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Case Report

Isavuconazole Therapy of Disseminated and Encephalic *Saprochaete Capitata* Infection in an Acute Myeloid Leukemia Patient Treated with Midostaurin

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Abstract. ***Background:*** ***Saprochaete capitata*** **is a rare and emerging opportunistic fungus, involving immunocompromised hosts, in particular, neutropenic patients after chemotherapy.** ***Case Report:*** **We report a case of disseminated and cerebral infection by** ***Saprochaete capitata,*** **in a 68-year-old woman affected by acute myeloid leukemia that was successfully managed with liposomal amphotericin B and isavuconazole.**
Conclusions: **This case illustrates the feasibility of isavuconazole therapy in the treatment of a** ***S. capitata*** **infection when co-administered with midostaurin.**

Keywords: Saprochaete capitata; Isavuconazole; Acute myeloid leukemia; Midostaurin; CNS.

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Introduction. *Saprochaete capitata* (formerly known as *Blastoschizomyces capitatus and Geotrichum capitatum)* is a rare and emerging opportunistic fungus, involving immunocompromised hosts, in particular, neutropenic patients after chemotherapy, with crude mortality estimates as high as 60%.[1,2] Herein we describe the first case, to our knowledge, of disseminated *S. capitata* infection successfully managed with isavuconazole.

Case Report. In 2019, a 68-year-old woman presented with chest pain, dyspnoea, and gum pain lasting one week. Hyperleukocitosis (WBC $241x10^9$/L) was sustained by monoblastic cells. Therefore, bone marrow aspiration was performed and confirmed an extensive infiltration (93% monocytic blasts) by acute myeloid leukemia (AML) with translocation t(9;11)(p21.3;q23.3) and Fms-related-tyrosine kinase 3 with a point mutation in the tyrosine kinase domain (FLT3-TKD) positivity. Therefore, she was treated with standard intensive chemotherapy '7+3' (ARA-C 100mg/m^2 ci. x 7 days and daunorubicin 60mg/m^2 x 3) and midostaurin (50 mg bid, day 8 to 28), a recently approved FLT3 inhibitor metabolized to its active metabolites GGP6221 and CGP52421 via CYP3A4 in the liver.[3,4] Due to the known interference of midostaurin with potent CYP3A4 inhibitors with the risk of side effects including QTc prolongation,[5] as per protocol, we decided not to give the standard posaconazole antifungal prophylaxis, and we planned a preemptive antifungal approach with weekly serum galactomannan monitoring and precocious chest

Computed Tomography (CT) in case of persisting neutropenic fever. On day +8, she developed neutropenic fever, and empirical anti-bacterial treatment with piperacillin/tazobactam and teicoplanin was started. After 48 hours, she was still febrile; therefore, she underwent a CT scan that revealed a 20 mm lung nodule, with halo-sign. Considering a possible invasive fungal infection (IFI) (serum galactomannan assay was negative), we started liposomal amphotericin B (3 mg/kg/day). Two days later, she was still febrile, and blood cultures showed *S. capitata* fungemia, galactomannan raised to 0.6 in two blood samples; therefore, liposomal amphotericin B dosage was increased to 5 mg/kg/day for 9 days, with defervescence within few days. Later, when neutropenia recovered, the CT-scan showed the evolution of the lung nodule into a cavitary lesion (**Figure 1A**), multiple liver abscesses (**Figure 1B**), and a single brain abscess in the left head of the caudate nucleus (**Figure 1C-D**). We then decided to discharge the patient and to shift antifungal treatment from intravenous liposomal amphotericin B to oral isavuconazole. We chose oral isavuconazole instead of oral voriconazole, which is a standard therapy of *S. capitata* infection[6,7] because isavuconazole is a mild/moderate inhibitor while voriconazole is a potent inhibitor of CYP3A4.[5] Isavuconazole was also chosen because of its in vitro activity against *S.capitata*[8,9] and the favorable pharmacokinetic profile in the central nervous system (CNS) infections.[10,11]

The patient successfully underwent two courses of consolidation with high doses of cytarabine and midostaurin while under isavuconazole therapy without any midostaurin related toxicity (the patient was monitored biweekly for QTc prolongation on each ambulatory visit). During maintenance with midostaurin, we performed a therapeutic drug monitoring (TDM) of isavuconazole 5.2 µg/ml (normal range 2-5 µg/ml), no adjustment was undertaken. Eight months later, AML is in complete remission, and fungal infection is improving on isavuconazole (**Figure 2**), despite the prolonged neutropenia induced by the

