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Real world challenges and unmet needs in the diagnosis and treatment of suspected invasive pulmonary aspergillosis in patients with hematological diseases: an illustrative case study

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Conflicts of interest

Martin Hoenigl has received a research grant for an investigator-initiated study from Gilead, and speaker's honoraria from MSD, Gilead, and Basilea. Juergen Prattes has received consulting fees from Gilead. Albert Wölfler has received speakers honoraria from Merck. Other authors: no conflicts of interest to declare.

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Abstract

Recent years have seen important advances in the diagnosis of invasive pulmonary aspergillosis (IPA), complemented by the introduction of new therapies. Despite this, IPA remains a major cause of infection-related mortality in patients with hematological diseases. There are two main reasons for this. First, diagnosis of IPA remains a challenge, since risk factors and the clinical, radiological and mycological presentations vary not only by fungal disease stage, but also by patient group (e.g. neutropenic versus non-neutropenic patients). Diagnosis is particularly challenging in patients receiving mold-active prophylactic or empirical treatment, which reduces the sensitivity of all diagnostic tests for IPA. Second, treatment of IPA is complex due to unpredictable pharmacokinetic profiles of antifungal agents, small therapeutic window in terms of exposure and adverse events, and multiple drug-drug interactions through the CYP450 system. Here we report a case of a 23-year-old male with severe aplastic anaemia and subpleural nodules. Diagnostic tests for IPA obtained during ongoing mold-active empirical treatment were negative. Intravenous voriconazole was stopped after visual disturbances and hallucinations. The patient then had an anaphylactic reaction to liposomal amphotericin B and was switched to intravenous posaconazole,

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which had to be discontinued due to a significant increase in transaminase levels. He was treated with oral isavuconazole with reduced dosage, triggered by increasing transaminases under the standard dosage. Even under reduced dosage, blood concentrations of isavuconazole were high and treatment was successful. The case illustrates real-world challenges and unmet needs in the diagnosis and treatment of IPA in patients with hematological diseases.

Introduction

Recent years have seen important advances in the diagnosis of invasive pulmonary aspergillosis (IPA), complemented by the introduction of new therapies. Despite this, IPA remains a major cause of infectious pneumonia-related mortality in immunocompromised hosts.[1,2] Diagnosis is based on host, clinical and mycological criteria, such as those recommended by the European Organization for Research and Treatment of Cancer (EORTC) and the Mycosis Study Group (MSG).[3] However, the clinical and radiological presentation of invasive aspergillosis (IA) is non-specific and can be atypical or insidious, particularly in non-neutropenic patients.[4] Also, a substantial proportion of patients with IPA do not meet the EORTC/MSG criteria for host factors,[3] which were largely based on expert opinion.[5,6] Mycological diagnosis is challenging, particularly since cultures of lower respiratory secretions in bronchoalveolar lavage (BAL) fluid have a low yield and sensitivity.[7] In addition to imaging by computed tomography (CT), diagnosis of IPA is typically based on fungal biomarkers (e.g., galactomannan [GM], beta-D-glucan [BDG], and lateral-flow device [LFD] testing) and on molecular tools (polymerase chain reaction [PCR]) of blood or BAL fluid.[8,9] Despite advances in the diagnostic arsenal, IPA remains difficult to diagnose. This is true in particular in patients receiving mold-active prophylaxis or treatment, which has been shown to reduce sensitivity of all diagnostic tests for IPA.[10–15]

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Factors which complicate the use of antifungal treatments in IPA include unpredictable pharmacokinetic profiles, strong relationships between exposure and both efficacy and adverse events, and multiple drug-drug interactions through the CYP450 system. These interactions have to be considered primarily during voriconazole treatment,[16,17] the current gold standard for treatment of IPA, but to a lesser degree are also observed with other triazole agents, such as posaconazole.[18,19]

Here we present a case that illustrates some of the challenges and unmet needs in the diagnosis and treatment of IPA.

The case

The patient

A previously healthy 23-year-old male presented to the emergency department with petechial bleeding, which had started two weeks earlier, and with hematoma on the right cubita. Pancytopenia had been detected by his family physician. While in the emergency department, the patient developed chills and fever.

