

Galactomannan detection in *Geotrichum capitatum* invasive infections: report of 2 new cases and review of diagnostic options

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Received 3 July 2008; accepted 12 August 2008

Abstract

We report 2 cases of *Geotrichum capitatum* infection in leukemia patients for which *Aspergillus* galactomannan (GM) assay was positive. The diagnostic options of *G. capitatum* infections in hematologic patients were reviewed. Although the pathogen was isolated from blood in 77% of cases, diagnostic difficulties remain and GM assay may have a role.

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Keywords: Galactomannan; *Geotrichum capitatum*; Acute leukemia; Aspergillosis

Geotrichum capitatum is an uncommon but frequently fatal cause of invasive infections in immunocompromised patients, particularly those with hematologic malignancies. In a recent retrospective multicenter study from Italy, the incidence of *G. capitatum* infection among patients with acute leukemia was 0.5%, with a 55.7% crude mortality rate (Girmenia et al., 2005). The clinical features of *G. capitatum* infections frequently resemble those of invasive candidosis; on the contrary, susceptibility pattern of *G. capitatum* is significantly different from that of *Candida* spp. In vitro susceptibility studies showed that amphotericin B and voriconazole are the more active drugs; several strains have a reduced susceptibility to flucytosine, fluconazole, and itraconazole; and caspofungin is intrinsically not active against most of isolates (Girmenia et al., 2003; Cuenca-Estrella et al., 2006). The optimal therapy has yet to be identified. In the cases found in the literature, conventional amphotericin B, alone or associated with other antifungal agents, was the drug most frequently used in 1st-line therapy. Although only a few cases in which voriconazole was used as initial or salvage antifungal therapy have been reported, in

vitro susceptibility data seem to suggest a promising role of the azole in the management of *G. capitatum* infections (Girmenia et al., 2005).

Recent clinical and laboratory data showed that *G. capitatum* produces a soluble antigen that is cross-reactive with an enzyme immunosorbent assay for *Aspergillus* galactomannan (GM), the Platelia[®] *Aspergillus* assay (Giacchino et al., 2006). This cross-reactivity seems to suggest that the GM detection may have a potential role in the management of invasive *G. capitatum* infections.

Here we describe 2 cases of acute leukemia patients who developed deep-seated infection by *G. capitatum* for which GM assay was positive. We also reviewed the diagnostic options now available for this severe fungal infection in patients with hematologic malignancies.

A 59-year-old man diagnosed with acute myeloid leukemia was admitted because of febrile neutropenia (neutrophils 100/mm³). Empiric therapy with piperacillin/tazobactam plus amikacin was started, but because of persisting fever, antifungal therapy with caspofungin was added. Despite persisting fever, induction chemotherapy was administered. After 5 days from the completion of chemotherapy, the patient was still febrile and antibiotic therapy was changed with the association meropenem, vancomycin, and amikacin. Blood cultures grew *Klebsiella*

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Table 1
Sites of infection and outcome in 100 cases of *G. capitatum* infections in patients with hematologic diseases

Site of infection	No. of cases	Mortality, no. of cases (%)
Fungemia, total no. of cases	77	44 (57.1)
Fungemia with/without invasive tissue infection	63/14	40 (63.5)/4 (28.6)
Fungemia with disseminated infection ^a	46	31 (67.4)
Cases of invasive infection without fungemia	23	11 (47.8)
Disseminated infection ^a	4	3 (75)
Lung ^b	9	7 (77.8)
Bone and joint ^b	4	0 (0)
CNS ^b	2	1 (50)
Esophagus ^b	2	0 (0)
Liver ^b	1	0 (0)
Kidney ^b	1	0 (0)

CNS = Central Nervous System.

^a Two or more organs involved.

^b Focal invasive tissue infection.

pneumoniae sensitive to meropenem. After 4 days, the patient developed respiratory failure and multiple pulmonary nodules were documented at computed tomography of the chest. Galactomannan assay from serum samples obtained in 3 consecutive days was positive (optical density index 3, 4.2, and >5 respectively). Caspofungin was substituted with posaconazole. After 2 days, the patient conditions worsened and the isolation of *G. capitatum* from blood was communicated by laboratory. Posaconazole was substituted with intravenous voriconazole, but the patient died early. Autopsy was not performed.

A 33-year-old woman with a diagnosis of acute myeloid leukemia underwent induction chemotherapy. Antimicrobial prophylaxis consisted of oral ciprofloxacin and posaconazole. On day 15 from the start of chemotherapy, while profoundly neutropenic (neutrophils 10/mm³), she developed fever and empiric therapy with piperacillin/tazobactam was started. After 4 days, because of persistence of fever and documenta-

tion of an *Escherichia coli* septicemia, piperacillin/tazobactam was substituted with meropenem. Fever disappeared and clinical conditions rapidly improved. After 7 days, the patient newly developed fever while still neutropenic. Computed tomography of the chest showed 2 nodular lesions; posaconazole was discontinued and antifungal therapy with liposomal amphotericin B was inserted. Galactomannan assay from sputum and from 2 serum samples was positive (optical density index: >5, 1.7, and 2.1, respectively), and sputum culture yielded *G. capitatum*. Patient died 2 days later. At autopsy, a pulmonary infiltration by septate hyphae, slightly bent with parallel disposition, spores, and fragmentation of the mycelium in arthroconidia, was observed. Mycological cultures yielded only *G. capitatum*.

