Fungi that were previously considered harm-
less colonizers or contaminants are emerging 
as new fungal pathogens, particularly in immu-
nocompromised patients [1]. Several risk factors predispose individuals to the 
development of fungal infections. These include neutropenia, cell-mediated immunodeficiency, 
immunosuppressive agents, chemotherapy, 
broad spectrum antibiotics and indwelling ve-
 nous catheters [2]. In particular, chemotherapy-
induced neutropenic periods entail a high risk of 
fungal infections usually caused by *Candida* and 
*Aspergillus* species, although many other molds 
and yeasts have emerged as causes of invasive infec-
tions and the prevalence of infectious fungi has 
been increasing in recent years [3].

*Geotrichum capitatum*, formerly known as *Tricho-
sporon capitatum* or *Blastochizomyces capitatus*, 
is similar to *Trichosporon* spp. since it produces 
hyphae which break up into arthroconidia, but 
it differs from *Trichosporon* because it is urease 
negative, it does not reproduce by budding and 
is unable to assimilate a large number of carbon 
Sources. Digestive and respiratory tracts have 
been reported as possible ways of entry [4]. 
Its reported clinical manifestations include sep-
tecemia, meningitis, encephalitis, vertebral os-
teomyelitis and discitis, endocarditis, respiratory 
tract and gastrointestinal infections and kidney, 
spleen and liver colonization [4]. These systemic 
infections are clinically similar to invasive candi-
diasis but it is associated with higher bloodstream 
recovery rates, more frequent deep organ involve-
ment and a poorer prognosis.

The majority of geotricosis were reported in Eu-
rope (85% of all cases) and USA (10%). Further-
more, 87% of the European cases occurred in Italy, 
Spain, and France. This finding, together with the 
marked clustering of cases in central and south-
ern Italy, seems to suggest that climatic factors 
might play a selective role in the epidemiology of 
*Geotrichum capitatum* infections [5].
Invasive geotrichosis is rare and it has been reported exclusively in immunocompromised patients, particularly those affected by haematological malignancies such as acute leukemia.

Moreover other types of human geotrichosis have been described. In 2009 Celik et al. reported six cases of spondylodiscitis due to Blastoschizomyces capitatus: osteoarticular involvement has been described in six cases and vertebral involvement has been seen in five of them [6]. Rarely Geotrichum capitatum infections have been documented in not severely immunocompromised patients. A single case of transient fungaemia in a drug abuser and a case of fungal endocarditis have been reported [7, 8]. In July 2002, a nosocomial outbreak of Blastoschizomyces capitatus associated with contaminated milk in a haematological unit occurred; surveillance cultures on food samples showed milk contamination due to this fungus. Milk vacuum flasks were withdrawn from all hospital units and no further Blastoschizomyces capitatus infection was detected [9].

**Antifungal susceptibilities and therapeutic strategies**

Since susceptibility breakpoints were not yet established for Geotrichum capitatum, it is possible to analyze only the distribution of the minimum inhibitory concentrations (MICs) values. The optimal therapy against systemic geotrichosis has not yet been identified due to limited data about its antifungal susceptibility.

The use of several therapeutic strategies and the low number of cases treated does not allow any comparative evaluation of the efficacy of these strategies. Several authors confirmed the high activity of amphotericin B against this species. On the contrary, Gadea et al. analyzed some strains of Blastoschizomyces capitatus and reported unsuccessfully treatment with a high dose of liposomal amphotericin B (L-AMB) in spite of in vitro susceptibility [10]. MICs of fluconazole were quite high, susceptibility rates ranging from 16 to 32 μg/mL, placing them in the NCCLS susceptible-dose-dependent category. Many strains were susceptible in vitro to 5-fluorocytosine although its bone marrow toxicity makes this antifungal very poorly attractive for haematologists. Moreover voriconazole (VRC) exhibits high activity in vitro, comparable to itraconazole (ITC) [10].

Some studies suggested that VRC and ITC have favorable activity against Blastoschizomyces capitatus isolates, however, unfortunately there are few clinical reports. The activity of fluconazole and echinocandins remained poor and limited at a low number of isolates. In 2000, DeMaio et al. described a case of hepatosplenic Blastoschizomyces capitatus infection unresponsive to standard amphotericin B therapy which subsequently responded when adjuvant interferon-γ was added [11].