First admission

The patient was admitted with suspected acute leukaemia. Severe aplastic anaemia was diagnosed on bone marrow biopsy and, in the absence of a human leukocyte antigen (HLA)-identical sibling, a search for an unrelated donor was initiated. Cefepime was administered for 7 days to treat neutropenic fever and the patient improved significantly. Anti-infective treatment was de-escalated to oral levofloxacin and fluconazole prophylaxis. Specific treatment for aplastic anaemia with antithymocyte antiglobulin (ATGAM) over 4 days and cyclosporine was initiated. Granulocyte-stimulating factor (GCSF) therapy was initiated but had to be interrupted twice due to severe pain, and absolute neutropenia continued over a course of more than 2 months.

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Three weeks after ATGAM treatment, the patient developed neutropenic fever, and cefepime was initiated empirically. The diagnostic work up showed a C-reactive protein (CRP) level of 127.5 mg/dL (normal range <5 mg/dL). He was cytomegalovirus-negative on whole-blood PCR. Serum tests for fungal infections remained negative (serum GM <0.2 optical density index [ODI]; serum BDG <15.38 pg/mL). Chest X-ray on day 2 of cefepime treatment indicated suspected pneumonia and a subsequent CT scan revealed three subpleural nodules up to 28 mm in diameter (Figure 1a). Cefepime was discontinued, and treatment with moxifloxacin, meropenem and vancomycin was introduced. In addition, due to suspicion of IPA, intravenous (i.v.) voriconazole was initiated on the day of the CT scan. The patient received a total of two doses of 6 mg/kg (i.e., 2 x 540 mg), but despite a slow infusion rate the patient experienced severe visual disturbances and hallucinations and voriconazole had to be discontinued. He was switched on the same day to i.v. liposomal amphotericin B (3 mg/kg), but developed a type 1 anaphylactic reaction during the first infusion (Grade 3 with hypotension, shortness of breath, hypoxemia and abdominal pain). Immediately after recovery, i.v. posaconazole was initiated on the morning of the next day (300 mg twice daily [bid] on day 1, then 300 mg daily). Bronchoscopy was performed three days after initiation of posaconazole treatment. GM in BAL fluid was 0.48 ODI, and negative results were obtained by the *Aspergillus* LFD, fungal and bacterial culture, as well as panfungal PCR and PCR for *Pneumocystis jirovecii*, *Legionella pneumophilia*, *Mycoplasma pneumonia* and for numerous other viral and bacterial causes of respiratory tract infections. Subsequent serum GM and BDG levels remained consistently below the cut-off levels for diagnosis of IPA.

Four days later, the patient was still febrile but the CRP level was decreasing and he had started to improve clinically. However, transaminase levels were increasing, exceeding (i.e., 3 to 5-fold) the upper limits of normal: alanine aminotransaminase (ALT) was 266 IU/L, aspartate aminotransaminase (AST) was 130 IU/L, gamma-glutamyl transpeptidase [GGT] was 327 IU/L and alkaline phosphatase was 143 IU/L. After consultation with the hepatologist, posaconazole was withdrawn after 10 days of treatment (moxifloxacin was also

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discontinued), caspofungin was started (70 mg, approximately 0.8 mg/kg, throughout treatment) and transaminase levels decreased. After five days of caspofungin treatment, a chest CT scan showed that the size of subpleural nodules was decreasing (now up to 16 mm in size), with pleural thickening next to one node (Figure 1b) and central cavitation of another node (Figure 1c). Nine days later another CT scan showed no significant changes (Figure 1d). The patient was improving clinically and the CRP level was decreasing. Vancomycin and meropenem were discontinued stepwise and oral levofloxacin was initiated. In preparation for discharge, caspofungin was also withdrawn. Oral isavuconazole was introduced, at a dose of 200 mg bid for the first two days and 200 mg qd subsequently, selected on the basis of its bioavailability and pharmacokinetic profile.

Three days after starting isavuconazole, the cyclosporine serum concentration doubled, with intermittent renal dysfunction which resolved after the cyclosporine dose was reduced. The patient was discharged four days later on oral isavuconazole (at a dose of 200 mg qd), levofloxacin and aciclovir, with a neutrophil count of 600/μL.

