

DISSEMINATED *GEOTRICHUM CAPITATUM* INFECTION WITH PREDOMINANT LIVER INVOLVEMENT IN A PATIENT WITH NON HODGKIN'S LYMPHOMA

Nicole Amft, Antonio Miadonna, Maria Anna Viviani,* Alberto Tedeschi

3rd Division of Internal Medicine and *Institute of Hygiene and Preventive Medicine, University of Milan, IRCCS Ospedale Maggiore Policlinico, Milan, Italy

ABSTRACT

Geotrichum capitatum is an emerging opportunistic pathogen which causes invasive disease in immunocompromized patients. We describe a patient with non Hodgkin's lymphoma and disseminated infection by *G. capitatum* with predominant liver involvement, which was proven by repeated positive blood cultures and a liver biopsy. Staining liver biopsy demonstrated the presence of hyphal elements consistent with *G. capitatum*. Combined antimycotic treatment with amphotericin B and 5-flucytosine did not eradicate the mycotic infection as shown by the persistence of liver lesions.

Key words: *Geotrichum capitatum*, invasive mycosis, liver involvement, non Hodgkin's lymphoma

Immunocompromized patients, notably those with hematologic malignancies and severe neutropenia, are often hosts for disseminated or invasive fungal infections. Although most of these mycoses are caused by *Candida* and *Aspergillus spp.*, it has been documented that *Geotrichum capitatum* (synonyms: *Trichosporon capitatum* and *Blastoschizomyces capitatus*)¹ is an emerging cause of systemic infections.² This fungus is similar to *Trichosporon spp.*, as it produces hyphae which break up into arthroconidia, but it differs from it in that it is urease negative, it does not reproduce by budding and is unable to assimilate a large number of carbon sources.¹ *G. capitatum* is an ubiquitous fungus which can be found in the soil, foods and in human skin and mucosae. Digestive and respiratory tracts have been reported as possible ways of entry.

About 30 cases of infection with *G. capitatum* have been described so far and have been more commonly observed in Europe (85% of reported cases) than in the USA (10% of reported

cases). The reported clinical manifestations of *G. capitatum* infection include septicemia, meningitis, encephalitis, vertebral osteomyelitis and discitis, endocarditis, respiratory tract and gastrointestinal infections and kidney, spleen and liver colonization.² Typically, the infection begins during a period of profound and prolonged granulocytopenia and the clinical picture is characterized by fever unresponsive to broad spectrum antibiotic treatment. Once the patient's neutrophil count has come back to normal value, *G. capitatum* is no longer detectable in blood and other biological fluids by currently available techniques.

Below we describe a patient who developed a systemic infection by *G. capitatum* with predominant liver involvement.

Case report

In February 1995 a 56-year-old Sicilian woman was admitted to our department because of left peripheral palsy of the VII cra-

nial-nerve, exophthalmos of the left eye and defect of the right VI cranial-nerve with episodes of diplopia.

In November 1994 a B-cell centrofollicular non Hodgkin's lymphoma (clinical stage IV B) was diagnosed by histologic and immunophenotypic analysis after excision of a lymph node of the left laterocervical region. The lymphoma was classified as belonging to group D according to the working formulation and equivalent to the category of centroblastic-centrocytic lymphoma in the modified Kiel classification. Bone marrow aspirate and a bone marrow-biopsy documented lymphoma infiltration in the marrow. A total body computerized tomographic (CT) scan showed lymphadenopathy in the mediastinal and ilear region and hepatosplenomegaly. Three courses of chemotherapy (CEOP: cyclophosphamide, epirubicin, vincristine and methylprednisolone) were administered with a temporary clinical response and normalization of the bone marrow biopsy.³

In January 1995 the patient started complaining of headache and an examination of cerebrospinal fluid (CSF) evidenced the presence of blasts. A CT scan of the brain revealed no abnormalities. She was hospitalized at Palermo and was treated with four courses of intrathecal injections of methotrexate (12 mg), cytosine arabinoside (40 mg) and betamethasone (2 mg) with a temporary clinical response and normalization of CSF analysis. On February 6, 1995 she suddenly developed a complete left peripheral facial palsy. She also complained of episodes of horizontal diplopia on rightward gaze and exophthalmos of the left eye. A CT scan of the brain showed diffuse cortical atrophy and an old ischemic lesion in the right pallidum.

