CASE 3: 23-YEAR-OLD MAN WITH PETECHIAL BLEEDING AND A HEMATOMA

PRESENTED BY MARTIN HOENIGL, MD.

Initial Presentation

A 23-year-old previously healthy male presented to the Emergency Department with petechial bleeding for 14 days, and a hematoma on his right cubita and pancytopenia. The patient was admitted with suspected acute leukemia.

Case Work-up and Treatment

Jamshidi biopsy revealed severe aplastic anemia, and because the patient had no human leukocyte antigen (HLA)-identical siblings, search for an unrelated donor was initiated. While hospitalized, the patient developed neutropenic fever, which was successfully treated with cefepime. After 5 days, the patient was discharged for

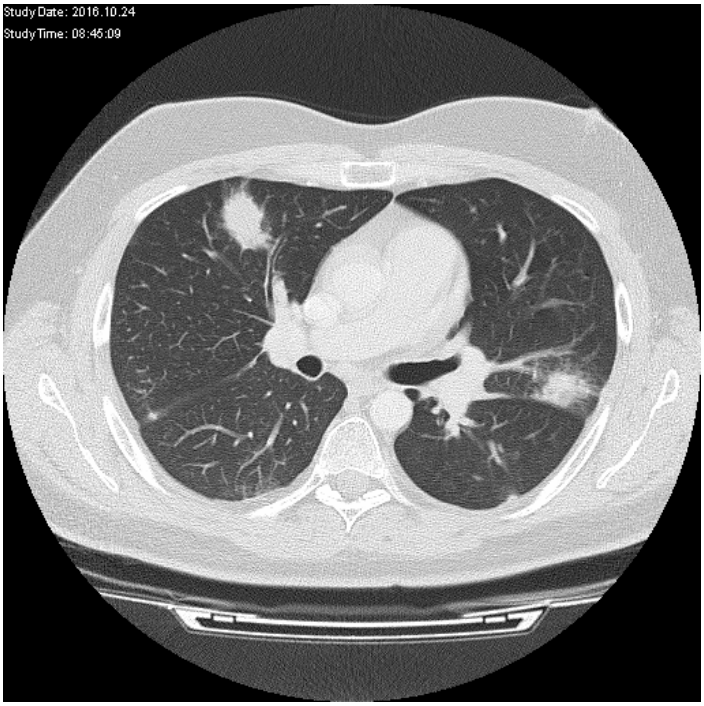
a few days on levofloxacin and fluconazole. At readmission 4 days later, chemotherapy with equine antithymocyte globulin (ATGAM) for 4 days plus cyclosporin A was initiated; granulocyte colony stimulating factor (G-CSF) stimulation had to be interrupted twice because of severe pain. The patient had no absolute neutropenia (0.0 neutrophils in the differential), which was ongoing over the next month. On the second admission, the patient had again developed a neutropenic fever and cefepime was empirically restarted.

Over the next days, serum galactomannan and serum beta-D-glucan screening always remained negative. The cytomegalovirus (CMV) PCR was negative, but the C-reactive protein showed significant elevation at 127.5 mg/dL (normal value <8 mg/dL).

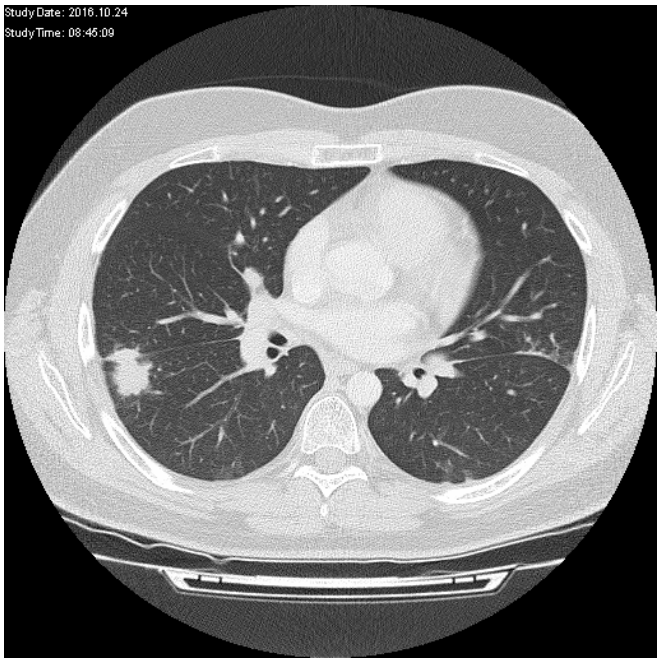
A chest X-ray on day 2 of cefepime revealed suspected pneumonia. This was followed by a computed tomography (CT) scan of the thorax, with the findings shown in Figure 1, panels A-C. The CT revealed 3 subpleural nodules up to 28 mm in diameter and multiple subpleural nodules up to 6 mm in diameter. The radiologist raised suspicion of atypical/fungal pneumonia.

