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# *Saprochaete clavata* invasive infection in a patient with severe aplastic anemia: Efficacy of voriconazole and liposomal amphotericin B with adjuvant granulocyte transfusions before neutrophil recovery following allogeneic bone marrow transplantation

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ABSTRACT

We report a case of a 27-year old man with severe aplastic anemia who developed a *Saprochaete clavata (Geotrichum clavatum)* disseminated invasive infection shortly prior a scheduled allogeneic bone marrow transplantation. Treatment with a combination of voriconazole, liposomal amphotericin B and adjuvant granulocyte transfusions was successful before neutrophil recovery.



## 1. Introduction

*Saprochaete clavata*, formerly called *Geotrichum clavatum*, is an ascomycetous yeast genetically closely related to *Magnusiomyces capitatus*, formerly called *Geotrichum capitatum* [1]. *S. clavata* is a very rare, but emerging, causative agent of invasive human infections [1–3]. Between September 2011 and October 2012, a multicenter outbreak of 30 invasive infections caused by *S. clavata* was observed in France with a peak of 18 cases over 2 months in 2012. The majority (90%) of patients had acute leukemia and severe neutropenia. The clinical presentations included fever, diarrhea, and pulmonary symptoms. *S. clavata* was isolated from blood, stools, and respiratory samples in 86.7%, 57.9%, and 40% of patients, respectively. Most patients (60%) had multiple body sites infected. Prognosis was extremely poor with a crude mortality of 80% at day 60, with death occurring at a median time of 7 days after diagnosis [1]. Three concomitant cases were observed in patients hospitalized in the same hematological ward for induction chemotherapy in the context of acute myeloid leukemia. Patients died on days 14, 23 and 43, even if 2 of them were treated by a bi-antifungal therapy with liposomal amphotericin B and voriconazole [4]. A successfully treated case of invasive *S. clavata* infection in an acute myeloid leukemia patient with severe neutropenia was reported in which treatment with voriconazole and neutrophil recovery on day 8 after diagnosis had improved the outcome [5].

Originalities of the present case report of invasive *S. clavata* infection in a patient with severe aplastic anemia are rarity of specie, type of hematological disease and resolution with voriconazole, liposomal amphotericin B and adjuvant granulocyte transfusions before neutrophil recovery. In most reported cases, patients had severe neutropenia following chemotherapy for acute leukemia but no case had previously been reported in patients with aplastic anemia free of chemotherapy [1,4,5]. Furthermore, previous reports suggest that resolution of infection mostly relies on neutrophil recovery [4,5]. As a consequence, a successful outcome before neutrophil recovery due to antifungal agents combined with granulocyte transfusions in this rare and severe invasive fungal infection is a valuable information.

## 2. Case

A 27-year old man was admitted on 4 September 2015 to an

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internal medicine unit of our hospital for pancytopenia (neutrophils: $0.8 \times 10^9$/L, hemoglobin: 9.4 gr/dl, platelets: $4 \times 10^9$/L) and mucocutaneous hemorrhages. Day 1 was defined as the day of admission. Marrow aspiration and trephine biopsy established the diagnosis of idiopathic severe aplastic anemia. Empirical broad spectrum antibiotherapy with piperacillin–tazobactam (16 gr/day for 10 days) and amikacin (15 mg/kg/day for 4 days) was started on day 5 for febrile neutropenia. The fever rapidly resolved without bacterial identification. The following days, neutropenia worsened with $0.3 \times 10^9$/L. Then, despite the diagnosis of aplastic anemia, oral prednisone (40 mg/day) was started on day 12. The patient was admitted to the intensive care unit (ICU) for septic shock on day 19. Prednisone was stopped. Piperacillin-tazobactam was restarted with success and completed with levofloxacin when blood cultures returned positive for *Streptococcus mitis* and *Klebsiella pneumoniae* on day 20. The patient completely recovered and was admitted to our hematology unit on day 24 with the same antibiotics. A central venous catheter (CVC) was inserted on day 25.

As fever reappeared on day 29, piperacillin–tazobactam and levofloxacin were empirically replaced by meropenem (3 gr/day) and an antifungal treatment by caspofungin (loading dose 70 mg, then 50 mg/day) was initiated. Fever persisted with poor clinical condition, diarrhea, abdominal pain, dry cough and left thoracic pain. As peripheral and central venous blood cultures performed on day 29 returned positive for septate hyphae on day 31, caspofungin was replaced by liposomal amphotericin B (3 mg/kg/day) associated with intravenous (IV) voriconazole (6 mg/kg × 2 on first day, then 4 mg/kg × 2/day). This therapeutic strategy was also supported by a stool examination performed on day 22 in ICU that revealed rare colonies of *S. clavata* identified by the matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry BioTyper system (Bruker Daltonics). On day 31, a CT scan revealed a left pulmonary nodular lesion, diffuse bowel thickening, together with multiple nodular lesions of spleen, kidneys, and liver. The liver function tests were normal. The CVC was removed (culture was negative). The patient complained of a left blurred vision. Cerebral CT scan and magnetic resonance imaging were normal. The ophtalmological examination revealed a left retinal hemorrhage. An echocardiogram excluded the diagnosis of fungal endocarditis. The patient remained severely neutropenic ($< 0.1 \times 10^9$/L). On day 33, *S. clavata* was identified from the first blood culture (performed on day 29). The clinical condition rapidly improved during the first days of bi-antifungal therapy although daily blood cultures returned positive for *S. clavata* until day 34. After day 34, weekly stool examinations and daily blood cultures returned negative. The fever persisted until day 42 without any further documented infection. Weekly galactomannan antigenemia results were negative. Voriconazole blood levels were weekly checked to target 1–5 μg/ml and averaged 2.4 μg/mL [6]. Antifungal susceptibility testing was assessed by broth microdilution EUCAST method [7]. The minimal inhibitory concentrations (MICs) for echinocandins (caspofungin and micafungin) and fluconazole were high ($\geq 4$ μg/ml and 32 μg/ml, respectively) and much lower for amphotericin B (0.25 μg/ml), 5-fluorocytosine (0.25 μg/ml), voriconazole and posaconazole (0.5 μg/ml for both).