The literature search yielded 100 reports of *G. capitatum* infection in patients with hematologic malignancies, including the 2 present cases (Batlle et al., 2004; Böck et al., 2006; Christakis et al., 2005; Etienne et al., 2008; Giacchino et al., 2006; Girmenia et al., 2005; Huang et al., 2004; Mejdoubi et al., 2008; Pimentel et al., 2005). Table 1 shows the reported sites of infection and outcome of these cases. Overall, the pathogen was isolated from blood in 77% of cases, whereas in 23% of cases, a focal or disseminated invasive infection without fungemia was documented. The overall mortality rate was 55%.

Including the present 2 reports, 5 cases of invasive *G. capitatum* infection in patients with acute leukemia for which GM assay was positive are available to date. The characteristics of these cases are detailed in Table 2. In all cases, the detection of GM antigen preceded the cultural documentation of the infection. In patients 1, 2, 4, and 5, the antifungal therapy was modified based on the GM assay results with the suspect of an underlying aspergillosis. Only in case 3 did the 1st GM-positive serum sample coincide with the isolation of yeasts from blood and skin. In this case, while awaiting for the identification of the pathogen (2 days later), voriconazole therapy was started considering the possibility of a *G. capitatum* infection based on the

Table 2
Clinical and microbiologic characteristics of 5 cases of *G. capitatum* infection for which GM assay was positive

Case (reference)	Age/sex	Site of <i>G. capitatum</i> isolation	Sample positive for GM	Days from the 1st positive GM sample and microbiologic documentation of the pathogen	Antifungal therapy modification after GM detection	Antifungal therapy modification after <i>G. capitatum</i> infection documentation	Outcome
1 (2)	7/M	CNS	Serum and cerebral abscess pus	7	Caspofungin was added to liposomal AmB	Caspofungin was replaced with voriconazole	Alive
2 (2)	9/F	Blood and skin	Serum	9	Liposomal AmB was added to caspofungin prophylaxis	No modification, death occurred the day of documentation	Death
3 (2)	49/M	Blood and skin	Serum	2	Liposomal AmB was replaced with voriconazole	No modification	Death
4 (present report)	59/M	Blood	Serum	2	Caspofungin was replaced with posaconazole	Posaconazole was replaced with voriconazole	Death
5 (present report)	33/F	Lung	Serum and sputum	3	Posaconazole prophylaxis was replaced with liposomal AmB	No modification	Death

AmB = amphotericin B; CNS = Central Nervous System.

knowledge of the cross-reactivity between a *G. capitatum* soluble antigen and the GM assay (Ahrazem et al., 2002; Giacchino et al., 2006).

The diagnosis of *G. capitatum* invasive infection appears to be easier compared with other fungal infections, considering that the pathogen is isolated from blood in the large majority of cases. However, blood cultures usually take several days to show detectable growth of yeast cells, and in the remaining cases of deep-seated infection without fungemia, the diagnostic approach may be very difficult. In several of these cases, the pathogen may be isolated from mucosal surfaces and respiratory specimens; however, because *G. capitatum* is a potential component of the normal microbial flora of the human digestive and respiratory tract, it may be difficult to distinguish between colonization and infection. The availability of noncultural markers of invasive infection by *G. capitatum* may be of great aid in the management of this severe complication; however, data on specific *G. capitatum* antigens or DNA detection are not available to date.

The above cases strongly suggest the potential role of GM detection in the management of *G. capitatum* infections and physicians should be aware of this possibility. In particular, the detection of GM in a neutropenic patient with clinical findings resembling an invasive candidosis, such as maculopapular skin lesions and disseminated nodular lesions in deep organs, could be suggestive for an underlying *G. capitatum* infection. Again, GM assay could be used as a marker to differentiate between colonization and deep infection in patients in which *G. capitatum* is isolated from respiratory tract and mucosal surfaces.

Although in a previous study (Giacchino et al., 2006) reactivity of Platelia *Aspergillus* assay with soluble antigens from suspensions of *G. capitatum* strains was significantly lower than that from *Aspergillus* spp., serum levels of GM cannot be used to differentiate between the 2 infections as demonstrated in the 2 present cases where serum GM levels were particularly high (ranging from 1.7 to >5). Probably, not only the intrinsic production of antigen by the fungus but particularly the extension of the infections may determine the levels of detectable GM. High GM serum levels during *G. capitatum* infections could be justified by the dissemination, which typically characterizes this mycosis in leukemia patients and the release of the antigen directly in the bloodstream.

In conclusion, when GM is detected from serum in a patient with a clinically suspected invasive candidosis or with pulmonary lesions and *G. capitatum* isolation from respiratory tract, the possibility of a deep *G. capitatum* infection should be considered. However, also in these cases, the detection of GM antigen cannot be considered a

specific diagnostic marker of *G. capitatum* deep infection because a coinfection with *Aspergillus* spp. may occur. Furthermore, lung infiltrates by *Aspergillus* spp. and *G. capitatum* may be indistinguishable each other in some cases. In the above settings, it could be suggested to choose an antifungal drug highly active against both *Aspergillus* spp. and *G. capitatum*, such as amphotericin B and voriconazole but not caspofungin.

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