Figure 1, panels A, B, C. CT thorax scans at different cuts showing subpleural nodules. Images courtesy of Martin Hoenigl, MD.

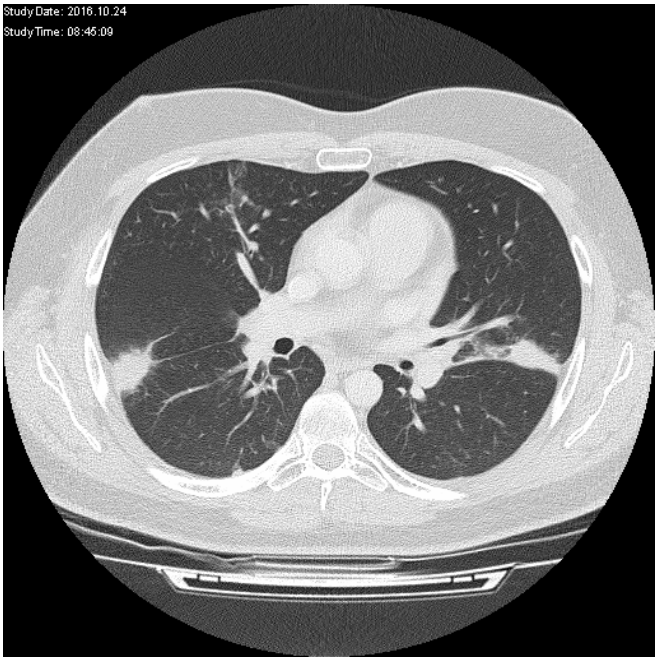
Panel A.



Panel B.



Panel C.



Following the CT, cefepime was discontinued, and moxifloxacin, meropenem, and vancomycin were initiated. In addition, liposomal amphotericin B (5 mg/kg/d) was initiated, but the patient developed a Type 1 anaphylactic reaction. Liposomal amphotericin B was discontinued and instead voriconazole 6 mg/kg IV bid on Day 1, followed by 4 mg/kg IV bid starting on Day 2 was initiated. Despite administration via a slow infusion, visual disturbances and hallucinations occurred over the next days.

Challenge Question 1. Which option below is true regarding visual disturbances and hallucinations occurring in this setting?

A. **Visual disturbances and hallucinations are associated with high voriconazole plasma trough concentrations >5.5-6 mcg/mL**
B. **It is unlikely that voriconazole is the cause of the visual disturbances and hallucinations**
C. **Voriconazole needs to be discontinued**

DIscussion

A. **Visual disturbances and hallucinations are associated with high voriconazole plasma trough concentrations >5.5-6 mg/L.** Visual disturbances and hallucinations associated with voriconazole have been described in several studies and are generally found in patients with high plasma concentrations[1].

B. **It is unlikely that voriconazole is the cause of the visual disturbances and hallucinations**. Visual disturbances, encephalopathy, and hepatic enzyme elevation are the most common adverse advents (AEs) associated with voriconazole[2]. Particularly, visual disturbances and encephalopathy are associated with high voriconazole plasma concentrations (VPCs) >5.5-6 mcg/mL, and they may be reversible once voriconazole plasma concentration decrease.

C. **Voriconazole needs to be discontinued**. Not necessarily, as it was shown in a randomized controlled study that routine therapeutic drug monitoring (TDM) of voriconazole may reduce drug discontinuation due to adverse events and improve the treatment response in invasive fungal infections[3]. TDM of voriconazole and—if necessary and high plasma concentrations are detected—reduction of voriconazole dosage may be an appropriate way to manage this AE.

Correct answer: A.

Continued Treatment

Voriconazole was continued, and the initial trough concentration on Day 3 was high at 6.3 mcg/mL, but subsequent VPCs were 5.1 mcg/mL and 4.2 mcg/mL and therefore within the therapeutic range. Visual disturbances and hallucinations improved and finally resolved.

Blood cultures remained negative. Bronchoscopy was performed after 4 days of voriconazole treatment, and the culture showed fungal growth. Microscopy showed mostly hyaline hyphae, and melanized hyphae after KOH treatment. Culture and internal transcribed spacer (ITS) sequencing identified the mold as *Lomentospora prolificans*.

Challenge Question 2. How would you proceed in terms of systemic antifungal treatment?

