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Case report

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Invasive infection caused by *Geotrichum capitatum* in three patients with acute myeloid leukemia

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Abstract

Geotrichum capitatum is an uncommon cause of invasive infections in immunocompromised patients. We report three cases of Geotrichum capitatum fungemia in neutropenic patients receiving chemotherapy for acute myeloid leukemia. All the three patients were neutropenic and presented a history of febrile sepsis not responding to broad-spectrum antibiotic therapy. The evolution under antifungal treatment was favorable in one case and the other two patients died one of failure of several organs and the other of acute respiratory distress syndrome. In conclusion, our three cases confirm the emergence of Geotrichum capitatum as an opportunistic agent and should alert clinicians caring for severely immunocompromised patients to consider infections caused by these fungal pathogens.

Introduction

The frequency of invasive fungal infections (IFIs) has significantly increased in recent decades. These IFIs are caused by opportunistic fungi [1]. In the presence of several predisposing factors, patients with hematological malignancies or hematopoietic stem cell transplantation (HSCT) may develop an IFI [1]. Although *Candida* and *Aspergillus* are the most implicated in IFIs in these patients, other less common fungi take place today because of the increasing incidence and the limit of treatment options [2]. Yeasts of the genus *Geotrichum* are responsible for IFIs, particularly in the hematology-oncology departments where they represent 5% of fungi other than *Candida and Cryptococcus* [2]. *Geotrichum (G.) capitatum*, the most isolated species, is mainly described in Europe, particularly in the Mediterranean region with 87% of cases, which suggests the influence of climatic factors in the emergence of these infections [3]. The *G. capitatum Invasive fungal infections* (IFI) is relatively rare. About 100 cases have been reported in patients with hematologic malignancies [4]. This IFI is mainly in the form of sepsis with occasional localizations [4]. Despite the presence of appropriate antifungal therapy, this IFI has been associated with a mortality rate greater than 50% [2]. We report three cases of *Geotrichum capitatum* septicemia in patients with acute myeloid leukemia (AML) and discuss the epidemiological, clinical and prognostic of this infection.

Patient and observation

Case 1: a 46-year-old woman who presented an AML in June 2016, hospitalized for induction chemotherapy according to the MRC 10 protocol. The patient was neutropenic since admission with a neutrophil count of 230/mm^3. At day 15 of her hospitalization, the patient developed a fever at 39-40°C without any additional clinical signs. However, the number of white blood cells was 100/mm^3 with zero neutrophils/mm^3. Empirical treatment with tazocillin for 4 days was initiated. In front of the persistence of fever, the therapeutic decision was to replace tazocillin with imipenem and ciprofloxacin. After two days of continuous fever, aspergillary antigenemia was negative. The patient was empirically exposed to amphotericin B. An oral specimen had isolated *G. capitatum*, and three blood cultures isolated *Geotrichum capitatum* after three days of incubation. Apyrexia has been maintained since the introduction of amphotericin B. At the end of aplasia, the patient received voriconazole. She remained alive for one year and 4 months, and then died of a relapse of her illness.

Case 2: a 34-year-old man who presented an AML in June 2016, hospitalized for induction chemotherapy according to the MRC 10 protocol. On admission, the patient was febrile and had a leukocytosis and a neutrophil count of 1640/mm^3. The patient was treated by tazocillin but without response. At day 5 of aplasia, the tazocilline was substituted with imipenem and ciprofloxacin. Dyspnea was appeared with bilateral crackling on auscultation. A lung high resolution computed tomography (HRCT) showed inflammatory infiltrates in both lungs, nodules in the lower lobe of the right lung, alveolar condensation with air

bronchogram in the left pulmonary base and subsegmental atelectasia in the right middle lobe without evidence of thoracic aspergillosis (Figure 1). Aspergillary antigenemia was negative. The decision was to add amphotericin B for the persistent fever. Three blood cultures were positive for *G. capitatum*. But the patient died as a result of a failure of several organs.

Case 3: this is a 32-year-old woman who presented an AML in June 2016, admitted for induction chemotherapy according to the MRC 10 protocol. Since admission, the patient was neutropenic with a neutrophil count of 130/mm^3. The patient received tazocillin. At day 4 of the aplasia, the patient was still febrile and tazocillin was substituted with imipenem and ciproloxacin. Two days later, the patient was empirically exposed to amphotericin B in response to this persistent fever. Thereafter, respiratory symptoms occurred with dyspnea, cough, and crackling at auscultation. A lung high resolution computed tomography (HRCT) showed bilateral and diffuse pulmonary intra-parenchymal nodules (Figure 2). Aspergillary antigenemia was positive. The patient developed a persistent severe hypokaliemia due to amphotericin B, and this last was replaced by voriconazole. The patient died of an acute respiratory distress syndrome. Two blood cultures was performed, one of them proved to be positive for *G. capitatum* after 3 days of incubation. According to the results of E-tests (bio Mérieux, France), the strain was susceptible to voriconazole with a MIC of 0.125 µg ml-1.

