CASE 1: 41-YEAR-OLD MALE WITH OBESITY AND A HISTORY OF STEM CELL TRANSPLANT

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Initial Presentation

A 41-year-old obese (140 kg [308 lbs]) man presents to an Emergency Department in Austria with dyspnea and intermittent chest pain for a few minutes, but without fever. He has a history of myelodysplastic syndrome (MDS) and secondary acute myeloid leukemia (AML), which were diagnosed 7 years ago. He has undergone an allogeneic stem cell transplantation 6.5 years ago and suffers from chronic graft-versus-host disease (GVHD) of the skin and mucous membranes with a keratoconjunctivitis sicca for 6 years. Other medical history includes chronic renal insufficiency and steroid-induced diabetes mellitus. The patient is currently receiving methylprednisolone 56 mg per day divided into 2 doses and cyclosporin 75 mg bid. He is on prophylaxis with posaconazole suspension 3 x 5 mL/d, trimethoprim/sulfamethoxazole 160/800 mg 3x/week, and azithromycin 250 mg every 2nd day. He is also taking amoxicillin/clavulanic acid 500/125 mg bid, which was prescribed by his primary care provider due to suspicion of pulmonary infection.

His c-reactive protein (CRP) comes back at 16 mg/dL, and he has leukocytosis with elevated neutrophils. After a few hours in the emergency department, he develops hemoptysis, after which he is admitted. Treatment with amoxicillin/clavulanic acid is discontinued and meropenem 3 x 1 g is initiated. Sputum results are negative for Ziehl-Neelsen (ZN) stain and acid-fast bacteria culture for tuberculosis.

Due to a suspicion of invasive pulmonary aspergillosis, a serum galactomannan test is ordered and comes back negative.

His chest computed tomography (CT) scan shows multiple nodules up to 80 mm in diameter disseminated over both lungs as well as nodules with central cavitations accentuated in the right upper lobe (Figure 1 and 2).

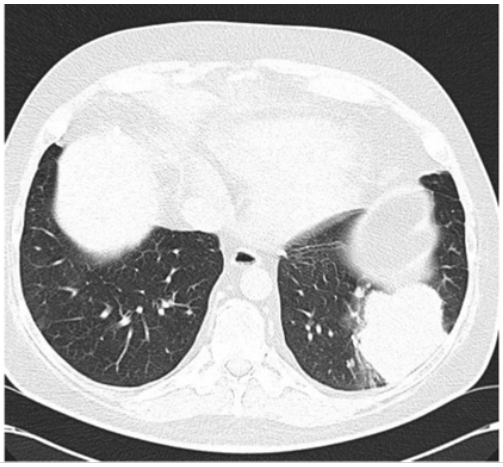

Figure 1. CT scan showing chest nodules. Image courtesy of Martin Hoenigl, MD.

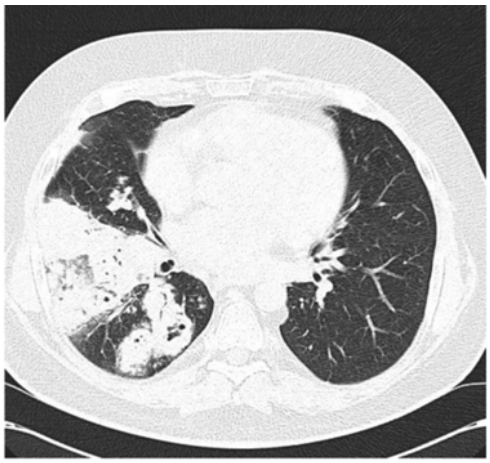

Figure 2. CT scan of chest showing nodules with central cavitations in the right upper lobe. Image courtesy of Martin Hoenigl, MD.

Challenge Question 1. How would you interpret the CT findings and laboratory test results?

A. Invasive aspergillosis is unlikely in this patient because of the absence of fever
B. Invasive aspergillosis is unlikely in this patient due to the absence of typical radiological signs, specifically the halo sign and the air-crescent sign
C. Invasive aspergillosis is unlikely because of the negative serum GM
D. A, B and C all are correct
E. A and B are correct
F. A and C are correct
G. B and C are correct
H. None are correct

Discussion

A. **Invasive aspergillosis is unlikely in this patient because of the absence of fever**
While fever is found in about 95% of neutropenic patients with invasive aspergillosis, fever is significantly less frequently observed in non-neutropenic patients with invasive aspergillosis, where only 50-70% develop fever. Also, cough is significantly less frequently observed in non-neutropenic patients with invasive aspergillosis. While our patient did have chest pain, this symptom is also absent in a significant proportion of non-neutropenic patients. Finally, dyspnea is frequently observed in non-neutropenic patients with invasive aspergillosis and was also reported by our patient[1,2].