- **A. Discontinue voriconazole and start an echinocandin**
- **B. Continue voriconazole monotherapy**
- **C. Continue voriconazole and add terbinafine**
- **D. Discontinue voriconazole and initiate liposomal amphotericin B again**

Discussion

A. Discontinue voriconazole and start an echinocandin. *Lomentospora prolificans* usually exhibits very high MICs against echinocandins[4], and an echinocandin monotherapy is not recommended.

B. Continue voriconazole monotherapy. Voriconazole monotherapy is the second-best option given here. However, combination therapy may be more appropriate, as discussed in the next option.

C. Continue voriconazole and add terbinafine. A recent retrospective review of the FungiScope® registry, which was the largest analysis to date, found that combination antifungal therapy was associated with increased 28-day survival vs monotherapy in patients infected with *Lomentospora prolificans*. In the analysis, the combination of voriconazole plus terbinafine trended toward a higher survival probability when compared with other antifungal regimens in Kaplan-Meier analysis[5]. As a result of that analysis as well as other evidence in literature, antifungal combination therapy and in particular the combination voriconazole plus terbinafine has been recommended as first line therapy for lomentosporiosis in the recent ECMM/ISHAM/ASM guideline[6].

D. Discontinue voriconazole and initiate liposomal amphotericin B again. *Lomentospora prolificans* usually exhibits high MICs against amphotericin B and AmB-therapy has been associated with inferior

clinical outcomes versus voriconazole-based therapies. In addition, the patient had previously developed a Type 1 anaphylactic reaction to liposomal amphotericin B.

Correct answer: C.

Case Continued

Parenteral voriconazole (with TDM) was continued and terbinafine 250 mg bid initiated.

Case Challenge 3. What is true regarding the prognosis of our case?

A. **The patient has a good chance of survival, with mortality matching what we see in invasive aspergillosis (30-40%).**

B. **Infections with *Lomentospora* spp. are associated with devastating mortality rates, particularly in patients with hematological malignancies.**

Discussion

A. **The patient has a good chance of survival with mortality matching what we see in invasive aspergillosis (30-40%).** This is not correct. Infections due to *Lomentospora* spp. are associated with devastating mortality rates, particularly for those with underlying hematological malignancies and those with disseminated infection (including those with positive blood culture)[7]. More effective antifungals are urgently needed, and currently two agents are under development; olorofim and fosmanogepix are both showing promising results in vitro, and olorofim is also showing promising results in a phase 2b clinical trial.

B. **Infections with *Lomentospora* spp. are associated with devastating mortality rates, particularly in patients with hematological malignancies.** Infections due to *Lomentospora* are associated with devastating mortality rates, particularly for those with underlying hematological malignancies and those with disseminated infection (including those with positive blood culture). In a recent analysis of 41 FungiScope® cases, fatal outcome attributed to the fungal infection was observed in 51% overall and in 77% of patients with underlying hematological malignancies[7].

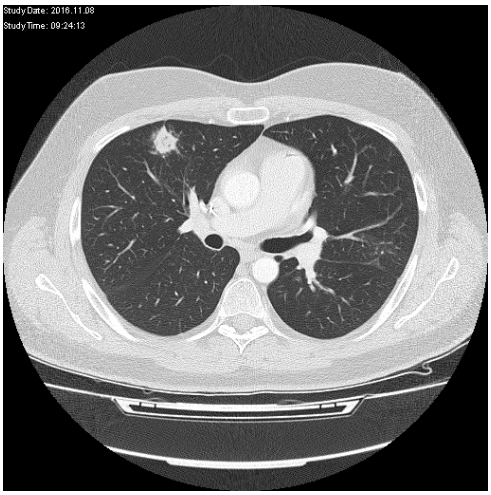
Correct answer: B.

Case Continued

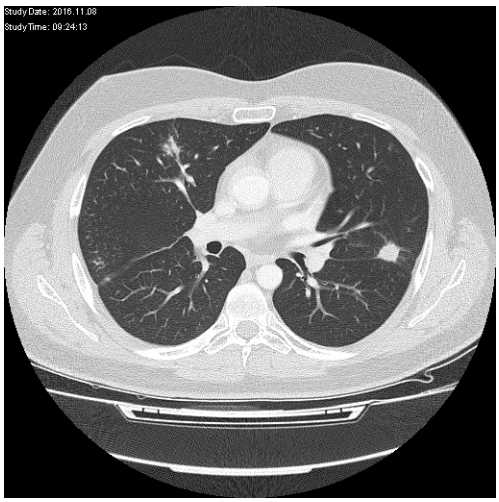
Over the next week the patient slowly improved, and his neutrophils recovered without him experiencing a temporary worsening of symptoms. A CT was performed and results are shown in Figure 2, panels A, B, and C. In the CT, the size of the subpleural nodules had decreased; they were now a maximum of 16 mm (previously a maximum of 28 mm) in size with central cavitation. In addition, pleural thickening next to the nodule in the middle/lower lobe was detected.

