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Case Report

Saprochaete capitata fungemia in patient with adult T-cell leukemia/lymphoma in Macedonia

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This is a case report of a fatal case of a patient with *Geotrichum capitatum* fungemia, who was suffering from T-cell leukemia/lymphoma. This is the first documented case of disseminated *Saprochaete capitata* reported from Macedonia. The identity of the isolate as *S. capitata* was confirmed using a Vitek-2 system (bioMérieux, France) with a probable value of 99%. The sensitivity to antifungal drugs was performed with E-test to fluconazole and amphotericin B. Minimal inhibitory concentrations (MICs) of *S. capitata* were 1 mg/L and 1.5 mg/L to amphotericin B and fluconazole, respectively. Patient's general condition was rapidly deteriorated, with widespread skin lesions, recurrence of conjunctival hyperemia, worsening dyspnea, appearance of polyserositis, and evolution towards cardio-respiratory insufficiency and death five days later. Patients with resistant fever and underlying haematological malignancy, fungal infection with *S. capitata* should be kept in mind, and early initiation of appropriate antifungal treatment must be overviewed.

Key words: *Saprochaete capitata* fungemia, T-cell leukemia/lymphoma, Bact/Alert system, Vitek-2 system.

INTRODUCTION

In the last two decades, systemic fungal infections are on the rise and they are a major cause for mortality in immunocompromised patients. Since the beginning of 1980, the percentage of candidemia has risen four times; more than 15% of the intrahospital blood infections were caused by different species from the genus *Candida* (Richardson et al., 2008).

The most common risk factors for these infections are: suppressed immunity, parenteral nutrition, treatment with broad spectrum antimicrobials, malignant diseases, cytotoxic therapy with prolonged neutropenia, hormonal disorders, diabetes, infectious diseases, acquired immunodeficiency (HIV infection), older age, trauma and burns; general surgery: transplantation of solid organs; treatment with glicocorticoids and immunosuppressive agents, permanent catheter (the risk grows proportionally with the duration of use of the catheter), peritoneal dialysis or haemodialysis, newborns and prematurely born babies, haematological disorders, implanted prostheses and devices, etc (Richardson et al., 2008; Miceli et al., 2011).

Aspergillus species is one of the most frequent causes of invasive fungal infections, but invasive *Geotrichum capitatum* infection is very rare. The clinical spectrum of *Saprochaete capitata* disseminated infections is very similar to that produced by *Candida*, being easily misinterpreted. The majority of *G. capitatum* infections have been registered in patients with haematological malignancies, from different regions of the World (Japan, Italy, Turkey, etc). These infections are potentially fatal, with a mortality rate ranging from 50% to 90% (Girmania et al., 2005; Aslınur et al., 2012; Kami et al., 2003).

In papers published from Macedonia, there are some data regarding isolation of fungi from blood in patients with fungemia: *Cryptococcus laurentii, Candida albicans*, some *non-albicans Candida* species (*C. parapsilosis, C. glabrata, C. tropicalis*), but there is still insufficient information on isolation of certain fungi, such as *S.*

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capitata (Mircevska et al., 2012).

G. capitatum, formerly known as *Trichosporon capitatum*, now known as *Saprochaete capitata*, belongs to the *Ascomycota* phylum, has been reported in patients with acute leukemia (Bonini et al., 2008; De Majo et al., 2000; Girmania et al., 2005).

CASE REPORT

In this case report, we present a patient with *G. capitatum* fungemia, who is suffering from malignant lymphoma. This is the first documented case of disseminated *S. capitata* reported from our country.

A 54 year old woman, was presented at the University Clinic of Haematology in Skopje, Macedonia, in July 2014 for investigation of leukocytosis. The medical history revealed allergic complaints, dating for more than six months. Many investigations were performed, but all were negative (HBS, HCV, HIV, BAB and alergic test). Chest radiography was normal. Dermatological diagnosis was allergic dermatitis with recommendations for treatment with antihistaminic drugs. Skin biopsy diagnosis was Paniculitis with recommendation for deeper biopsy.