B. **Invasive aspergillosis is unlikely in this patient due to the absence of typical radiological signs, specifically the halo sign and the air-crescent sign**
While our patient presented with nodules and cavitation in the chest CT, which are considered typical signs of invasive aspergillosis (IA), it is important to emphasize that non-specific infiltrates or consolidations are most frequently observed in non-neutropenic patients with IA. Due to different pathophysiology with primarily airway invasive growth (as opposed to angioinvasive growth in neutropenic patients), typical radiologic signs like the halo sign or the air-crescent sign are only observed in a small proportion (<10%) of non-neutropenic patients with IA. Overall, typical radiologic signs for IA according to European Organisation for Research and Treatment of Cancer/Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) definitions are only observed in 30-50% of proven non-neutropenic IA cases, emphasizing that these criteria are less applicable to this group of patients[3].

C. **Invasive aspergillosis is unlikely because of the negative serum GM**
Animal models have shown that serum GM concentrations were significantly higher in Ara-C induced neutropenia vs immunosuppression with cyclosporin/prednisolone (eg, non-neutropenic) models[4]. The same has been shown in humans with underlying hematological malignancies, in that serum GM sensitivity decreased in association with increasing neutrophil number and markedly lower sensitivities were observed in non-neutropenic patients (eg, 20% in one study meaning 4/5 non-neutropenic patients with IA had a negative serum GM, in another study the sensitivity was 37% as opposed to 90% in neutropenic patients)[5,6]. In addition, sensitivity of serum GM decreased markedly in patients receiving mold-active prophylaxis[7]. Remember, this patient was on posaconazole oral solution.

D. **None are correct**
This seems to be the most appropriate response. Non-neutropenic patients at risk for IA are those with the greatest unmet needs in the hematologic malignancy setting:
- Airway invasive growth
- Clinical presentation is less typical (fever only present in 50% of patients)
- Chest CT: Non-specific infiltrates or consolidations are more frequently observed vs. typical signs of IA
- Blood biomarkers, in particular serum GM, have lower sensitivity

Correct answer: D.

Suspected Diagnosis

Invasive aspergillosis is clinically suspected, and a bronchoscopy is planned. Also, a posaconazole trough plasma level is ordered and comes back at < 0.20 mcg/mL, which is below the limit of detection.

Challenge Question 2. Is this relevant?

A. No, intracellular concentrations of posaconazole, particularly those in the lung, are much higher than plasma concentrations and therefore breakthrough infections are rare.
B. Yes, breakthrough infections may be rare under posaconazole prophylaxis, but if they do occur, they mostly occur in those with low posaconazole plasma concentrations (PPC).

Discussion

A. **No, intracellular concentrations of posaconazole, particularly those in the lung, are much higher than plasma concentrations and therefore breakthrough infections are rare.**
Intracellular posaconazole concentrations, in particular those in the lung (eg, lung epithelial cells), have indeed been shown to be up to 40 times higher than plasma concentrations[8].This may also explain why usually the lowest rates of breakthrough infections are observed in those with posaconazole prophylaxis vs other antimould prophylactic regimens[9].

B. **Yes, breakthrough infections may be rare under posaconazole prophylaxis, but if they do occur, they mostly occur in those with low posaconazole plasma concentrations (PPC).**
Despite a lower rates of breakthrough infections with posaconazole-containing prophylaxis regimens vs other antimould prophylaxis regimens, breakthrough invasive aspergillosis does occur in patients treated with posaconazole prophylaxis[10], and those who develop breakthrough infections usually have very low PPCs[11,12]. Finally, very low PPCs may also be an indicator of non-adherence[12]. Measurement of posaconazole plasma concentrations is more relevant in those who receive the posaconazole oral solution, which requires intake with a fatty meal and is overall less well absorbed than the posaconazole delayed-release tablets, which are associated with much higher and more reliable plasma concentrations.

Correct answer: There is some truth to both, but **B** is the most appropriate response.

Case Work-up

Bronchoscopy is performed, and the bronchoalveolar lavage fluid (BALF) GM comes back highly positive with a 5.09 optical density index. BALF culture remains negative and doesn't show fungal growth. When asked, the patient reports that he hasn't taken the posaconazole solution for the last 2 weeks.

