I mmunocompromised 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 \textit{Candida} and \textit{Aspergillus} spp., it has been documented that \textit{Geotrichum capitatum} (synonyms: \textit{Trichosporon capitatum} and \textit{Blastoschizomyces capitatus}) is an emerging cause of systemic infections. This fungus is similar to \textit{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. \textit{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 \textit{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 \textit{G. capitatum} infection include septicemia, meningitis, encephalitis, vertebral osteomyelitis and discitis, endocarditis, respiratory tract and gastrointestinal infections and kidney, spleen and liver colonization. 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, \textit{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 \textit{G. capitatum} with predominant liver involvement.

\textbf{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 hystologic 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 computed 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.

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 etoposide (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 neutropenia 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 antifungal drugs admin-
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 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. 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. described a transient fungemia in an intravenous drug abuser and Arnold et al. in a patient with endocarditis. Four cases with underlying hematologic malignancies were cured of the G. capitatum infection: three patients with acute leukemia showed no signs of fungal infection after 0.5, 3 and 5 years of follow-up; D’Antonio et al. 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; 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., 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 antymycotic 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 immunocompromised patients. As observed by Cofrancesco et al., 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. 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., 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**