Case Report

Liver cirrhosis caused by *Exophiala dermatitidis*

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We report a case of liver cirrhosis caused by *Exophiala dermatitidis* in a previously healthy child. The infecting organism was initially mistaken as capsule-deficient *Cryptococcus neoformans*.

Case report

An 11-year-old female patient presented with abdominal pain of 3 months' duration and generalized weakness. The patient was previously healthy. A pet hamster raised in the patient's house died just after the onset of clinical symptoms in the patient. The dead animal was left in the house for a week. On examination, the patient had a chronically ill appearance, pallor and a flat abdomen with mild shifting dullness. The liver was palpable 6 cm below the right costal margin. Laboratory tests performed on admission indicated a haemoglobin level of 6.7 g dl⁻¹, an iron level of 7.5 µg dl⁻¹, a total iron-binding capacity of 320.7 µg dl⁻¹, a ferritin level of 4.1 ng ml⁻¹, a total bilirubin level of 0.4 mg dl⁻¹, an aspartate aminotransferase level of 42 IU l⁻¹, an alanine aminotransferase level of 33 IU l⁻¹, an alkaline phosphatase level of 865 IU l⁻¹, a γ-glutamyltransferase level of 291 IU l⁻¹ and an albumin level of 2.4 g dl⁻¹. Serological studies for hepatitis B surface (HBs) antigen, anti-HBs antibody and anti-hepatitis C virus antibody were all negative. Plain chest radiography showed bilateral pleural effusion. Abdominal computed tomography (CT) images showed severe periportal oedema, splenomegaly and ascites, which were suggestive of the presence of a diffuse infiltrative lesion of the liver. Magnetic resonance imaging of the abdomen demonstrated thick periportal infiltration and fibrosis with macrolobular cirrhotic changes and intrahepatic duct dilation.

A liver biopsy was performed at the Asan Medical Center. The biopsy showed granulomatous inflammation, numerous budding yeast-like structures and periductal infiltration of inflammatory cells. Some organisms with a light-brown-pigmented wall were seen (Fig. 1). Hyphae were not observed. The organisms reacted positively with the periodic acid–Schiff stain, Gomori methenamine–silver stain and Fontana–Masson stain (FMS). The organisms showed a weakly positive reaction with the alcian blue stain and a negative reaction with the mucicarmine stain. Cultures of blood, urine, ascites, liver tissue and cerebrospinal fluid grew no micro-organisms. Based on these results, the case was diagnosed as liver cirrhosis caused by

capsule-deficient *Cryptococcus neoformans* (CDCN). The patient was treated with intravenous administration of amphotericin B (1 mg kg⁻¹ per day) and oral 5-flucytosin (100 mg kg⁻¹ per day). After treatment for 4 months, the amount of ascites decreased and there was relief of clinical symptoms. However, an abdominal CT image showed no improvement.

The patient was transferred to Seoul National University Hospital, where another liver biopsy was performed. The biopsy showed similar findings to those from the biopsy performed at the Asan Medical Center. The same diagnosis, liver cirrhosis caused by *C. neoformans*, was made. The patient was treated with intravenous administration of amphotericin B (1 mg kg⁻¹ per day) and itraconazole (3 mg kg⁻¹ per day). Three months later, the patient developed pleural fluid and ascites. An abdominal CT image demonstrated an exacerbation of liver cirrhosis. A liver biopsy was performed again and the tissue specimen was placed onto Sabouraud dextrose agar. After a week, black colonies grew on the agar (Fig. 2). The colonies appeared black from the front and the reverse, wet and mucoid. Hyphae, conidiophores, phialides and yeast cells were observed under a microscope. The hyphae were sparse, septate and olivaceous. Conidia were brown, one-celled and found in clusters at the apices of the phialides and down the sides of the conidiophores. The phialides were brown and flask-shaped to cylindrical and did not have a collarette. Based on the morphology, the ability to grow at 40 °C and the lack of nitrate assimilation, the organism was identified as *Exophiala dermatitidis* (Padhye *et al.*, 1978). Molecular identification from analysis of the DNA sequences of the 26S and 28S rRNA genes confirmed the identification of the micro-organism. A pathologist reviewed the previously performed biopsy slides and confirmed the previous yeast-like micro-organisms as *E. dermatitidis*.

Etest (AB Biodisk) for the isolated *E. dermatitidis* determined a fluconazole MIC of 256 mg l⁻¹, itraconazole MIC of 0.064 mg l⁻¹, amphotericin B MIC of 1.0 mg l⁻¹ and voriconazole MIC of 0.016 mg l⁻¹. Based on the Etest results, the patient received voriconazole (4 mg kg⁻¹ per day) for 5 months. The clinical symptoms improved,

Abbreviations: CDCN, capsule-deficient *Cryptococcus neoformans*; CT, computed tomography; FMS, Fontana–Masson stain.