On February 17, 1995 the patient was admitted for the first time to our department. Analysis of CSF showed a relapse of central nervous involvement with lymphoma. Bone marrow aspirate was normal. Systemic treatment with high dose cytosine arabinoside (3 g/sm bid, day 1 to 5) and ethoposide (100 mg/sm, day 6 to 9) was started together with intrathecal chemotherapy (four courses at weekly intervals) with methotrexate (12 mg), cytosine arabinoside (40 mg) and betamethasone (2 mg). Severe neu-

tropenia appeared two weeks after systemic chemotherapy was started and the patient developed fever unresponsive to wide spectrum antibiotic therapy. *G. capitatum* was isolated from five consecutive daily blood cultures performed with the Isolator system and one urine sample. The fungus was identified on the basis of the macro and micromorphology on corn meal agar; furthermore, the carbohydrate assimilation pattern was assessed by the use of ID32C (Bio-Merieux, Lyon, France), and the urease production was studied on Christensen's urea agar slant incubated at 30°C. The minimal inhibitory concentrations (MICs) for *G. capitatum* were 0.05 mg mL⁻¹ itraconazole, <0.05 mg mL⁻¹ 5-flucytosine, 0.4 mg mL⁻¹ amphotericin B and 12.5 mg mL⁻¹ fluconazole. Prophylactic treatment with itraconazole (200 mg daily, initiated along with chemotherapy) was discontinued because of nausea and vomiting, and intravenous amphotericin B (1 mg/kg/day) was administered. Amphotericin B (Fungizone®) was discontinued after a total dose of 875 mg, when the patient developed an intestinal obstruction caused by a hematoma of the ileum, concomitantly with severe thrombocytopenia (March 24, 1995). Laboratory findings also showed an increase of alkaline phosphatase. The patient was transferred to the department of surgery, where ileostomy with terminal-lateral entero-entero anastomosis was performed. On re-admission to our department (April 4, 1995) a massive intestinal hemorrhage with severe and rapid anemia was observed because of bleeding from a diverticulum of the cecum; a hemicolectomy was then performed. Nodular lesions of the liver were found during surgery and a liver biopsy demonstrated the presence of hyphal elements, some divided by septation, consistent with *G. capitatum* (Figure 1). Abdominal ultrasound and CT scan showed multiple focal lesions in the liver. Treatment with amphotericin B was started again in association with intravenous infusions of 5-flucytosine (Ancotil®, 7.5 gr daily). The patient complained of mild headache, nausea, vomiting and abdominal pain, and parenteral nutrition was required. A worsening of clinical conditions, persisting nausea and vomiting, and lack of response to the antimycotic drugs admin-

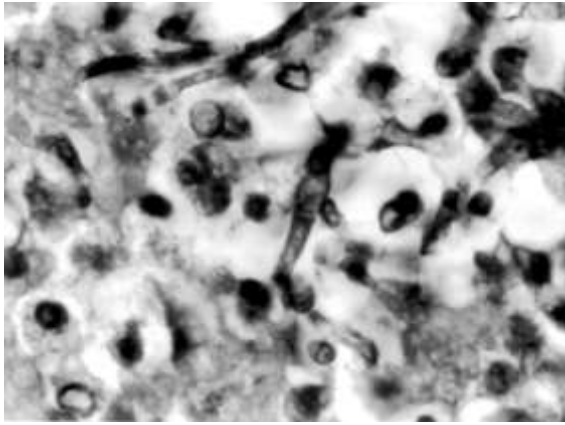


Figure 1. Liver section showing the presence of hyphal elements, some with septum, consistent with *G. capitatum*. This fungus had been repeatedly isolated from blood and urine cultures (Periodic Acid-Schiff stain; 500 \times).

