New Microbiologica, 39, 4, 307-309, 2016, ISN 1121-7138

CASE REPORT

Management and treatment of *Magnusiomyces capitatus* (*Geotrichum capitatum*) pleural infection in a non-neutropenic patient with posaconazole. A new therapeutic opportunity?

Grazia Brunetti[1], Valeria Visconti[1], Maria Cristina Ghezzi[2], Sara Mantovani[3], Giancarlo Ferretti[4], Giammarco Raponi[2]

[1]*Department of Molecular Medicine;*
[2]*Department of Public Health Science and Infectious Disease;*
[3]*Department of Thoracic Surgery;*
[4]*Department of Tropical Medicine, Azienda Policlinico Umberto I, Sapienza University of Rome, Italy*

SUMMARY

Magnusiomyces capitatus may cause uncommon yet severe infections, especially in patients with haematologic disorders. Diagnosis may be difficult and time-consuming and newer approaches are required including the MALDI-TOF technique implemented with the detection of fungal antigens in the body fluids. The recommended treatment includes amphotericin B alone or in combination with flucytosine. We describe a case of a non-neutropenic patient with *M. capitatus* pleural infection, as identified by MALDI-TOF, positivity for galactomannan antigen in the BAL fluid, and successfully treated with oral posaconazole in single therapy.

Received November 11, 2015 *Accepted* March 2, 2016

INTRODUCTION

Magnusiomyces capitatus (teleomorph form of *Saprochaete capitata*, previously named *Geotrichum capitatum, Trichosporon capitatum* or *Blastoschizomyces capitatus*) (Arendrup *et al.,* 2014) is a cosmopolitan and ubiquitous fungus, widespread in nature, that can be found in the normal microbial flora colonizing humans. Infections affecting immunocompromised patients are accompanied by a high mortality rate (Saghrouni *et al.,* 2012; Bonini *et al.,* 2008; Trabel*si et al.,* 2015), but data in the immunocompetent patient are rare (Miglietta *et al.,* 2015). Diagnosing the infection may be difficult, especially in the early stages of the disease, and cultural procedures may fail to reveal the fungus in clinical samples. Amphotericin B alone or in combination with flucytosine is the mainstay of therapy for this infection. This study describes the case of *M. capitatus* pleural infection in a non-neutropenic patient successfully treated with oral posaconazole.

CASE REPORT

A 75-year-old female dyslipidemic hypertensive patient had a history of invasive carcinomas as follows: in 1987 bilateral ductal carcinoma of the breast (pT1, pN0, M0) complicated in 2009 with cutaneous metastasis; and right lung adenocarcinoma (pT2a N0) treated with lower lobectomy and lymphadenectomy in 2012. In January 2015 she was admitted to Umberto I University Hospital in Rome (Italy) for asthenia, productive cough and low-grade fever (<37.5°C) non-responsive to lengthy antibiotic therapy. On admission, laboratory examinations showed moderate leukocytosis, and elevated CRP (*Table 1*). Under observation, the patient was treated with nebulized colistin (10^6 units, twice daily) and antipyretics as needed. On day 15, fever peaked to 38.8°C and therefore a contrast CT total body and a bronchoalveolar lavage (BAL) were performed. The CT disclosed a fluid abscess in the posterior right side of the pleural space along with two fistulae (*Fig. 1*). BAL showed negative cytology for cancer cells, subsequently confirmed by pulmonary biopsy. The levels of galactomannan (GM) antigen, as detected in the BAL by ELISA test (Platelia® Aspergillus, BioRad Italy), resulted positive (0.7 U/mL). BAL culture revealed the growth of 10^4 CFU/mL *Enterococcus faecalis*. Rifampin therapy was initiated (600 mg/die i.v. for ten days). On day 26 due to the persistence of low-grade fever, leukocytosis and elevated inflammatory markers (*Table 1*), the abscess was broken by fibroscopic and DYNA-CT guide. The drainage material was sent to the microbiology laboratory where the gram staining revealed septate mycelial filaments and unbranched arthrospores. Culture was performed and *M. capitatus* was identified on the basis of morphology, biochemical characteristics (API ID32C bioMerieux, France) and MALDI-TOF mass spectrometry (Bruker, Germany). MALDI-TOF mass spectrometry clearly discriminated

Key words:
Magnusiomyces capitatus, Pleural infection, Galactomannan antigen, MALDI-TOF identification, Posaconazole.

