	4
Anidulafungin	>32
Micafungin	>32

Challenge Question 2: Which antifungal treatment regimen would you choose?

- **A.** Liposomal amphotericin B 5 mg/kg monotherapy
- **B.** Liposomal amphotericin B 10 mg/kg monotherapy
- **C.** Continue caspofungin and add liposomal amphotericin B
- **D.** Liposomal amphotericin B and posaconazole or isavuconazole
- **E.** A or C
- **F.** B or D

Discussion

A. **Liposomal amphotericin B 5 mg/kg monotherapy.** Liposomal amphotericin B is the primary choice for treatment of mucormycosis, and recipients of high doses tended to have increased response rates, so a dose of 10 mg/kg is primarily recommended[4]. Hence, 5 mg/kg is not the best dose.

B. **Liposomal amphotericin B 10 mg/kg monotherapy.** For CNS infection especially, which is feared in this patient, a dosage of 10 mg/kg is preferred. Liposomal amphotericin B is highly protein-bound like other amphotericin B formulations but has shown superior clinical activity against CNS infections vs other amphotericin B formulations[5]. Since the entry of the drug into CSF and brain is governed by the free fraction of drug in serum, the amphotericin B CSF concentrations after the intravenous application of the liposomal preparations were over 100-fold lower than the serum levels[1,6].

C. **Continue caspofungin and add liposomal amphotericin B**. Caspofungin, when used in combination with liposomal amphotericin B, has shown synergistic effects[7]. However, the lack of CNS penetration of echinocandins together with the high MICs observed in our patient may not make this option particularly attractive in this case.

D. **Liposomal amphotericin B and posaconazole or isavuconazole**. This is also a possible treatment regimen. Both posaconazole and isavuconazole have some activity against some of the Mucorales[8], and although not supported by the guidelines, have sometimes been used in combination with liposomal amphotericin B.

E. **A or C.** Neither A nor C is the best option, so this option is not correct.

F. **B or D**. This is the most appropriate response.

Correct answer: F.

Antifungal Treatment

Caspofungin was discontinued, and liposomal amphotericin B 10 mg/kg bodyweight (900 mg) per day with slow infusion was initiated together with posaconazole suspension 10 mL bid.
In addition, topical treatment of the fungal lesion with liposomal amphotericin B solution was initiated.

Challenge Question 3. Regarding posaconazole, which of the following statements are true?

A. Posaconazole tablets would have been preferable due to higher and more reliable plasma concentrations
B. Therapeutic drug monitoring (TDM) to measure plasma concentrations starting on Day 5-7 of treatment may be helpful.
C. Posaconazole does not penetrate the CNS
D. A and B
E. A and C
F. A, B, and C

Discussion

A. **Posaconazole tablets would have been preferable due to higher and more reliable plasma concentrations.** Posaconazole oral suspension requires food, especially fatty food, co-administration with an acidic drink or multiple doses per day to achieve maximal drug absorption[9]. Proton pump inhibitors also reduce absorption. Posaconazole tablets are significantly more likely to result in therapeutic drug concentrations than the oral suspension[10].

B. **Therapeutic drug monitoring with measurements of plasma concentrations starting Day 5 -7 may be helpful.** Therapeutic drug monitoring is specifically recommended for the posaconazole oral suspension (as used here) and, when used as treatment, with first trough level measured during steady state.

C. **Posaconazole does not penetrate the CNS.** Posaconazole is a lipophilic molecule which favors enrichment in brain tissue. However, posaconazole may show limited CNS penetration in healthy individuals, with CSF concentrations being 100-fold lower than plasma concentrations. However high CSF levels of posaconazole have been reported in patients with CNS infections suggesting that inflammatory disruption of the blood–brain barrier could promote CNS penetration of posaconazole[11].

D. **A and B.** Options A and B are true, but option C is also true, so this is not the correct answer.

E. **A and C**. Options A and C are true, but option B is also true, so this is not the correct answer.

F. **A, B and C**. This is the correct answer as all the three options are true.

Correct answer: F.

