First European Case of Serotype A MATa Cryptococcus neoformans Infection

To the Editor: Cryptococcus neoformans is an opportunistic fungus that causes meningoencephalitis, primarily in immunocompromised patients. However, C. neoformans can also cause illness in apparently normal hosts. The yeast is a heterothallic basidiomycete with two mating types, MATa and MATα identified in all the four serotypes, A, B, C, and D. However, the mating type a of serotype A is a rare and recent finding. The MATa strain was mating defective (1,2). We report the isolation of a serotype A strain from the Italian environment; the first Tanzanian AIDS patient and a second case in Budapest because of septic fever. The patient had a history of hematologic malignancy (Hodgkin disease), which was diagnosed in 1991. He had received several courses of chemotherapy and radiation. After 4 years when his cancer was in remission, in September 1995, the disease recurred (stage IVa) for which he was treated with chemotherapy and radiation. At the last admission, in August 1998, he was pancytopenic and had septic fever. Salmonella enteritidis was cultured from his blood. The salmonella septicemia was successfully treated with ceftriaxone. As palliative treatment, he received 4x10 mg vinblastine for his residual disease. On September 30, he became febrile again. Cryptococcus neoformans was isolated from his blood, although cerebrospinal fluid culture and serologic tests were negative. On the right fossa cubitalis, cellulitis and a tender mass were present, although he did not have a history of recent central line or cytostatic treatment on this side. Cryptococcus neoformans was isolated from the sample taken from the mass. Antifungal treatment was started with 600 mg fluconazole per day and continued with amphoterin B, 1 mg/kg/day. The patient died 6 weeks after the isolation of Cryptococcus, probably because of his uncontrolled Hodgkin disease. As far as the physician was aware, the patient had not visited other countries.

The strain, isolated from the patient’s blood during the European Confederation of Medical Mycology Cryptococcosis Survey, was sent for typing to the European Convenor. The isolate, IUM 99-3617, was identified as serotype A using Crypto Check serotyping kit from Iatron Laboratories (Tokyo, Japan) and genotyped as VN6 by multiplex polymerase chain reaction (PCR) (3) by using the primers previously described (4,5). The sequences were then aligned with the reported sequences of IUM 96-2828 (2,8), the Tanzanian isolate 295.1 (1), and the congeneric JEC 20 and JEC 21 strains. The IUM 99-3617 sequences were found to be identical to those of IUM 96-2828 and of the Tanzanian isolate 295.1. The MFαA and the STE20αA sequence of IUM 99-3617 have been submitted to GenBank database (available from URL: www.ncbi.nlm.gov/Bankit/nhpbankit.cgi) under accession number AY182035 and AY182036, respectively.

Virulence studies in the mouse model demonstrate that, like IUM 96-2828, the strain is significantly less virulent than H99. The latter strain caused 100% deaths day 29, while IUM 99-3617 took until day 60 to kill 60% of mice (unpub. data). No difference was observed among the three serotype A strains when virulence factors such as capsule, melanin, phospholipase activity, and ability to grow at 37°C were tested.

The serotype A of C. neoformans was long regarded as extinct or as existing in an undiscoversed ecologic niche until the recent
finding of the clinical and the environmental isolate (1,2). The existence of MATα in nature is also supported by recent studies designed to established the origin of the serotype AD strains (4,5). These studies demonstrated that AD strains were diploid or aneuploid hybrids derived from a fusion of serotype A and D parents and that several of them were harboring a serotype A MATα locus. These hybrid strains have been found fairly often in Europe (9,10).

The finding of this isolate provides evidence of the pathogenic role of this rare mating type, emphasizes the critical function of molecular genetic tools in the characterization of C. neoformans populations, and represents an advance in knowledge of this fungal species whose genome is undergoing identification by a worldwide research team.

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References

5. Lengeler KB, Cox GM, Heitman J. Serotype AD strains of Cryptococcus neoformans are diploid or aneuploid and are heterozygous at the mating-type locus. Infect Immun 2001;69:115–22.

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Severe Acute Respiratory Syndrome: Relapse? Hospital Infection?

To the Editor: Severe acute respiratory syndrome (SARS) is an emerging infectious disease worldwide, and relapsing SARS is a major concern. We encountered a 60-year-old woman who was admitted to the Princess Margaret Hospital in Hong Kong on March 29, 2003, with a fever of 39°C, chills, cough, malaise, and sore throat for 2 days before admission. She had no history of travel within 2 weeks of admission. She also had no close contact with patients who had a diagnosis of suspected or confirmed SARS. Chest radiograph on admission indicated consolidation over the right middle zone. In accordance with the diagnostic criteria proposed by the World Health Organization (WHO), this patient’s condition was diagnosed as SARS in view of her symptoms, temperature, and chest radiograph findings (1).

Standard microbiologic investigations to exclude common respiratory virus and bacterium for community-acquired pneumonia, including Mycobacterium tuberculosis, were negative in our patient. Reverse transcriptase-polymerase chain reaction (RT-PCR) of nasopharyngeal aspirate samples was negative for coronavirus twice. The coronavirus antibody titer was less than 1/25. The patient was initially treated with oral clarithromycin (500 mg twice a day) and intravenous amoxicillin-clavulanate combination (1.2 g three times a day). Despite the negative evidence for coronavirus infection, she was treated with intravenous ribavirin (24 mg/kg once a day) and hydrocortisone (10 mg/kg once a day) after 48 hours of antibiotics therapy (2). The patient’s symptoms were relieved, and she remained afebrile 3 days after admission. Tolerance for medication was good except for a moderate degree of hemolytic anemia (her hemoglobin level dropped to 9.1 g/dL) and hypokalemia that developed during treatment. On day 15, the chest radiography was clear. The patient was discharged after 3 weeks of hospital stay.

The patient attended outpatient clinic on day 35, complaining of exertional dyspnea, low-grade fever, and malaise since her discharge. Her chest radiography showed extensive shadowing. Computer tomographic scan of the thorax indicated widespread ground-glass shadowing in both lung fields, which was especially prominent at left lower and lingular lobes.