istered led us to substitute conventional amphotericin B with liposomal amphotericin B (AmBisome®). However, in spite of prolonged parenteral antimycotic treatment with amphotericin B (1.2 gr of conventional amphotericin B, 5 g of liposomal amphotericin B) and 5-flucytosine, a CT scan showed progressive diffusion and enlargement of the liver lesions (Figure 2). No spleen lesions were seen but micronodular lesions were observed in the anterior segment of the right upper lobe of the lung. In the first week



Figure 2. Computerized tomographic (CT) scan of the liver showing numerous hypodense rounded areas, consistent with fungal focal lesions. This CT scan was performed after prolonged antifungal treatment, which did not eradicate the infection.

of June vesicular lesions of herpes zoster in the right thorax dermatome developed. In the same period *Aspergillus fumigatus* was identified in the sputum; furthermore, repeated oro-pharyngeal swabs showed the presence of *Pseudomonas aeruginosa*. During the last six weeks of hospitalization the patient required an increasing support with platelet and erythrocyte concentrates. A worsening of clinical conditions and an increase of lactate dehydrogenase levels suggested the progression of lymphoma. On her own request, the patient was transferred to another hospital in Sicily near the residence of her family. The day before the patient died, signs of acute mental confusion appeared. She died three weeks after discharge, eight months after the diagnosis of lymphoma. An autopsy was not performed.

Discussion

G. capitatum is an ubiquitous fungus whose pathogenicity was rarely documented in humans until 1980.⁴ An increasing number of invasive *G. capitatum* infections have been reported recently, which suggests that this fungus is an emerging opportunistic pathogen with an often fatal outcome, in particular in immunocompromized patients. However, *G. capitatum* infections have been documented also in some patients who were not severely immunocompromized. Moreno *et al.*⁵ described a transient fungemia in an intravenous drug abuser and Arnold *et al.*⁶ in a patient with endocarditis. Four cases with underlying hematologic malignancies were cured of the *G. capitatum* infection: three patients with acute leukemia² showed no signs of fungal infection after 0.5, 3 and 5 years of follow-up; D'Antonio *et al.*⁷ described another acute leukemia patient affected with osteomyelitis and intravertebral discitis who did not show any sign of infection after a one-year follow-up. One additional case of disseminated infection in a patient with Hodgkin's disease was described;⁸ the authors reported the resolution of clinical manifestations and no evidence of *G. capitatum* isolation in peripheral blood after 24 days of treatment with amphotericin B; no follow-up examination was described. A chronic

infection by *G. capitatum* was presented in the case described by Girmenia *et al.*,⁹ at the autopsy, a persisting *G. capitatum* meningeal invasion was documented, although meningeal syndrome had clinically disappeared, and prolonged treatment (11 months) with oral fluconazole had been administered.

In our patient, the risk factor for development of an invasive *G. capitatum* infection was represented by immunodepression caused by underlying malignancy and by severe neutropenia and damage of the gastrointestinal flora resulting from chemotherapy. The prophylactic administration of itraconazole (200 mg daily) did not avoid systemic infection by *G. capitatum*; furthermore, prolonged parenteral antimycotic treatment with amphotericin B and 5-flucytosine was unable to eradicate the liver infection by *G. capitatum*, as evidenced by an increase of the liver nodular lesions at CT scan control after therapy. We had the opportunity of performing a liver biopsy during surgery and we demonstrated *in vivo* that *G. capitatum* is localized in the liver and causes diffuse nodular lesions characterized by a central necrotic area surrounded by epithelioid giant cells. Hyphal elements, some divided by septum, consistent with *G. capitatum*, could be detected in the necrotic areas of the liver. The granuloma formation is a typical expression of host defenses against fungi when neutrophil count returns to normal value. The difficulty in eradicating the infection may have been caused by the inadequate antifungal drug concentration in the granuloma lesions including *G. capitatum*.