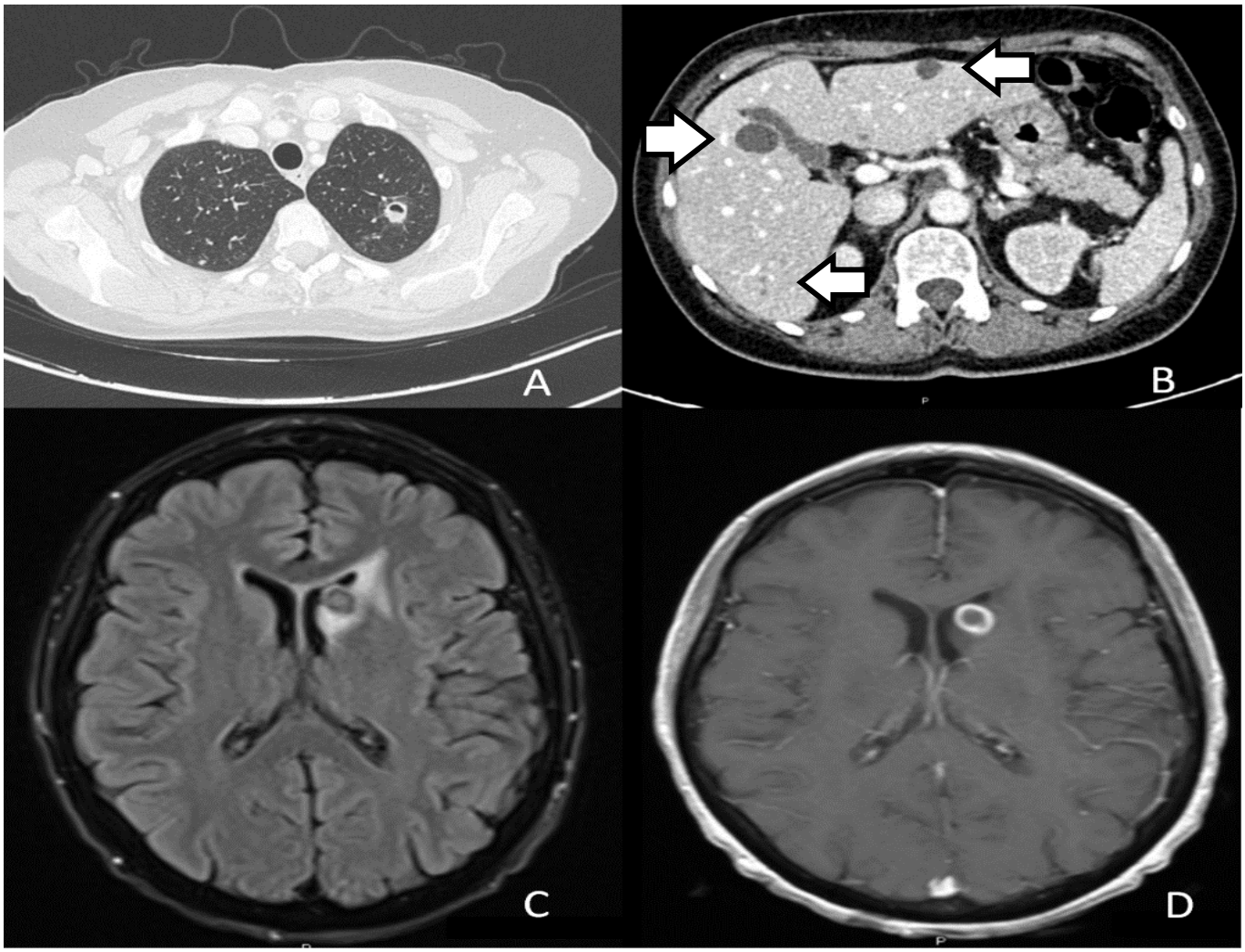

Figure 1. A) CT scan. In the left lung is present a 20 mm excavation filled with fluid: air-crescent sign. **B**) CT scan of the abdomen. Two hypodensae cystic hepatic lesions of 2 and 1.5 cm; other millimetric lesions can be seen (white arrows). **C**) Brain MRI: T2 weighted sequence. An 11 mm cystic lesion is present in the left head of the caudate nucleus, with compression of the left lateral ventricle. Mild peri-lesional edema is present. **D**) Brain MRI: T1 weighted gadolinium contrast-enhanced sequences. The same cystic lesion showing a concentric rim of contrast.