Discussion

Invasive geotrichosis is an emerging opportunistic infection. *G. capitatum* is the most frequently isolated species of these systemic infections [3]. An environmental source of *G. capitatum* infection has not been found, but the hypothesis of a particular geographical distribution of this fungal infection continues to be valid [5]. The geographical distribution of reported cases is limited: 87% of cases were observed in Europe (38 cases in Italy, 30 cases in Spain and 7 cases in France), 5% in the USA, 7% in Asia and 1% in several other countries [5]. In Tunisia, nine cases of *G. capitatum* sepsis in patients with acute leukemia have been reported [6]. Two recent studies, one concerning 99 cases of invasive geotrichosis between 1965 and 2004 and the other concerning 104 cases between 1977 and 2013, have shown that these infections occur in more than 90% of cases in patients with predominantly neutropenic hemopathy at the time of infection (82%) [5]. In previously colonized neutropenic patients, the presumed mode of transmission is digestive, respiratory or cutaneous. Disseminated lesions, pulmonary and hepatosplenic localizations are also possible. In addition, there are fewer geotrichosis associated with a central venous catheter, even if it is a possible entryway, and mortality is lower (56% versus 77%) [4,5]. Other studies have reported nosocomial epidemics associated with *G. capitatum*: clonal dissemination was confirmed in a series of seven patients whose source was not found and in another of four patients associated with bottles of contaminated milk [7]. Some cases of localized deep infections have been described in non-neutropenic patients, such as endocarditis, pneumonia, meningitis, dermatitis or arthritis, often in a traumatic or postoperative setting [7].

Diagnosis: although the sensitivity of blood cultures in geotrichosis is high compared to other IFIs (about 70%), the diagnostic difficulties persist regarding the importance of *Geotrichum* isolation, the difficulty to differentiate between colonization and infection, the inaccuracy species identification and indirect diagnostic tools [7,8]. The diagnostic criteria are defined by the EORTC [8]. Girmenia *et al*. showed that 50% of colonized patients had developed proven invasive geotrichosis, taking into account the isolation of yeast from superficial sites, including respiratory sites, neutropenia and the clinical presentation [5]. For fungi, a period of positivity, often with long blood cultures, does not allow early diagnosis, especially since direct examination contributes little to differentiating *Geotrichum* from other yeasts [9]. Mycological diagnosis is based on conventional identification

methods associated with biochemical tests. These methods are unprofitable and often unable to distinguish the three species. The use of more efficient techniques, such as mass spectrometry or molecular biology, is sometimes necessary [9]. In addition, there are no specific serological tests for geotrichoses, but cross-reactions have been observed with aspergillus galactomannan antigen, which may be a useful diagnostic tool [10]. The release of parietal β-D-glucan by yeast has been demonstrated in vitro in culture supernatants and in patient samples, but further studies are needed to evaluate its usefulness in diagnosis [10].

Treatment: currently, sensitivity thresholds for antifungals are not available for *Geotrichum*. Few studies have investigated the in vitro susceptibility of these yeasts, all showing concordant results suggesting the good activity of amphotericin B, voriconazole and posaconazole, and reduced susceptibility of some strains to flucytosine, fluconazole and itraconazole, with high minimal inhibitory concentrations [7,8]. It is important to note that *Geotrichum* has a natural resistance to echinocandins [7]. Due to the rarity of invasive geotrichosis, correlations between in vitro and in vivo results are lacking in order to determine the optimal treatment. This is why it is strongly recommended to carry out an antifungal sensitivity test of the yeast. According to the cases reported in the literature, liposomal amphotericin B alone or in combination with flucytosine or voriconazole could be used in the first line [7]. Some authors have suggested the potential value of the combination of voriconazole and amphotericin B, and voriconazole and caspofungin despite its in vitro ineffectiveness [6]. In addition, several cases of echinocandin geotrichosis have been described, which discourages the use of this class and encourages the rapid introduction of voriconazole and/or amphotericin B in cases of non-invasive fungal infection documented and not responding favorably to the usual caspofungin reactions [8]. In addition to appropriate antifungal therapy, early removal of the potentially infected central venous catheter and exit from neutropenia are the most effective measures to control infection [7].