Corresponding author:
Giammarco Raponi MD, PhD
E-mail: giammarco.raponi@uniroma1.it

Table 1 - *Diagnostic parameters detected during patient hospitalization.*

Parameters	*0n admission*	*Day 26th*	*Before discharge*
BT (°C)	37,1	38,8	36,8
WBC x103/mL	9100	15800	7470
PMN x103/mL	7100	14000	5500
LYM x 103/mL	1200	800	900
Mϕ 103/mL	620	740	460
RBC x 103/mL	3780	3340	3390
HGB g/L	10,4	9	9,4
PTL x 103/uL	461	490	359
CRP mg/L	106	84	4
GM* U/mL on BAL	-	0,70	0,15
FERRITIN ng/mL	289	-	-
FIBRINOGEN mg/dL	705	-	-

*GM: galactomannan antigen detection.

the fungus. In fact, as shown in the species dendrogram gained from our database (5627entries, *Fig. 2*), there is enough distance between species to discriminate between *M. capitatus, Geotrichum candidum and Saprochaete clavata*. The susceptibility test (Sensititre YeastOne YO10, Thermo Fisher Scientific, USA) disclosed MIC values of 0.5 µg/mL for posaconazole, 0.12 µg/mL for voriconazole, 1µg/mL for amphotericin B, 8 µg/mL for fluconazole and 8 µg/mL 5-flucytosine. On the basis of microorganism identification, therapy was immediately implemented with amphotericin B (Ambisome 250 mg/die i.v). However, due to an immediate appearance of a cutaneous rush reaction, antimycotic therapy was shifted to oral posaconazole (400 mg B.I.D., delayed-release tablets for ten days). With the new antifungal therapy her fever curve continuously decreased until complete remission. Similarly, leukocytosis, CRP and galactomannan antigen remitted after 5 days of antimycotic treatment (*Table 1*). At 60th day of hospitalization, a one-way Zephyr 5.5 valve was placed on the larger fistula, and fibrin glue was instilled on the smaller fistula. Chest CT scan showed fistulas and abscess resolution.

DISCUSSION

M. capitatus is predominantly found in Europe as an opportunistic pathogen mainly observed in immune-compromised patients. Risk factors for the development of infections are immune suppression, the destruction of the normal microbial flora due to the use of broad spectrum antibiotics, cytotoxic chemotherapy, catheterization, and neutropenia (less than 100/mm^3) (Girmenia *et al.,* 2005). In neutropenic patients *Geotrichum* species may cause both invasive disseminated and bloodstream infections (77%) (Bonini *et al.,* 2008). Nevertheless, gastrointestinal, urinary and cutaneous involvement have been reported (Özkaya-Parlakay *et al.,* 2012), and pulmonary association is common in *M. capitatus* sepsis (Girmenia *et al.,* 2005, Martino *et al.,* 1990). Local infections have been rarely observed in the immunocompetent patients (Özkaya-Parlakay *et al.,* 2012, Subramanya Supram *et al.,* 2015). In this report we describe the first case of pleural infection in a non-hematologic patient, successfully treated with oral posaconazole.

Diagnosis of M. *capitatus* infections may be difficult and the data reported in the literature on the identification of *M. capitatus* are conflicting. Desnos-Ollivier *et al.* showed misidentification between species of *S. clavata, M. capitatus* and *Galactomyces candidus* (Desnos-Ollivier *et al.,* 2014). In their study, performed by sequencing the internal transcribed spacer regions, the nucleotide sequences of *S. clavata* and *M. capitatus* were either misidentified or too short (163 bp). However, other studies proved that MALDI-TOF MS is an excellent diagnostic tool to provide reliable identification of most (98%) of the tested strains to the species level, with good discriminatory power (Kolecka *et al.,* 2013). Additionally, the detection of serum galactomannan (GM) in the diagnosis of *M. capitatus* was reported in the case of disseminated infection (Bonini *et al.,* 2008; Özkaya-Parlakay *et al.,* 2012; Giacchino *et al.,* 2006). To our knowledge, no sound studies reported that GM could be detected in the BAL fluid during a pleural infection sustained by *M. capitatus*, as was the case of our

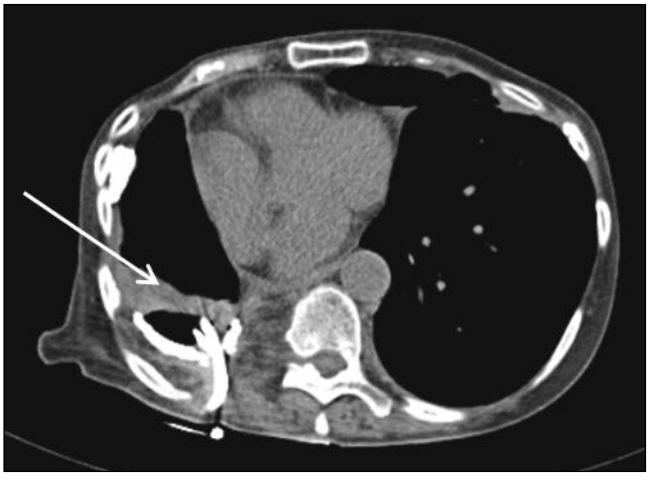

Figure 1 - *CT total body: abscess in the posterior right side of the pleural space with the insertion of the drainage tube (arrow).*