At presentation, she had intensive itching, cough, dyspnea and skin tumorous formation of the left forearm (4 × 3 cm). Physical examination revealed tumorous formations in the left forearm (4 × 3 cm), no peripheral adenopathy, no organomegaly. Laboratory investigation showed anemia (Hb 10.1 g/dl), leukocytosis (WBC 33 × 10^9 /L) and thrombocytopenia (Plt 54 × 10^9 /L), elevated urea 10.0 mmol/L, elevated LDH-1094 U/L and other biochemical findings (including serum calcium) within normal range. Peripheral blood smear revealed 25% eosinophils, 45% lymphocytes, 35% neutrophyls and 5% monocytes.

The histopathological finding of the bone marrow biopsy was not distinctive. Differential diagnosis was granulomatous disease or Lennert's lymphoma. Another skin biopsy from tumorous formations confirmed lymphoma. During first admission to the clinic, another bone marrow biopsy was performed. The smear from the bone marrow showed lymphoid infiltration of 80-90%. She received only steroids while waiting for the results. The histopathological finding came latter as malignant lymphoma. Bone marrow aspirate analyzed with PCR showed dominant monoclonal population of T lymphocytes.

Flow-cytometry finding was adult T-cell leukemia/lymphoma with expression of CD3+ (90%), CD2+ (95%), CD4+ (18%), CD5+ (94%), CD7+ (95+), CD8+ (7,7%), CD10+ (92,2%), CD25+ (90%), CD38+ (34%), and FCM7-, CD79b-, CD22-.

The patient was readmitted to University Clinic of Haematology for treatment; aggressive evolution of the disease and taking into consideration the presence of acute renal failure, our colleges decided to initiate treatment with CHOP protocol instead of more aggressive treatment with Hyper-C-VAD regimen, supportive treatment with packed red blood cells and platelets, and anti-viral drug, Acyclovir.

After the first cycle, the condition of the patient was slowly improving, with disappearance of the skin lesions and decrease of the spleen size, gradual decline in the number of leukocytes and disappearance of the atypical lymphocytes in peripheral blood, normalization of serum urea and creatinine. The patient received two cycles of CHOP chemotherapy. At the third cycle of chemotherapy, she complained about difficulties in walking. Therefore, she received the third cycle of CHOP chemotherapy.

The patient remained in a stable condition until November 2014, when skin lesions reappeared very extensively all over the body as macule-papule formations with itching and atypical lymphocytes recurred in peripheral blood. Decision was made to continue treatment with Hyper-C-VAD regimen, so the patient received Course A with some improvement of the skin lesions. Antihistaminic drugs were also administered.

Her general condition gradually deteriorated, and in December 2014, she presented with extensive skin macule-papule formations all over the body, hyperemia, itching, desquamations and skin erosions. Hematological parameters were: Hb 109 g/dl, WBC 26,6 × 10^9 /L, Plt 106 × 10^9 /L. The peripheral blood smear revealed lymphocytosis (68%) with atypical cells. Biochemical findings were: serum urea (14.8 mmol/L), serum creatinin (111.7 umol/L), uric acid (626 umol/L), LDH (449 U/L), Ca (2.16 mmol/L). The patient received Course B of Hyper-C-VAD regimen. The seventh day after application of the regimen, the patient became febrile with fever. CBC was Hb 8.9 g/dl, Le 1.7 × 10^9 /L, Plt 23 × 10^9 /L. Laboratory samples recorded hypoproteinaemia, hypoalbuminaemia, normal serum calcium.

Due to suspicion of a sepsis, a microbiological investigation of a blood was performed. Blood was tested with automated Bact/Alert 3D system (bioMerieux, France). After incubation of 48 h in this system (continuous incubation, agitation 37°C), a signal gives information about a positive blood culture. A Gram stain of the blood smear revealed Gram positive arthroconidia which are typical structures for these yeasts (Figure 1A).