The prognosis of disseminated Geotrichum capitatum infection has been reported to be extremely poor, with a mortality rate of approximately 50-75%, despite intensive antifungal therapy. Ikuta et al. described a case of systemic geotrichosis treated with L-AMB which suppressed the infectious activity of Geotrichum capitatum [3]. VRC also seemed to be effective in this case because chemotherapy had been continued without L-AMB. The recovery from neutropenia may also have contributed to overcoming the infection, therefore using granulocyte colony stimulating factor (G-CSF) should be considered if the status of the infected patients permits [3].

**CASE REPORT**

In January 2013 a 78 year old patient was referred to our ematology department because of worsening asthenia, repeated episodes of epistaxis and severe leukocytosis. The patient showed many comorbidities such as arterial hypertension, hepatitis B and type 2 diabetes. Bone marrow aspiration was performed and a diagnosis of acute myelogenous leukemia (AML) was made. Immunophenotyping by flow cytometry revealed 80% of blast cells expressing myeloid markers CD33+ CD117+ CD34+-/ CD56-/+ HLA-DR+. The first induction therapy consisted of mitoxantrone, etoposide and cytarabine while antifungal prophylaxis was performed by administration of 200 mg/day of posaconazole from the time of admission. At the end of the induction therapy, a complete remission of AML occurred. Forty days later, a consolidation therapy using etoposide, cytarabine and idarubicin while antifungal prophylaxis was performed by administration of 200 mg/day of posaconazole from the time of admission. At the end of the induction therapy, a complete remission of AML occurred. At the end of consolidation treatment, our patient refused autologous peripheral blood stem cell
transplantation. Unfortunately, four months later, a leukemic relapse occurred. On June 6th, the laboratory data on admission showed that his white cells count (WBC) was 97.9×10³ /µL, with a differential of 28.8% neutrophils, 0.5% lymphocytes, 0.2% monocytes, 0% eosinophils, 0.5% basophils, and 70% blasts. The haemoglobin concentration was 9.8 g/dL (13-17.5 g/dL) with a mean corpuscular volume of 102.2 fl (80-95 fl) indicating mild macrocytosis. The platelet count was 20 × 10³ /µL (150-400 × 10³ /µL) and revealed thrombocytopenia. Biochemical data included AST of 12 U/L (8-48 U/L), ALT of 7 U/L (7-55 U/L), and an elevated lactate dehydrogenase (LDH) of 1385 U/L (230-460 U/L), CRP of 34.7 mg/L (<10 mg/L), and serum ferritin of 1894 ng/mL (20-400 ng/mL). The bone marrow aspirate, as shown in Figure 1, was markedly hypercellular and frankly leukemic. A diagnosis of AML relapse was given.

Immunophenotyping by flow cytometry revealed 90% of blast cells expressing myeloid markers CD33+ CD117+ CD34+/- CD56-/+ HLA-DR+.

On June 7th, this patient was enrolled in a multicenter randomized double-blind, placebo-controlled, clinical study of cytarabine combined with or without an experimental chemotherapy drug or placebo. It’s not possible to know if the patient was included in the experimental group or in the control group since the trial is still in progress. On day 7 after the beginning and two days after the end of the salvage therapy, the patient showed abdominal pain and vomiting. In the following days many febrile episodes occurred, however there were no positive blood culture. Severe neutropenia appeared nine days after systemic chemotherapy started and the patient developed fever (38°C) unresponsive to wide spectrum antibiotic therapy (cotrimoxazole, tigecycline and micafungin). On day 14 the bone marrow aspirate showed again 20% of blasts. Galactomannan antigen positivity of 0.8 ng/mL (<0.5 ng/mL) was found on day 17 with CRP of 134.4 mg/L (<10 mg/L) and PCT of 0.15 ng/mL (<0.05 ng/mL).

Giacchino and Bonini have described similar events in their reports [12, 13]. Enzyme-linked immunosorbent assay (ELISA) is widely used in diagnosing invasive aspergillosis, but a recurring problem with the detection of circulating galactomannan antigen is the occurrence of false positive results, which in some cases, have been shown to be related to a soluble antigen that is cross-reactive with Aspergillus galactomannan [12]. The possibility of fungal infection was confirmed by microscopic examination of positive blood cultures taken on day 18: vast numbers of septate hyphae with narrow angle branching were observed. Yeast-like fungi multiplying mainly by blastoconidia were evident on blood culture after 24 hours of incubation. A few arthroconidia were also observed.

Chrom agar Candida (bioMérieux, France) showed white and dry colonies after 24 hours of incubation. Cream-colored, dry and wrinkled colonies were highlighted on Dextrose Sabouraud agar and Chrom agar Candida at 96 hours.