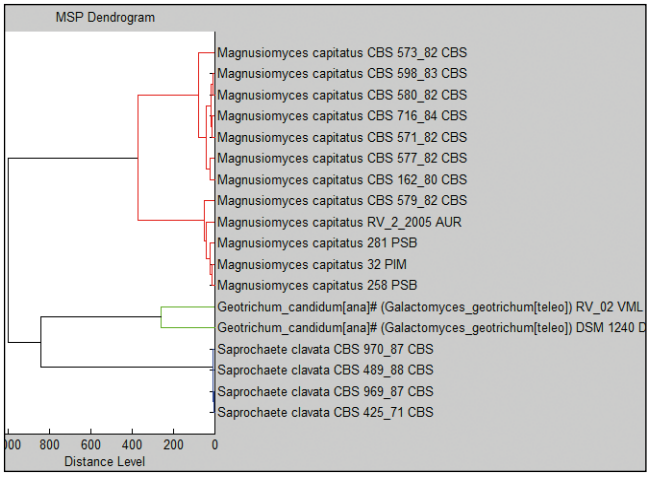

Figure 2 - *MALDI-TOF Biotyper OC 3.1 dendrogram. Distant levels between M. capitatus, Geotrichum candidum and Saprochaete clavata allow species discrimination.*

patient. Our finding was supported by the observation that the measurement of GM antigen in the BAL seems to be a better diagnostic tool in localized infections than in serum (Kono *et al.,* 2013). However, our observation must be interpreted with caution, since GM indices between 0.5 and 1 in BAL samples, especially from non-immunocompromised patients, might represent false positive results. Several studies reported false positive results of GM detection in patients receiving beta lactam antibiotics, including carbapenems (Viscoli *et al.,* 2004; Boonsarngsuk *et al.,* 2010). However, our patient was treated with rifampin, and the negativity of the GM antigen after antifungal therapy excluded a false positive result. Nowadays treatment of *M. capitatus* infection remains debatable (Arendrup et al., 2014, Saghrouni *et al.,* 2012). Amphotericin B, alone or in combination with flucytosine (Martino et al., 1990, Schiemann *et al.,* 1998, D'Antonio *et al.,* 1996), seems to be the most effective regimen. *In vitro* the broad spectrum fungicides such as voriconazole, posaconazole and ravuconazole seemed to be effective in the treatment of invasive fungal infections (Arendrup *et al.,* 2014, Schiemann *et al.,* 1998, Blau *et al.,* 2000, Granier, 2000). Girmenia *et al.* reported a high activity of amphotericin B and voriconazole against *M. capitatus* and the poor susceptibility of some strains to flucytosine, fluconazole and itraconazole. Our patient had an adverse reaction to amphotericin B therapy and treatment was shifted within 24 h to oral posaconazole based on the higher feasibility of the drug, cost effectiveness, better compliance of the patient with the oral therapy and lower MIC values of susceptibility test (Girmenia *et al.,* 2003). The remission of the symptomatology, together with the closure of the fistulas after treatment, seemed to testify a successful therapeutic choice.

In conclusion, our data showed that early diagnosis of *M. capitatus* infection should include MALDI-TOF identification, galactomannan antigen detection and that oral posaconazole treatment might be an excellent therapeutic opportunity.

Note. Due to the clinical information contained in this article, informed consent was gained from the patient. The research has complied with all relevant international guidelines and institutional policies.

Potential conflict of interest. All authors: No potential conflict.

References

Arendrup M.C., Boekhout T., Akova M., Meis J.F., Cornely O.A., Lortholary O. (2014). ESCMID and ECMM joint clinical guidelines for the diagnosis and management of rare invasive yeast infections. European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group; European Confederation of Medical Mycology. *Clin Microbiol Infect*. **20**, 76-98.

Blau I.W., Fauser A.A. **(**2000). Review of comparative studies between conventional and liposomal amphotericin B (Ambisome) in neutropenic patients with fever of unknown origin and patients with systemic mycosis. *Mycoses*. **43**, 325-332.

Bonini A., Capatti C., Parmeggiani M., Gugliotta L., Micozzi A., Gentile G., et al. (2008). Galactomannan detection in Geotrichum capitatum invasive infections: report of 2 new cases and review of diagnostic options. *Diagnostic Microbiology and Infectious Disease*. **62**, 450-452.

Boonsarngsuk V., Niyompattama A., Teosirimongkol C., Sriwanichrak K. (2010). False-positive serum and bronchoalveolar lavage Aspergillus galactomannan assays caused by different antibiotics. *Scand J Infect Dis*. **42**, 461-468.