Further admissions

One month later, the patient had a significant increase in aminotransaminases to levels several-fold higher than the upper limit of normal (ALT 339 IU, AST 179 IU/L, alkaline phosphatase 232 IU/L). Subsequently, after consultation with the hepatologist and the infectious diseases specialist, the isavuconazole dose was reduced to 100 mg qd, resulting in an isavuconazole plasma concentration of 5.38 μg/mL (using high-performance liquid chromatography) two weeks after the dose was reduced, and aminotransaminase levels returned to normal. Five weeks later (i.e. after 7 weeks of isavuconazole at the reduced dose of 100 mg qd) the isavuconazole concentration was 2.3 μg/mL.

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Outcome

Five months after the first CT scan had shown multiple subpleural nodules up to 28 mm in diameter, a control CT scan showed clear improvement. The two largest nodules were now only 4 and 7 mm in diameter (Figure 1e). Thereafter, the patient successfully underwent allogeneic hematopoietic stem cell transplantation (HSCT) from an HLA-matched unrelated donor on prophylaxis with isavuconazole, for which the dosage was successfully re-escalated to 200 mg qd. At last follow-up on day +42 after HSCT, the patient was still receiving isavuconazole and doing well, with fully recovered blood counts and close to normal aminotransaminase levels.

Discussion

Aspergillus infection is a major cause of fungal pneumonia in neutropenic patients,[20] but diagnosis of IPA can be complicated, particularly when antifungal therapy has already been initiated. In this patient, despite negative serum GM levels, suspicion of IPA in the CT scan led to diagnostic bronchoscopy while the patient was receiving mold-active antifungal treatment (i.v. posaconazole). Even though the GM level (0.48 ODI) was below the suggested cut-off of 0.5 ODI in individuals receiving mold-active antifungal therapy,[13,14] and both the *Aspergillus* LFD and antifungal culture were negative, the radiological and clinical course remained suggestive of IPA, although infection by another mould or other pathogen cannot be completely ruled out.

Previous studies have shown that although the performance of diagnostic tests for IPA are superior in BAL fluid compared to blood,[14] the sensitivities of all diagnostic tests are substantially reduced in the presence of mold-active antifungal prophylactic or empirical treatment. Reinwald et al prospectively evaluated GM levels in BAL samples from 29 patients being treated for probable or proven IA and found a GM cut-off of 0.5 ODI to be more sensitive (79%) but equally specific (96%) to a 1.0 ODI cut-off.[10] Subsequently, Eigl

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and colleagues showed that a GM cut-off in BAL samples of 0.5 ODI provided 71% sensitivity in patients receiving mold-active antifungal therapy at the time of sampling compared to 95% in untreated patients.[11] A 1.0 ODI cut-off gave sensitivities of 52% and 81%, respectively. Thus, in patients receiving mold-active antifungal agents, a 0.5 ODI cut-off for BAL GM seems reasonable – but sensitivity is still impaired compared to untreated individuals. Importantly, the sensitivity of BAL GM is likely to have been overestimated in those studies since GM was used as a mycological criterion for defining probable IPA, which represented the majority of cases in those studies. The *Aspergillus* LFD in BAL samples shows a similar reduction in sensitivity to GM testing (56% sensitivity in treated patients versus 86% in untreated patients), and is therefore less reliable in patients receiving antimold prophylaxis or treatment.[11,15,21] Mold-active antifungal therapy also affects *Aspergillus* PCR monitoring of blood samples (specificity and sensitivity 52% and 50%, respectively, compared to 71% and 92% in drug-naive patients)[12] and BAL fluid samples.[13] Given this reduced sensitivity in patients receiving mold-active antifungals, particularly in blood samples, combined use of more than one biomarker or test is advisable. For example, one study found that *Aspergillus* PCR and GM testing in BAL fluid, combined with BAL culture and serum GM testing, achieves a sensitivity and specificity of 75% and 95%, respectively.[14] When only BAL fluid is analyzed for GM and *Aspergillus* PCR, and when a positive result for either test is considered to be diagnostic, sensitivity and specificity have both been reported to be 85%.[13] These results clearly indicate that there is a need for novel biomarkers for IPA. However, if the search for a single 'magic bullet' biomarker is ultimately unsuccessful, these new biomarkers could be used in combination with established tests[22] to further improve diagnostic performance, particularly in patients receiving mold-active prophylaxis.