The patient underwent a sibling allogeneic bone marrow transplantation on day 42 after a conditioning regimen combining IV cyclophosphamide 300 mg/m$^2$, IV fludarabine 30 mg/m$^2$ both from day 35 to 38, and IV alemtuzumab 20 mg from day 36 to 39. Cyclosporine was started on day 41 for graft-versus-host disease prophylaxis. Because of severe prolonged neutropenia, immunosuppression by conditioning regimen and reported dismal prognosis in the literature, we decided to performed 5 granulocyte transfusions on days 39, 40, 41, 48 and 49 despite rapid clinical improvement with bi-antifungal therapy and negativity of blood cultures after day 34. The patient received 4.3, 3.8, 3, 3, and $2.9 \times 10^{10}$ neutrophils/transfusion, respectively. No toxicity was observed. The neutrophil counts reached 0.5 to $1 \times 10^9$ /L the day after each transfusion and returned below $0.1 \times 10^9$/L the day after in the absence of transfusion. After day 42, the fever did not recur and the patient remained in good clinical condition. The neutrophil count reached $0.5 \times 10^9$/L on day 68 without granulocyte colony-stimulating factor. Voriconazole was given orally the same day but replaced by posaconazole (tablets, 300 mg/day once a day) on day 84 because of nausea and vomiting caused by voriconazole. Liposomal amphotericine B was discontinued on day 84. An abdominal ultrasound on day 84 showed only small splenic residual lesions. The patient left the unit on day 88 with posaconazole (tablets, 300 mg/day once a day) as secondary prophylaxis. Afterwards, fever did not recur and left vision progressively normalized. After a 4-month follow-up, the patient had no recurrence of infection or complication of transplantation.

## 3. Discussion

The optimal therapy of invasive infection caused by *S. clavata* and *M. capitatus* has yet to be established and remains a challenge. Echinocandins are not recommended because of intrinsic resistance. Some breakthrough infections have indeed been reported in patients receiving echinocandins [1,2,4,8,9]. In contrast, voriconazole, posaconazole (but not fluconazole), amphotericin B and 5-fluorocytosine are suitable antifungal agents because of better *in vitro* and *in vivo* activities [1,2]. There is no convincing data in the literature to recommend any combination of antifungal agents. In our case, we empirically chose to add liposomal amphotericin B to voriconazole because the clinical condition rapidly worsened and the *in vitro* antifungal susceptibility testing showed low MICs. We also decided to performed 5 adjuvant granulocyte transfusions because of expected poor prognosis, immunosuppression by conditioning regimen, and severe neutropenia, despite unproven benefit of this strategy in neutropenic patients with invasive fungal infections [10,11]. The benefit of these transfusions is extremely difficult to assess since the clinical condition of our patient rapidly improved with bi-antifungal therapy before granulocyte transfusions. Moreover, negative blood cultures were obtained 5 days before the first transfusion. Whether or not early removal of CVC may have favored the outcome in our case despite stools colonization remains an open question as it has been reported as an important complementary treatment in some cases [2].

Originalities of our case are rarity of *S. clavata*, type of hematological disease, and resolution of infection before neutrophil recovery. In contrast to *M. capitatus*, *S. clavata* has only very infrequently been reported as human pathogen [1–3]. Nevertheless, we must acknowledge that frequency in the literature might be underestimated by difficult species identifications. In the rare reported cases of *S. clavata* invasive infections, most patients had acute leukemia and neutropenia caused by chemotherapy [1,4,5]. In these reports, gut colonization and translocation favored by chemotherapy-induced intestinal tract damages may have played an important role. In our case, the patient had *S. clavata* gut colonization but did not receive any chemotherapy before diagnosis of fungal infection. As a consequence, our case indicates that gut translocation should be considered even if the digestive tract is not damaged by chemotherapy. Interestingly, the resolution of infection in our case was obtained with bi-antifungal therapy several days before neutrophil recovery. The benefit of granulocyte transfusions cannot be excluded but is difficult to assess and remains hypothetical. Risks factors for infection in our patient were severe neutropenia, gut colonization, and possibly previous therapy with broad spectrum antibiotics and prednisone.

In conclusion, we report a case of an invasive infection to *S.*

*clavata* in a patient with severe aplastic anemia, successfully treated by voriconazole and liposomal amphotericin B with adjuvant granulocyte transfusions before neutrophil recovery following allogeneic bone marrow transplantation. Our case clearly supports the possibility of successful treatment of disseminated *S. clavata* infection despite severe prolonged neutropenia and expected poor prognosis.

## Conflict of interest

There are none.

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