Case Continued

A posaconazole trough level was obtained on Day 7 of treatment and showed a concentration of 460 ng/mL, therefore dosage of the posaconazole oral solution was increased to 400 mg tid (10 mL tid). Subsequent posaconazole trough concentrations were above 700 ng/mL.

The patient's neutrophil count slowly recovered, and the patient showed clinical improvement. Subsequent imaging of the CNS continued to show no brain involvement. However, the patient's renal function worsened, and his blood creatinine levels increased.

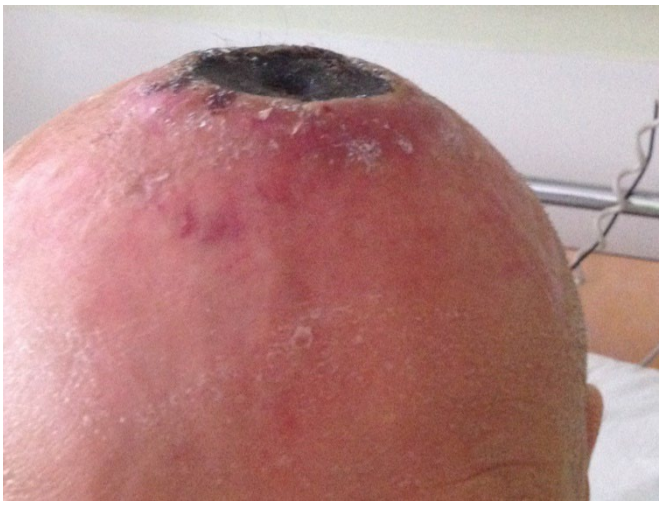

Figure 5. Patient's recovering parietal head injury. Image courtesy of Thomas Valentin.

Challenge Question 4. What is the most likely reason for the decreased renal function?

A. Liposomal amphotericin B
B. Posaconazole

Discussion

A. **Liposomal amphotericin B.** Liposomal amphotericin B causes less renal toxicity than conventional amphotericin B but it is still associated with decreases in renal function, especially at the dose used here (10mg/kg)[3].

B. **Posaconazole.** Although the patient receives a relatively high dose of posaconazole, it is unlikely the cause of the decreased renal function. The most frequently observed adverse event with posaconazole is hepatic toxicity, with increasing transaminases.

Correct answer: A.

Case Management and Outcome

Liposomal Amphotericin B dosage was subsequently reduced to 5 mg/kg body weight per day, while posaconazole was continued at 10 mL tid.

On Day 28 after the second course of idarubicin and cytarabine (IA II), the patient's neutrophil count had recovered, and he received a skin graft (Figure 6).

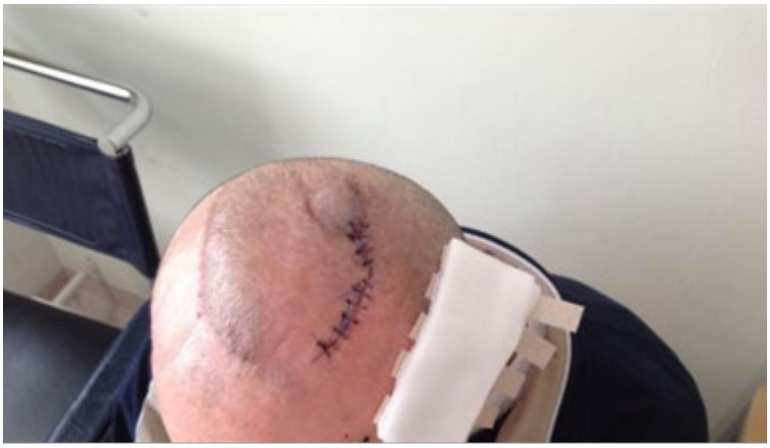

Figure 6. Image of patient's head after receiving a skin graft. Image courtesy of Thomas Valentin.

Antifungal treatment with liposomal amphotericin B was discontinued, and posaconazole was discontinued 5 weeks later. The patient did not experience a recurrent infection**.** Later, the patient underwent allogeneic stem cell transplantation, and posaconazole was restarted as secondary prophylaxis.

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