This case also illustrated that antifungal management of IPA is complicated. Our patient developed various serious adverse events necessitating drug switching and dose changes. Following the CT scan, voriconazole was started empirically, but was immediately

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discontinued due to visual and hallucinatory side effects. Liposomal amphotericin B, recommended as alternative treatment for IPA,[23] had also to be discontinued due to a rare type I anaphylactic reaction. It was replaced by i.v. posaconcazole which, in turn, led to a significant increase in aminotransaminase levels and conversion to caspofungin. Isavuconazole, a triazole recommended for use in IPA,[23] was then selected for long-term oral treatment and secondary prophylaxis during allogeneic HSCT, due to its excellent bioavailability and favorable pharmacokinetic profile. Isavuconazole may offer an advantage with regards to hepatotoxicity versus certain other triazoles. The randomized, double-blind SECURE study compared isavuconazole to voriconazole for invasive fungal disease caused by *Aspergillus* species or other filamentous fungi, and showed equivalent efficacy but fewer drug-related adverse events in the isavuconazole group – including fewer drug-related hepatobiliary disorders (9% versus 16% with voriconazole, p=0.016). It has been reported that there is no exposure-response relationship between isavuconazole exposure and risk for elevated ALT or AST when isavuconazole is given at a standard dose.[24] In this case, however, we found that temporarily halving the isavuconazole dose from 200 mg/day to 100 mg/day led to a reduction in elevated aminotransaminase levels, while still being effective as treatment for the suspected *Aspergillus* infection.

One point of interest is the high blood concentrations of isavuconazole despite the reduced dose of 100 mg/day. Oral isavuconazole was initiated at a dose of 200 mg tid, followed by 200 mg/day, which has been shown to result in a mean trough concentration of ~3 µg/mL.[25] Here, despite reduction of the isavuconazole dose to 100 mg/day in response to increased liver function tests, the isavuconazole concentration was 2.3 µg/mL a month later i.e., above the MIC_{90} of isavuconazole against *Aspergillus* spp (2 µg/mL).[26] This concentration may reflect the fact that the patient was receiving cyclosporine. One study found that concomitant cyclosporine increased the mean peak concentration of isavuconazole by 30% via inhibition of CYP3A4, although mean area under the curve (AUC) is almost unaffected (3% increase).[27]

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Conversely, the triazole class of antifungal agents can affect the pharmacokinetics of drugs metabolized by the cytochrome P450 system, including immunosuppressants such as cyclosporine. Cyclosporine AUC has been reported to increase by 29% and peak concentration by 6% in the presence of isavuconazole.[27] This effect is less extensive than for other triazole antifungals: cyclosporine dose reductions of up to 50% have been recommended during concomitant treatment with voriconazole or fluconazole.[28] Here, cyclosporine dose reduction led to normalization of the cyclosporine blood concentration and resolution of renal dysfunction arising from cyclosporine-related nephrotoxicity.

This case highlights two aspects of IPA management in the patient with hematological malignancy. First, the low sensitivity of biomarkers and other tests mean that a negative result should not be regarded as definitive. Where IPA is suspected, alternative diagnostic tests should be undertaken. Second, the safety profiles of triazole antifungal agents vary, and in this case, *Aspergillus* infection was successfully controlled without liver dysfunction through use of low-dose isavuconazole. Given the complexity of diagnosis and clinical management of IPA, emphasis should be placed on initiatives promoting excellence in clinical care.

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Figure 1. CT scan results (a) During admission 2, before initiation of moxifloxacin, meropenem and vancomycin, showing three subpleural nodules up to 28 mm in diameter and multiple subpleural nodules up to 6 mm diameter, compatible with suspected atypical fungal pneumonia (b and c) During admission 2, sixteen days after antimould therapy was started, showing smaller subpleural nodules (up to 16 mm), one with central cavitation (c). Pleural thickening was seen next to the nodule in the middle/lower lobe (b). (d) Nine days later there was no significant change. (e) Five months after the initial CT scan showing clear improvement.

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