Challenge Question 3. What would you do now in terms of antifungal treatment?

A. Discontinue posaconazole and initiate oral voriconazole 2x200 mg
B. Discontinue posaconazole and initiate IV voriconazole 2x6 mg/kg on Day 1 followed by 2x4 mg/kg
C. Discontinue posaconazole and initiate IV liposomal amphotericin B 3-5 mg/kg.
D. Discontinue posaconazole and initiate isavuconazole 3x200 mg IV/PO for the first 2 days, then 1x200 mg starting Day 3

Discussion

A. **Discontinue posaconazole and initiate oral voriconazole 2x200 mg**
Please remember that the patient weighs 308 lbs (140 kg); therefore, higher doses of voriconazole are recommended. Also, voriconazole plasma concentrations vary widely and overall are significantly lower in those receiving oral voriconazole vs those receiving IV voriconazole. It is, therefore, generally recommended to start with higher IV and bodyweight adjusted dosing, with the option to step down to oral voriconazole later.

B. **Discontinue posaconazole and initiate IV voriconazole 2x6 mg/kg on Day 1 followed by 2x4 mg/kg**
This response is correct. In fact, voriconazole is strongly recommended as first-line treatment for invasive aspergillosis in all 3 of the most important clinical guidelines in the field[13,14,15].

C. **Discontinue posaconazole and initiate IV liposomal amphotericin B 3-5 mg/kg**
This may be considered the best option in settings in which a relevant proportion of *Aspergillus* spp. exhibits resistance to azoles, and in fact liposomal amphotericin B becomes the first-line treatment in these settings. However, in Austria, the rate of azole resistance in *Aspergillus* spp. is extremely low. Another argument may be the fact that our patient was on posaconazole prophylaxis when developing invasive aspergillosis, however the fact that he reported not taking the posaconazole solution may be an argument against it. There are also arguments against the use of liposomal amphotericin B as first line treatment for invasive aspergillosis, including the only “moderate” recommendation for using it as IA first line in the two most recent guidelines[13,14]. Maybe the most important argument against liposomal amphotericin B in this patient is the fact that he has a chronic renal insufficiency as underlying disease, which may be worsened by liposomal amphotericin B, which exhibits nephrotoxic adverse events in a large proportion of cases.

D. **Discontinue posaconazole and initiate isavuconazole 3x200 mg IV/PO for the first 2 days, then 1x200 mg starting Day 3**
This response is also correct. Isavuconazole is now also strongly recommended for first-line treatment of IA with recommendations mirroring those for voriconazole[13,14]. In fact, isavuconazole has been shown to be better tolerated than voriconazole, with a reduced incidence of liver and skin toxicity as well as eye disorders[16]. In general, isavuconazole plasma concentrations are reliable, and therapeutic drug monitoring (TDM) is likely not necessary (in contrast to voriconazole). However, isavuconazole may not be available in all settings and, if available, it is also more expensive.

Correct answer(s): B and **D** are the most appropriate responses.

Case Treatment

We initiated voriconazole 2x6 mg/kg IV day 1, followed by 2x4 mg/kg starting day 2.
Please remember the patient's history, which stated "He has a history of myelodysplastic syndrome (MDS) and secondary acute myeloid leukemia (AML) which were diagnosed 7 years ago; he has undergone allogeneic stem cell transplantation 6.5 years ago and suffers from chronic graft-versus-host disease of the skin, and mucous membranes with a keratoconjunctivitis sicca for 6 years. Other medical history includes chronic renal insufficiency and steroid-induced diabetes mellitus. The patient is currently receiving methylprednisolone 56 mg per day divided into 2 doses, and cyclosporin 75 mg bid."

Challenge Question 4. Now that we initiated voriconazole, what needs to be specifically monitored?

A. Voriconazole plasma concentrations (VPCs)
B. Renal function
C. Cyclosporin dosing and concentrations
D. A and C
E. A and B

Discussion

A. **Voriconazole plasma concentrations (VPCs)**
Given the high intrapatient and interpatient variability of VPCs and their association with treatment failure (eg, low concentrations) but also drug-related toxicity (high concentrations), TDM should be performed starting on Day 2-5 of voriconazole treatment. Numerous studies have demonstrated that low concentrations of voriconazole are associated with treatment failure, although the lower threshold has variously been reported as < 1 mcg/mL[17], < 1.7 mcg/mL[18], or < 2.05 mcg/mL[19]. Additionally, a voriconazole concentration of < 1 mcg/mL was associated with higher mortality in a pediatric population[20].