The yeast colonies grew well on blood agar and Sabouraud dextrose agar after 24 h of incubation. They were creamy white and slightly hairy with a fruity odour (Figure 1B and C). On ageing, hyphal growth was predominant at the periphery of the colony, especially after 48 h. The second Gram stain from the culture showed hyaline hyphae disarticulated into arthroconidia. The isolate was able to grow at 42°C. The identity of the isolate as *S. capitata* was confirmed using a Vitek-2 system (bioMérieux, France) with a probable value of 99%. The sensitivity to antifungal drugs was performed with E-test to fluconazole and amphotericin B. Minimal inhibitory concentration (MICs) of amphotericin B to *S.*

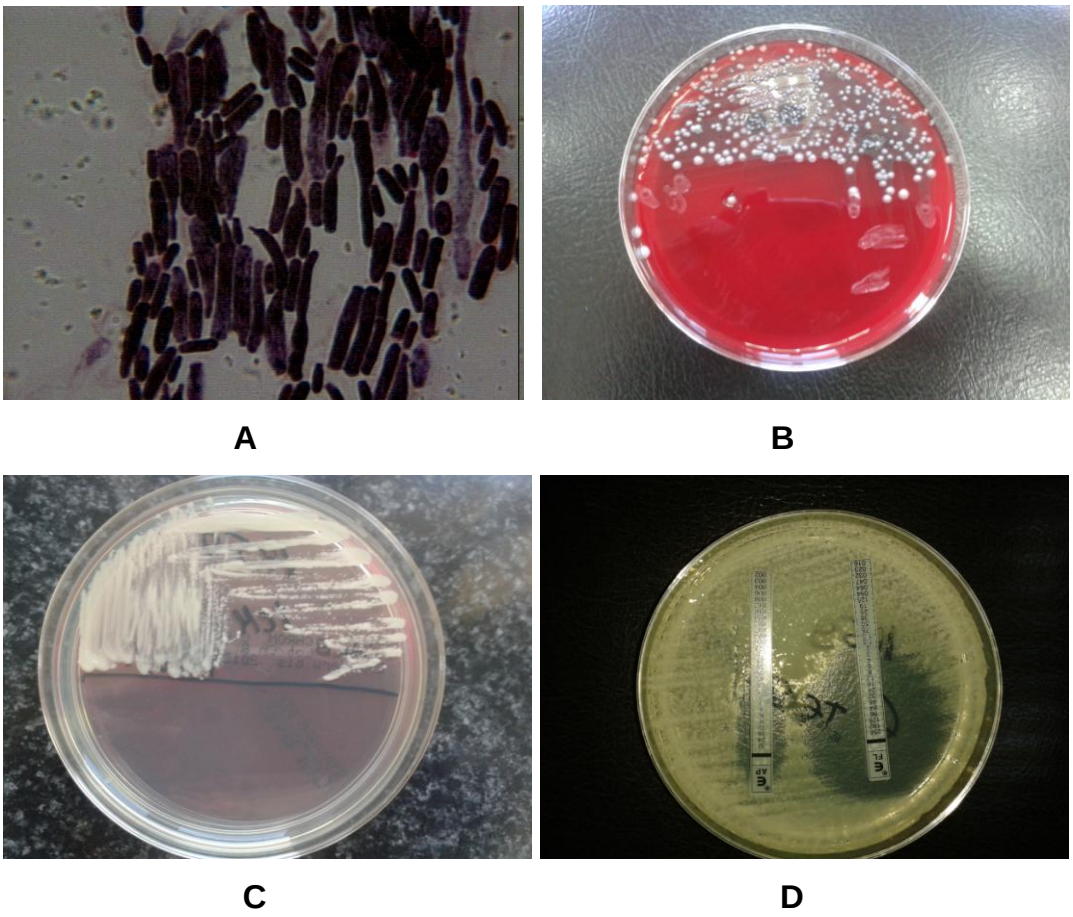

Figure 1. (A) Gram positive stain-artroconidiae, (B) Blood agar – *S. capitata* colonies, (C) Sabouraud agar – *S. capitata* colonies, and (D) E test – susceptibility to fluconazol and amphotericin B.

capitata were 1 mg/L and 1.5 mg/L to fluconazole (Figure 1D).