Our findings underline the difficulty of eradicating *G. capitatum* infection after localization in the liver in severely immunocompromized patients. As observed by Cofrancesco *et al.*,¹⁰ an increase in serum alkaline phosphatase may be an early sign of liver involvement with *G. capitatum*. Liver involvement by a *Trichosporon cutaneum* infection was reported previously by Korinek *et al.*¹¹ The case described was a 33-year-old woman with acute myelomonocytic leukemia who developed hepatomegaly and abnormal liver enzymes with high serum bilirubin. Although the blood cultures were negative, percutaneous liver

biopsy revealed granulomatous fungal hepatitis due to *Trichosporon cutaneum*. Administration of amphotericin B and 5-flucytosine did not eradicate the infection and the patient died of fungemia and polymicrobial sepsis.

A conclusion that can be drawn from the cases reported by Cofrancesco *et al.*,¹⁰ Korinek *et al.*¹¹ and by us is that ultrasound and/or CT scans should be performed to detect the presence of mycotic lesions in the liver when serum alkaline phosphatase is raised. Furthermore, if blood cultures are negative, a percutaneous liver biopsy could help identifying the presence of fungi in the liver, an aggressive prompt treatment with maximum tolerated doses of antifungal agents is also needed when fungal localization in the liver is only suspected.

References

1. de Hoog GS, Guarro J. Atlas of Clinical Fungi. Baarn and Delft: Centraalbureau voor Schimmelcultures and Reus: Universitat Rovira i Virgili, 1995.
2. Martino P, Venditti M, Micozzi A, et al. *Blastoschizomyces capitatus*: an emerging cause of invasive fungal disease in leukemia patients. *Rev Infect Dis* 1990; 12:570-82.
3. Lambertenghi Delilieri G, Butti C, Baldini L, et al. A cooperative study of epirubicin with cyclophosphamide, vincristine and prednisone (CEOP) in non-Hodgkin's lymphoma. *Haematologica* 1995; 80:318-24.
4. Deicke P, Geimenhardt H. Embolisch-metastatische pilzenzephalitis durch *Trichosporon capitatum* nach infusions therapie. *Deutsche Gesundheitswesen* 1980; 35:673-7.
5. Moreno S, Buzòn L, Sánchez-Sousa A. *Trichosporon capitatum* fungemia and intravenous drug abuse. *Rev Infect Dis* 1987; 9:1202-3.
6. Arnold AG, Gribbin B, De Leval M, MacCartney F, Slack M. *Trichosporon capitatum* causing recurrent fungal endocarditis. *Thorax* 1981; 36:478-80.
7. D'Antonio D, Piccolomini R, Fioritini G, Iacone A, Betti S, Fazii P, Mazzoni A. Osteomyelitis and intervertebral discitis caused by *Blastoschizomyces capitatus* in a patient with acute leukemia. *J Clin Microbiol* 1994; 32: 224-7.
8. Sycova-Mila Z, Sufliarsky J, Trupl J, Jasenska Z, Blahva M, Krcmery V. Catheter-associated septicaemia due to *Trichosporon capitatum*. *J Hosp Infect* 1992; 22:257-8.
9. Girmenia C, Micozzi A, Venditti M, et al. Fluconazole treatment of *Blastoschizomyces capitatus* meningitis in an allogenic bone marrow recipient. *Eur J Clin Microbiol Infect Dis* 1991; 10:752-6.
10. Cofrancesco E, Viviani MA, Boschetti C, Tortorano AM, Balzani A, Castagnone D. Treatment of chronic disseminated *Geotrichum capitatum* infection with high cumulative dose of colloidal amphotericin B and itraconazole in a leukaemia patient. *Mycoses* 1995; 38: 377-84.
11. Korinek JK, Guarda LA, Bolivar R, Stroehlein JR. *Trichosporon* hepatitis. *Gastroenterology* 1983; 85:732-4.