Response to therapy is enhanced when the VPC is kept above a target concentration, which in one study was > 1.5 mcg/mL[21] and in another > 2.2 mcg/mL[22]. However, voriconazole plasma concentrations > 5 mcg/mL have been associated with an increased probability of adverse events[21,23], including visual disturbances and hallucinations[18]. Hence, maintaining the VPC above the threshold concentration for efficacy, but below the threshold for toxicity, requires routine TDM. Please remember also that the patient weights 308 lbs (140 kg), therefore TDM may be particularly relevant.

B. **Renal function**
While the patient has chronic renal insufficiency, voriconazole is not known to particularly impair renal function.

C. **Cyclosporin dosing and concentrations**
Voriconazole is metabolized by the CYP3A4 system (also by CYP2C19 and CYP2C9), as are cyclosporin, sirolimus, tacrolimus, meropenem, and multiple other medications. For those receiving voriconazole and ciclosporin it is recommended that ciclosporin dosages be reduced with frequent monitoring of ciclosporin blood concentrations[24,25].

Correct answer: D.

Case Continued

The cyclosporin dosage was reduced to 50 mg bid, and at this reduced dose, cyclosporin concentrations were within the targeted range and remained constant. Meropenem was discontinued.

Voriconazole plasma concentrations were in the targeted range (1.5-5.5 mcg/mL) and the patient improved slowly. Voriconazole was switched to oral 300 mg bid, after which VPCs were below the targeted range. After adjusting the oral dose to 400 mg bid, VPCs increased to 3.5 mcg/mL and remained constant. Electrocardiograms (ECGs) did not show a QT prolongation. A follow up chest CT performed 6 weeks after admission is shown in Figures 3 and 4.

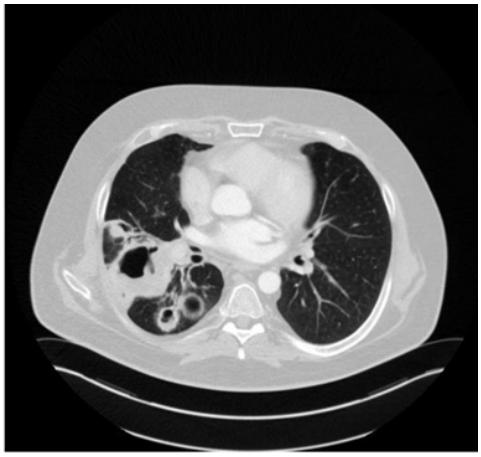

Figure 3. The patient's follow-up chest CT scan showing cavernous lesions in the right upper lobe. Images courtesy of Martin Hoenigl, MD.

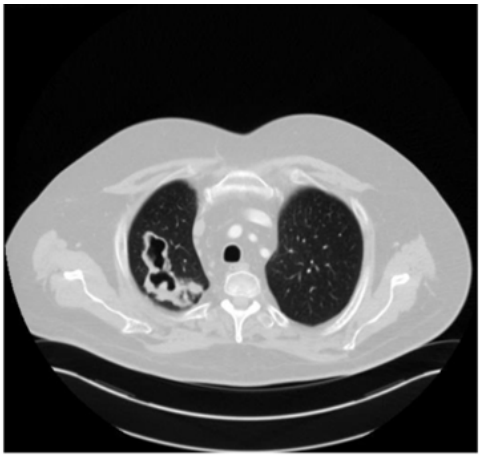

Figure 4. CT scan of patient's chest showing a reduction of solid lesions compared with baseline. Images courtesy of Martin Hoenigl, MD.

These images were interpreted as improvement, with multiple thick-walled cavernous lesions up to 60 mm in diameter in both lungs accentuated in the right upper lobe (Figure 3) and a decrease of solid lesions, compared to the baseline and prior follow-up CTs (Figure 4).

The patient was discharged with oral voriconazole 400 mg bid with the recommendations to perform voriconazole trough concentrations once weekly as well as ECG controls (to monitor QT time). Despite voriconazole concentrations that were continuously between 3-6 mcg/mL and therefore in the higher targeted range, the patient was readmitted 4 months later to the Emergency Department with a fever of 39°C/102.2°F despite piperacillin/tazobactam (4.5 g tid). A chest CT was performed, which is shown below in Figure 5. The CT showed that the lesions had consolidated and increased in size compared to the discharge CT.