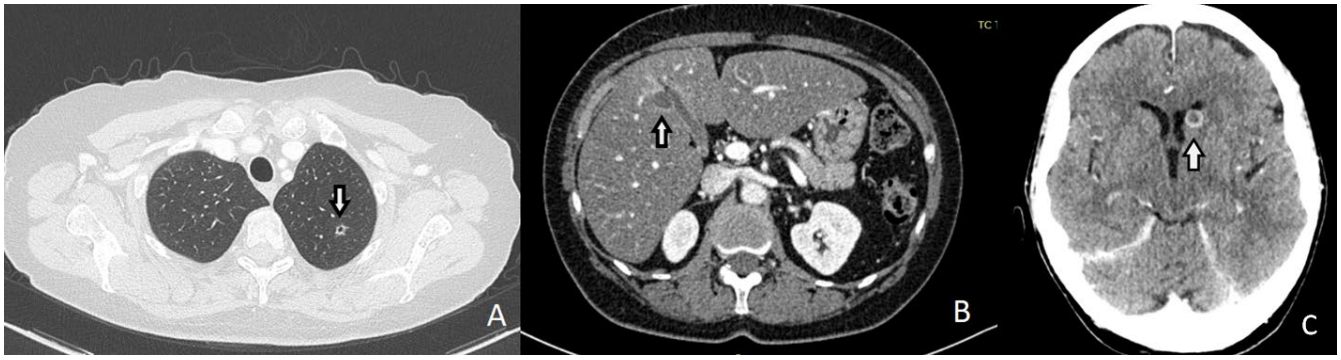

Figure 2. CT scan after 8 months from *S. capitata* infection. **A**) In the left lung is present a 7 mm excavation scar (white arrow). **B**) CT scan of the abdomen. Shrunken hypodensae cystic hepatic lesion of 11 mm. **C**) Brain CT: A 9 mm cystic lesion surrounded by concentric rim is present in the left head of the caudate nucleus.

consolidation cycles.

Discussion. This case illustrates that isavuconazole may be an option in the treatment of *S.capitata* infections, and that may be a safe choice if a co-administration with midostaurin is required. A further case of safe isavuconazole and midostaurin therapy in an AML patient with a possible pulmonary fungal infection has been recently reported.[12]

Indeed, our case raises the challenging question of the appropriateness of administering midostaurin concomitantly with a CYP3A4 inhibitor.

Posaconazole and voriconazole are drugs of the first choice in the primary antifungal prophylaxis and therapy of invasive aspergillosis and other IFIs, respectively.[13,14] However, in patients affected by FLT3 positive AML caution is requested when triazoles are administered concomitantly with midostaurin, given the possible toxicity related to the increased exposure to the FLT3 inhibitor, being posaconazole and voriconazole potent inhibitors of CYP3A4. Furthermore, an increased risk of QTc prolongation should be considered when patients receive midostaurin in association with other drugs that can prolong QTc, as the above triazoles.[4,5]

This limitation in the prevention and treatment of IFIs in FLT3 positive AML patients represents a challenging issue in the clinical practice, considering that IFIs significantly affect complete remission achievement and long-term survival of AML patients [15]. Again, the protective effects of mold active antifungal prophylaxis during induction and salvage chemotherapy for AML may have long-lasting benefits that extend even after the allogeneic stem cell transplant procedure, which is indicated in FLT3 positive AML patients after the achievement of complete remission because of the high risk of leukemia relapse.[16]

On the other hand, the contraindication of the concomitant use of midostaurin and triazoles is controversial. Ouatas et al. analyzed data from the Ratify study focusing on the subset of patients with concomitant use of midostaurin and fluconazole, posaconazole, or voriconazole in prophylaxis.[3,17] In that study, concomitant use of various CYP3A4 inhibitors and antifungals agents was permitted with caution but without any specific recommendation on how to perform dose adjustment. More than half of patients received posaconazole or voriconazole during induction, consolidation, or maintenance therapy. In those patients in which midostaurin plasma levels were measured, a 1.44-fold increase in midostaurin through levels was observed when the strong CYP3A4 inhibitors posaconazole or voriconazole were co-administered, and no increase of adverse events nor impact on efficacy outcomes were observed, therefore dose modification does not seem required.[17] Isavuconazole is not in-label for IFI prophylaxis, but retrospective studies[18,19] suggest it could be an interesting option to be investigated in settings similar to our case.

Interestingly, few data exist about isavuconazole penetration in cerebral tissue, and experiences are mediated from mice models.[20] In a patient with AML and cerebral aspergillosis, isavuconazole concentrations measured in the inflammatory brain tissue surrounding the abscess were similar to plasma, while the concentration in the liquid of the abscess was quasi-null.[10] Two other patients with cerebral aspergillosis were treated with isavuconazole and required surgery for the progression of the infection. Bioptic samples showed increased drug concentration in the abscess and inflamed meninges compared to unaffected brain tissue.[11] Differently from these cases, the outcome of our patient was favorable. Similarly, isavuconazole was also utilized with success to treat Rhino-Orbital-Cerebral Mucormycosis.[23]

Conclusions. In conclusion, our case illustrates the feasibility of isavuconazole therapy in the treatment of a *S. capitata* infection when co-administered with midostaurin. Considering that the warning about the risk of severe side effects of midostaurin treatment when administered concomitantly with potent CYP3A4 inhibitors, even if not confirmed, it can be speculated that the use of a mild/moderate CYP3A4 inhibitor, as

isavuconazole, could be a safer choice particularly in an outpatient setting, when the strict monitoring of adverse events is less feasible. We think it could have clinical implications when treating patients with a rare yeast infection. However, prospective data in this setting would be helpful in the next future, also considering the emergence of *S. capitata* in central Europe.[21,22]

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