Conclusion

G. capitatum infection is very rare but potentially life threatening invasive infection. In Tunisia, this invasive infection is unknown. Our 3 cases confirm the emergence of *G. capitatum* as an opportunistic agent and should alert clinicians caring for severely immunocompromised patients to consider infections caused by these fungal pathogens.

Competing interests

The authors declare no competing interest.

Authors' contributions

All authors contributed to the conception of this case report. All authors have read and approved the final manuscript.

Figures

Figure 1: a lung high resolution computed tomography (HRCT) (A, B, C, D, E): showing inflammatory infiltrates in the both lung, nodules in the lower lobe of the right lung, alveolar condensation with air bronchogram in the left pulmonary base and subsegmental atelectasia in the right middle lobe.

Figure 2: a lung high resolution computed tomography (HRCT) (A, B, C): showing bilateral and diffuse pulmonary intra-parenchymal nodules

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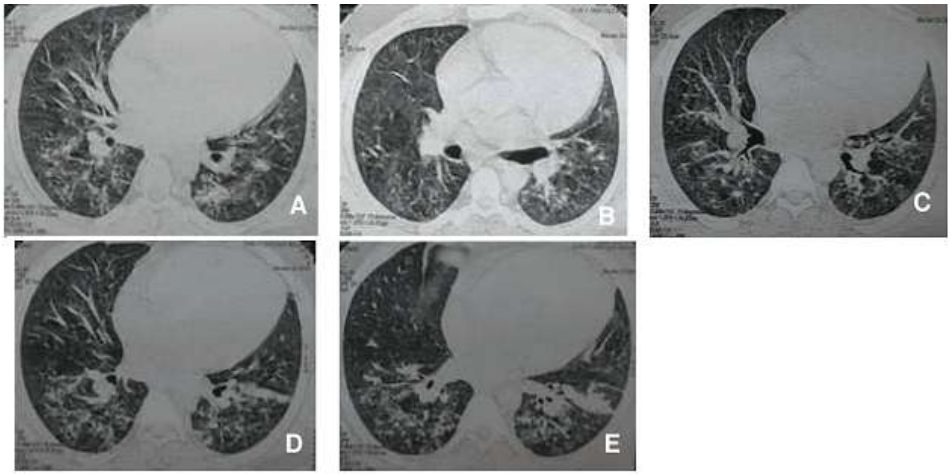

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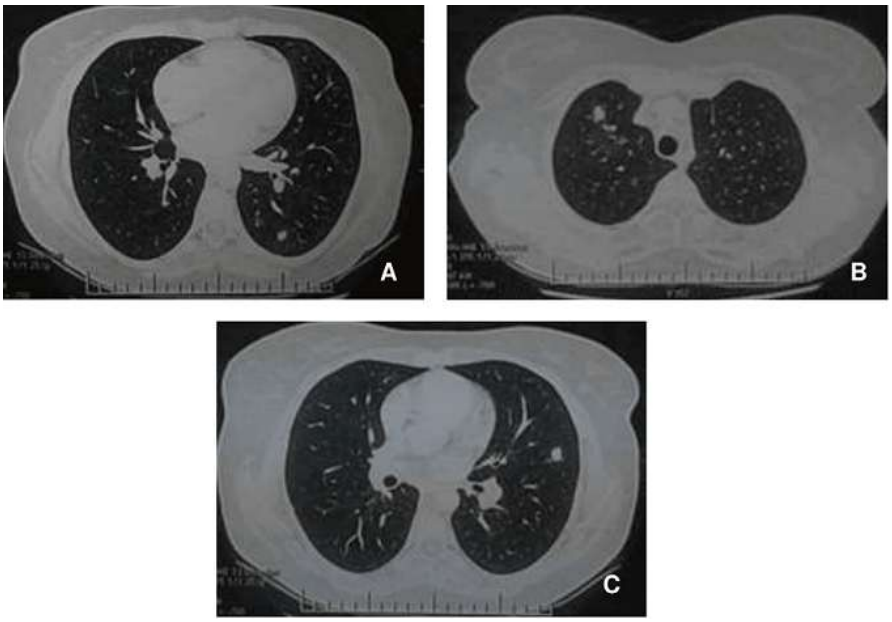

Figure 2: a lung high resolution computed tomography (HRCT) (A, B, C): showing bilateral and diffuse pulmonary intra-parenchymal nodules