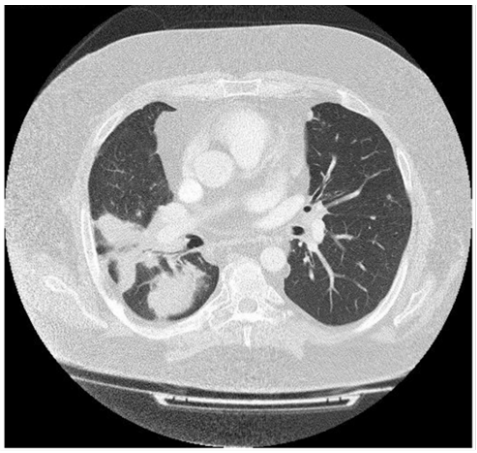

Figure 5. Chest CT scan showing consolidated and enlarged lesions. Image courtesy of Martin Hoenigl, MD.

Challenge Question 5. What would you do next in terms of antifungal treatment?

A. Discontinue voriconazole and start liposomal amphotericin B
B. Discontinue voriconazole and start isavuconazole
C. Continue voriconazole but switch to weight adjusted parenteral dosing

Discussion

A. **Discontinue voriconazole and start liposomal amphotericin B**
As the patient showed radiologic and clinical worsening on voriconazole despite having appropriate plasma concentrations, switching to another class of antifungal would be the best option. Liposomal amphotericin B has a broad spectrum of activity that includes *Aspergillus*, so this approach would be the best option here.

B. **Discontinue voriconazole and start isavuconazole**
Given that the patient showed radiologic and clinical worsening despite high VPCs, a switch to a new class of antifungals would be the better option here. If an antifungal from the same class is used, underlying resistance and co-infection with another mold (eg, Mucorales) become more likely to be potential causes of treatment failure, as compared to the earlier situation where the patient was not adherent to posaconazole.

C. **Continue voriconazole but switch to weight adjusted parenteral dosing**
This is unlikely to be effective as VPCs were in the higher targeted range even on oral therapy.

Correct answer: A.

Antifungal Treatment and Outcome

Following the chest CT, piperacillin/tazobactam was increased to 9 g tid (308 lb/140 kg bodyweight), voriconazole was discontinued, and cyclosporin dose was increased again to baseline (75 mg bid). Liposomal amphotericin B was initiated with a daily dose of 700 mg (eg, 5 mg/kg).

Three days later, liposomal amphotericin B had to be discontinued due to progression of renal insufficiency (the glomerular filtration rate was 18ml/min), and piperacillin/tazobactam was also reduced to 4.5 g qid.

Isavuconazole was initiated 200 mg tid for 2 days followed by 200 mg qid starting on Day 3. Although not usually recommended, isavuconazole plasma levels were measured given the patient's high body weight. The TDM showed isavuconazole levels within the targeted range, as did cyclosporin blood concentrations. No decrease of dosage was necessary; isavuconazole has been reported before to show fewer interactions with cyclosporin and other immunosuppressants as compared with other antifungal agents[25,26]. The patient showed clinical improvement and normalization of inflammatory parameters, and piperacillin/tazobactam was discontinued. Seven days later the patient was discharged on isavuconazole 200 mg qid.

The patient improved further, and 3 months after isavuconazole was initiated, a follow-up chest CT was performed, which also showed clear radiological improvement (Figure 6).

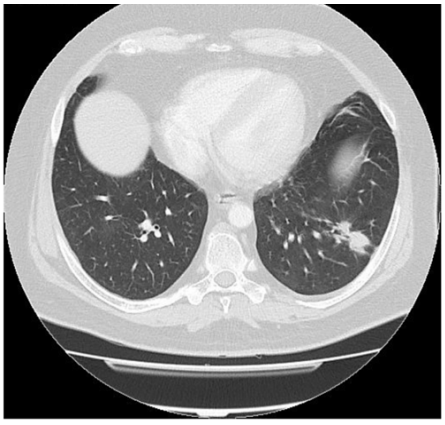

Figure 6. Chest CT scan 3 months after initiation of isavuconazole. Image courtesy of Martin Hoenigl, MD.

Isavuconazole was discontinued, and posaconazole delayed-release tablets were initiated as secondary prophylaxis given the patient's GVHD. No relapse was observed.

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