The patient's general condition deteriorated rapidly, with widespread skin lesions, recurrence of conjunctival hyperemia, worsening dyspnea, appearance of polyserositis, and evolution towards cardio-respiratory insufficiency and death five days later. It was unfortunate that by the time the fungus was isolated from blood and antifungal susceptibility results were available, it was too late to manage the patient appropriately.

DISCUSSION

Patients with *S. capitata* septicaemia can present similarly to those with other fungal infections. In patients with resistant fever and underlying haematological malignancy, fungal infection and *S. capitata* should be kept in mind, and early initiation of appropriate antifungal treatment must be overviewed (Miceli et al., 2011; Cofrancesco et al., 1995).

All fungal infections occur as a result of colonization of the respiratory, urogenital or gastrointestinal tract systemic infection as a common finding. *S. capitata* can be found in the normal microbial flora of the human digestive and respiratory tracts, such that discrimination between colonization and infection is difficult. However, in many studies, it has been proven that the isolation of these yeasts from superficial sites is significantly correlated with the development of invasive infection. The probable portal of entry is the respiratory and gastrointestinal system or skin and nosocomial transmission which has been suggested in a number of cases. Like other opportunistic yeasts colonizing the gastrointestinal tract, it is reasonable to infer that *S. capitata* infection originates from the gastrointestinal tract, where damaged mucosa as a result of cytotoxic therapy facilitates invasion and haematogenous dissemination. In this context, a recent report of a nosocomial outbreak of *S. capitata* infection in a haematological unit linked to consumption of contaminated milk is noteworthy (Pottier et al., 2008; Gurgui et al., 2011).

In contrast to disseminated candidiasis, the involvement of lungs is common in invasive infections

caused by *S. capitata*. Coughing, expectoration, chest pain, spontaneous pneumothorax and pulmonary infiltrates are frequently observed. Therefore, the isolation of this microorganism from sputum or bronchoalveolar lavage in neutropenic patients with well documented pneumonia, and in the absence of other pathogens, is indicative of probable pulmonary geotrichosis for some authors (Romano et al., 2005; Pagano et al., 2006).

Pulmonary involvement in cases from the literature is common in *S. capitata* septicaemia. Similar to invasive pulmonary aspergillosis, the halo sign and the air crescent sign are also present in *S. capitata* infection (Battle et al., 2010). However, these findings were not present in our patient, but all of these pathways, as mentioned before, could be the possible routes for this fatal fungemia. Infections with arthroconidial yeasts yield higher recovery rates in blood cultures (~80%), and they show a greater propensity to cause tissue invasion and are associated with higher mortality. Blood culture is positive in more than 70% of invasive saprochaete infections. Central venous catheters have also been recognized as a potential portal of entry (Aslmur et al., 2012).

In a recent study (Nakase et al., 2006), a case of disseminated *S. capitata* in a child with relapsed acute myeloid leukaemia following bone-marrow transplantation has been described. The aetiological role of the fungus was established by its repetitive isolation from blood, tracheal secretion and urine.

S. capitata is a non-fermentative, non-encapsulated, urease-negative ascomycetous yeast (Birrenbach et al., 2012). Microbiological diagnosis of infection with this yeast is relatively easy because there is no need for different special media. This fungus can be detected from blood in media appropriate for Bact/Alert 3D system (FAN aerobic and anaerobic). Detection is almost identical to the bacteria (typically 48 to 72 h are sufficient). For primary cultures on Sabouraud agar, 24 h usually were sufficient for incubation; fungal growth was clearly visible after 24 h of incubation and somewhat more evident by 48 h. Also, regarding the incubation of samples with expected isolation of these fungi on Sabouraud agar, 24 h are usually sufficient. This shows that if *S. capitata* exist in the sample, it is almost always proven (Figure 1).