D'Antonio D., Mazzoni A., Iacone A., Violante B., Capuani M.A., Schioppa F., Romano F. (1996). Emergence of fluconazole-resistant strains of Blastoschizomyces capitatus causing nosocomial infections in cancer patients. *J Clin Microbiol.* **34**, 753-755.

Desnos-Ollivier M., Blanc C., Garcia-Hermoso D., Hoinard D., Alanio A., Dromer F. (2014). Misidentification of Saprochaete clavata as Magnusiomyces capitatus in clinical isolates: utility of internal transcribed spacer sequencing and matrix-assisted laser desorption ionization-time of flight mass spectrometry and importance of reliable databases. *J Clin Microbiol.* 52, 2196-2198.

Giacchino M., Chiapello N., Bezzio S., Fagioli F., Saracco P., Alfarano A., et al. (2006). Aspergillus galactomannan enzyme-linked immunosorbent assay cross-reactivity caused by invasive Geotrichum capitatum. *J Clin Microbiol.* **44**, 3432-3434.

Girmenia C., Pagano L., Martino B., D'Antonio D., Fanci R., Specchia G., et al. and the GIMEMA Infection Program. (2005). Invasive infections caused by Trichosporon species and Geotrichum capitatum in patients with hematological malignancies: a retrospective multicenter study from Italy and review of the literature. *J Clin Microbiol.* **43**, 1818-1828.

Girmenia C., Pizzarelli G., D'Antonio D., Cristini F., Martino P. (2003). In vitro susceptibility testing of Geotrichum capitatum: comparison of the E-Test, disk diffusion, and Sensititre colorimetric methods with the NCCLS M27-A2 broth microdilution reference method. An*timicrob Agents Chemother.* **47**, 3985-3988.

Granier F. (2000). Invasive fungal infections. Epidemiology and new therapies. *Presse Med.* **29**, 2051-2056.

Kolecka A., Khayhan K., Groenewald M., Theelen B., Arabatzis M., Velegraki A., et al. (2013). Identification of medically relevant species of arthroconidial yeasts by use of matrix-assisted laser desorption ionization-time of flight mass spectrometry. J *Clin Microbiol.* **51**, 2491-2500.

Kono Y., Tsushima K., Yamaguchi K., Kurita N., Soeda S., Fujiwara A. et al. (2013). The utility of galactomannan antigen in the bronchial washing and serum for diagnosing pulmonary aspergillosis. *Respir Med***. 107**, 1094-1100.

Martino P., Venditti M., Micozzi A., Morace G., Polonelli L., Mantovani M.P., et al. (1990). Blastoschizomyces capitatus: an emerging cause of invasive fungal disease in leukemia patients. *Rev Infect Dis*. **12**, 570-582.

Miglietta F., Vella A., Faneschi M.L., Lobreglio G., Rizzo A., Palumbo C., et al. (2015). Geotrichum capitatum septicaemia in a haematological patient after acute myeloid leukaemia relapse: identification using MALDI-TOF mass spectrometry and review of the literature. *Infez Med.* **23**, 161-167.

Özkaya-Parlakay A., Cengiz A.B., Karadağ-Öncel E., Kuşkonmaz B., Sarıbaş Z., Kara A., Oğuz B. (2012). Geotrichum capitatum septicemia in a hematological malignancy patient with positive galactomannan antigen: case report and review of the literature. *Turk J Pediatr.* **54**, 674-678.

Saghrouni F., Ben Abdeljelil J., Ben Youssef Y., Ben Abdeljelil N., Gheith S., Fathallah A., Ben Said M. **(**2012). Geotrichum capitatum septicemia in patients with acute myeloid leukemia. Report of their cases. *Med Mycol Case Reports*. **1**, 88-90.

Schiemann R., Glassmaker A., Bailly E., Horre R., Molitor E., Leutner C., et al. (1998). Geotrichum capitatum septicemia in neutropenic patients: case report and review of the literature. *Mycoses*. **41**, 113-116.

Subramanya Supram H., Gokhale S., Chakrabarti A., Rudramurthy S.M., Gupta S., Honnavar P. **(**2015). Emergence of Magnusiomyces capitatus infections in Western Nepal. *Med Mycol.* pii: myv075.

Trabelsi H., Néji S., Gargouri L., Sellami H., Guidara R., Cheikhrouhou F., et al. (2015). Geotrichum capitatum septicemia: case report and review of the literature. *Mycopathologia*. **179**, 465-469.

Viscoli C., Machetti M., Cappellano P., Bucci B., Bruzzi P., Van Lint M.T., Bacigalupo A. (2004). False-positive galactomannan platelia Aspergillus test results for patients receiving piperacillin-tazobactam. *Clin Infect Dis*. **38**, 913-916. Epub 2004 Feb 27.