Figure 1 - Bone marrow cytology (May-Grünewald-Giemsa stain) performed at the time of leukemic relapse.

Figure 2 - Geotrichum capitatum; septate hyphae observed in Gram stained smear performed on a positive blood culture.
Fungus was identified on day 19 using the commercially available Vitek 2 Yeast Biochemical Card (bioMérieux, France). The identification was confirmed by using Maldi time of flight (TOF) analysis (Bruker Daltonik Maldi Biotyper), performed at the Institute of Microbiology (Università Cattolica del Sacro Cuore, Rome, Italy).

Susceptibility testing using Sensititre Trek Custom Susceptibility Plates showed low MIC for amphotericin B, itraconazole, posaconazole and voriconazole while the MIC values for echinocandin resulted high as shown in Table 1.

Micafungin (MCFG) was replaced by 240 mg/day of L-AMB on day 19 because of the MIC informations. Neutropenia remained during the last days of hospitalization; in addition the patient required an increasing support with platelet and erythrocyte concentrates. Liposomal amphotericin B appeared to be effective with a temporary reduction of hyperpyrexia. On day 21 and over the days that followed, there was a worsening of clinical conditions combined with a significant increase of glycemic decompensation in spite of frequent glycemic measurements and high parenteral administration of insulin. Furthermore clinical signs of renal failure occurred. In the last week serum creatinine increased from 0.59 to 3.43 mg/dL (0.7-
Geotrichum capitatum septicaemia in a haematological patient after acute myeloid leukaemia relapse

1.3 mg/dL) with a simultaneous increase of urea from 13.02 to 46.42 mmol/L (3-8.33 mmol/L). Three days after, the patient slipped into a coma and he died on day 25.

**DISCUSSION**

The close relationship between the field of haematology and invasive fungal infections is now been established in the last decennia. Emerging fungal pathogens, such as *Geotrichum capitatum*, are often associated with poor prognosis and represent a new challenge in modern medicine. The severity of systemic geotricosis in immunocompromised patients require shorter response times; in this context the current and future applications of MALDI-TOF mass spectrometry are of great interest.

Various therapeutic strategies have been used to treat *Geotrichum capitatum* septicemia, however the low number of clinical reports does not allow to identify specific therapeutic protocols. The use *in vivo* of several antifungal agents often highlighted conflicting results since *in vitro* antifungal susceptibility findings are sometimes contradictory to those observed in the clinical practice [14]. The efficacy of treatment with liposomal amphotericin B remains controversial, on the contrary the high levels of susceptibility to VRC and ITC are in agreement in every published reports. In our case this fungus showed high susceptibility *in vitro* only to amphotericin B, itraconazole, posaconazole and voriconazole.

It is clear how the general conditions of patients may have an impact on the effectiveness of treatment irrespective of mere efficacy of antifungal therapies. In our report the patient presented severe neutropenia and subsequently signs of renal failure and he was unsuccessfully treated, despite *in vitro* susceptibility, with liposomal amphotericin B.

Salih et al. in a recent study demonstrated how the risk of mortality was associated with renal dysfunction; differently, type of chemotherapy and neutrophil count did not influence the mortality following invasive fungal infection [15]. On the contrary, several authors identified neutropenia as the main factor associated with unsuccessful outcome.

Further studies will allow the acquisition of new data on these rare fungal infections in order to establish a better understanding and a more appropriate therapy in invasive geotricosis.

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**Conflict of interest**

The authors declare that they have no conflict of interest.

**Keywords**: *Geotrichum capitatum, septicaemia, haematology, MALDI-TOF.*
Emerging fungal pathogens, such as *Geotrichum capitatum*, are often associated with poor prognosis and represent a new challenge in modern medicine. Invasive *Geotrichum capitatum* infection is rare and has been reported exclusively in patients who showed signs of severe immunodeficiency, particularly those affected by haematological malignancies. The optimal therapy against systemic geotropicosis has not yet been identified due to limited data about its antifungal susceptibility. The use of several therapeutic strategies and the low number of cases treated does not allow identification of specific therapeutic protocols. Furthermore, in spite of antifungal therapy, mortality rates reach very high levels. We report a case of systemic *Geotrichum capitatum* infection in a 78-year-old male treated with salvage therapy after acute myeloid leukaemia (AML) relapse. *Geotrichum capitatum* was isolated from his blood culture and identified by using Vitek 2 and MALDI-TOF. The infection was unsuccessfully treated, despite *in vitro* susceptibility, with micafungin and liposomal amphotericin B.

REFERENCES