Identification of *S. capitata* is possible by analyzing the Gram stain with typical arthroconidia and the other typical yeast's element (annelloconidia). Identification is confirmed by creamy white and slightly hairy colonies with a fruity odour. But, the final identification is well confirmed by a reliable method such as Vitek-2 system, with very high probability (Birrenbach et al., 2012; El Omri et al., 2005).

Susceptibility to antifungal agents was performed with Vitek-2 system where MICs of drugs were determined. In our case, we investigated the sensitivity with E – test to only two antifungal drugs (amphotericin B and fluconazol) often used for antifungal treatment of these infections. Nonetheless, interpretation of MICs was not difficult (Girmenia et al., 2003; Matar et al., 2003; Savini et al., 2011).

There is no known optimal treatment strategy for *S. capitata* disseminated infections. Cases of infection are scarce and *in vitro* anti-fungal susceptibility findings are sometimes contradictory to those observed in the clinical practice. However, there is a considerable degree of consensus that *S. capitata* shows adequate susceptibility to polyenes such as amphotericin B and azoles such as voriconazole, posaconazole and itraconazole. Nevertheless, some strains show decreased susceptibility or poor clinical response to itraconazole or amphotericin B (Schuermans et al., 2011; Etienne et al., 2008).

Susceptibility testing and *in vitro* susceptibility data suggest *S. capitata* is susceptible to flucytosine (MIC values of 0.25-0.5 mg/L), itraconazole, voriconazole and posaconazole (MIC ranges: 0.12-0.50, 0.25-0.5 and 0.03-0.25 mg/L, respectively). *S. capitata* can be considered intrinsically resistant to echinocandins. According to CLSI, isolates for which MICs are < or = 8 mg/L are susceptible to fluconazole, whereas those for which MICs are > or = 64 mg/L appear resistant. In addition, interpretive breakpoints for amphotericin B have not been established, but strains with MIC >1 mg/L are very likely to be resistant (National Committee for Clinical Laboratory Standards, 2003; Etienne et al., 2008).

Our findings confirm previous observations on the high activity of amphotericin B against *S. capitata*, because our isolate showed susceptibility to amphotericin B (MIC value of 1.0 mg/L). This yeast was also susceptible to fluconazole (MIC value of 1.5 mg/L). Available data about susceptibility of *S. capitata* to antifungal agent are limited; however, fluconazole-resistant strains have been reported. It was unfortunate that by the time the fungus was isolated from blood and antifungal susceptibility, the results were already available, as such it was too late to manage the patient appropriately (Savini et al., 2011).

There are not enough clinical data to assess the optimal treatment for *S. capitata* in haematology patients. However, based on *in vitro* data and the limited clinical data available, any amphotericin B formulation with or without flucytosine can be recommended (Confrancesco et al., 1995). Failure despite high dose of liposomal amphotericin B (7 mg/kg) has been reported in the context of hepatosplenic infection and neutropenic sepsis. Voriconazole exhibits a promising activity *in vitro* and some authors have suggested the use of voriconazole and amphotericin B combination therapy (Etienne et al., 2008; Savini et al., 2011). Reports on the emergence of multidrug resistant strains are sporadic, it is a big concern for clinicians due to a limited number of antifungal drugs available for optimal management (Garcia-Ruiz et al., 2013).

Adult T-cell leukemia/lymphom a (ATLL) affects almost

exclusively adults and is extremely rare in children, although a few cases in childhood have been described. The median age is around the mid-1960s and there is no gender prevalence. Familiar ATLL has been documented in Japan, the USA and England; it is unknown whether a genetic predisposition plays a role in the development of the disease in such cases (Kami et al., 2003). Haemophagocytic syndrome as the first sign of transformation has been described in smouldering ATLL (Kami et al., 2003; Okamura et al., 2005). Unfortunately, patient's general condition deteriorated rapidly and had a fatal outcome five days later, so it was too late for an appropriate management. It can be concluded that in those patients with resistant fever and underlying haematological malignancy, fungal infection with *S. capitata* should be kept in mind, and early initiation of appropriate antifungal treatment must be overviewed.

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