Figure 2, panels A, B, and C. Results of CT scan at different cuts showing decreased nodule size. Images courtesy of Martin Hoenigl, MD.

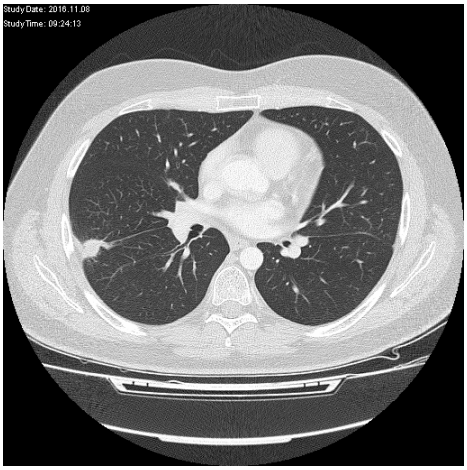
Panel A.



Panel B.



Panel C.

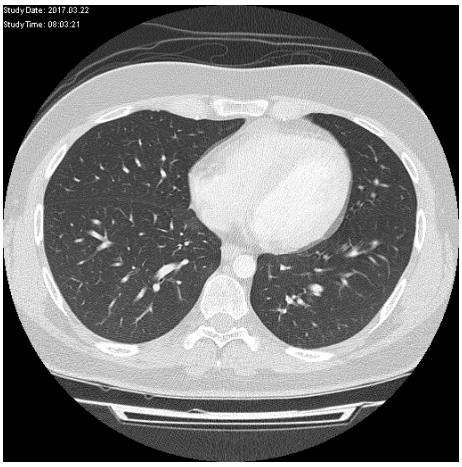


Voriconazole was switched to oral, and the patient was discharged with antifungal combination therapy.

Follow-up and Outcome

A few months later a chest CT showed further improvements (Figure 3). The radiologists now described 2 nodules: a nodule of 7-mm diameter in the lower right lobe with cavitation and spiculated tail and a nodule of 4-mm diameter in the middle lobe.

Figure 3. Chest CT scan after a few months showing 2 nodules. Image courtesy of Martin Hoenigl, MD.



Terbinafine was discontinued, while voriconazole was continued as secondary prophylaxis, given that the patient had agreed to allogeneic stem cell transplantation.

References

1. Zonios DI, Gea-Banacloche J, Childs R, et al. Hallucinations during voriconazole therapy. *Clin Infect Dis.* 2008;47(1):e7-e10. doi:10.1086/588844
2. Kim SH, Yim DS, Choi SM, et al. Voriconazole-related severe adverse events: clinical application of therapeutic drug monitoring in Korean patients. *Int J Infect Dis*. 2011;15(11):e753-8. doi:10.1016/j.ijid.2011.06.004
3. Park WB, Kim NH, Kim KH, et al. The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. *Clin Infect Dis*. 2012;55(8):1080-7. doi:10.1093/cid/cis599
4. Wu Y, Grossman N, Totten M, et al. Antifungal susceptibility profiles and drug resistance mechanisms of clinical *Lomenentospora prolificans* isolates. *Antimicrob Agents Chemother.* 2020;64(11):e00318-20. doi:10.1128/AAC.00318-2
5. Jenks JD, Seidel D, Cornely OA, et al. Voriconazole plus terbinafine combination antifungal therapy for invasive *Lomentospora prolificans* infections: analysis of 41 patients from the FungiScope® registry 2008-2019. *Clin Microbiol Infect.* 2020;26(6):784.e1-784.e5. doi:10.1016/j.cmi.2020.01.012
6. Hoenigl M, Salmanton-García J, Walsh TJ, et al. Global guideline for the diagnosis and management of rare mould infections: an initiative of the European Confederation of Medical Mycology in cooperation with the International Society for Human and Animal Mycology and the American Society for Microbiology [published correction appears in Lancet Infect Dis. 2021 Apr;21(4):e81]. *Lancet Infect Dis*. 2021;21(8):e246-e257. doi:10.1016/S1473-3099(20)30784-2
7. Jenks JD, Seidel D, Cornely OA, et al. Clinical characteristics and outcomes of invasive *Lomentospora prolificans* infections: analysis of patients in the FungiScope® registry. *Mycoses*. 2020;63(5):437-442. doi:10.1111/myc.13067