Fig. 1. Liver biopsy. Many round, yeast-like organisms are present within the multinucleated giant cells. Some organisms with a brown-pigmented cell wall are seen (haematoxylin & eosin staining; $\times 1000$).

including the ascites, as did the laboratory test results. A follow-up culture did not produce any micro-organisms. The patient was judged to be improved and was discharged from the hospital. After discharge, the patient received follow-up in the outpatient clinic. One year later, the patient received a liver transplant from a cadaver donor. A week after the transplantation, an acute allograft rejection occurred. The patient expired at postoperative day ten. Cultures of liver tissue, hilar tissue and portal thrombi again grew *E. dermatitidis*.

Discussion

Exophiala (formerly *Wangiella*) *dermatitidis* is a type of dematiaceous fungus that causes phaeohyphomycosis. The taxonomy of this species is controversial. Some investiga-

tors prefer to classify the species in the genus *Wangiella* as *Wangiella dermatitidis*. This organism is recognized with increasing frequency as a cause of human disease (Taj-Aldeen *et al.*, 2006). Human infection caused by *E. dermatitidis* can be separated into three types: superficial infections, cutaneous and subcutaneous disease or visceral or systemic disease (Matsumoto *et al.*, 1993). Most cases of phaeohyphomycosis caused by *E. dermatitidis* are included in the first two categories (Zeng *et al.*, 2007). Visceral or systemic disease is very rare. Cases of pneumonia, fungaemia, central nervous system infection, endocarditis and peritonitis have been reported (Vartian *et al.*, 1985; Kenney *et al.*, 1992; Kusenbach *et al.*, 1992; Hiruma *et al.*, 1993; Lye, 1993; Ajanee *et al.*, 1996; Nachman *et al.*, 1996; Chang *et al.*, 2000; Greig *et al.*, 2003; Taj-Aldeen *et al.*, 2006; Ozawa *et al.*, 2007). Systemic diseases have occurred mostly in patients with predisposing factors (Taj-Aldeen *et al.*, 2006). Predisposing factors for human infection with *E. dermatitidis* include a solid organ transplant, leukaemia, cystic fibrosis, HIV infection and dialysis (Collee *et al.*, 1988; Sharkey *et al.*, 1990; Blaschke-Hellmessen *et al.*, 1994; Nachman *et al.*, 1996; Diemert *et al.*, 2001; Vlassopoulos *et al.*, 2001; Liou *et al.*, 2002; Revankar *et al.*, 2002). An association with catheter-related infection and cystic fibrosis is well documented (Haase *et al.*, 1990, 1991; Kusenbach *et al.*, 1992; Kabel *et al.*, 1994; Simpson & Nightingale, 1995; Nachman *et al.*, 1996; Tseng *et al.*, 2005). There is one known case of *E. dermatitidis* infection with liver involvement (Tsai *et al.*, 1966). This case was a disseminated infection. As well as the liver, the brain, lymph nodes and pancreas were also involved. As in the case reported by Tsai *et al.* (1966), a fungal infection of the liver usually presents as a part of a disseminated fungal infection. Our case, however, was a liver infection without dissemination. The liver was the only involved site. In addition, the patient had no predisposing factors. As far as we know, there has been no other case reported with such

Fig. 2. Black colonies of *E. dermatitidis* growing on Sabouraud dextrose agar.

features. We do not know how this infection occurred. *E. dermatitidis* has been occasionally isolated from animals and from the environment, although the natural habitat of the organism is not known (Dixon *et al.*, 1980; Mok & Luizao, 1981; Mok *et al.*, 1984; Muotoe-Okafor & Gughani, 1993; Taj-Aldeen *et al.*, 2006).

Another interesting point of this case was the difficulty of discriminating CDCN from *E. dermatitidis* in tissue sections. The organism was initially mistaken as CDCN based on the FMS and other staining results. Although the FMS is very useful for the differentiation of CDCN, other dematiaceous species may be positive for a reaction with the FMS (Kwon-Chung *et al.*, 1981; Cheon *et al.*, 2006). *E. dermatitidis* should be considered when a yeast-like organism with a dark wall is observed in a tissue section. Other methods, such as tissue culture or a molecular study, may be needed for the differentiation between CDCN and *E. dermatitidis*.

No approved antifungal MIC standards exist for *E. dermatitidis*. A study reported that *E. dermatitidis* is susceptible to miconazole, terbinafine, itraconazole, voriconazole, albaconazole and amphotericin B with MICs lower than $0.5 \mu\text{g ml}^{-1}$ (Meletiadiis *et al.*, 2000). In the present case, the isolated strain was resistant to fluconazole and was susceptible to voriconazole. The patient was treated with voriconazole. Previous cases of systemic infection have been treated with fluconazole, itraconazole, miconazole and amphotericin B (Kenney *et al.*, 1992; Kusenbach *et al.*, 1992; Lye, 1993; Benaoudia *et al.*, 1999; Chang *et al.*, 2000; Liou *et al.*, 2002; Greig *et al.*, 2003; Mukaino *et al.*, 2006).

In conclusion, we believe this to be the first report of liver cirrhosis without dissemination caused by *E. dermatitidis*. This fungus should be considered as a cause of liver cirrhosis and other visceral infections, even in a previously healthy person. The organism can be mistaken as CDCN in a tissue section.

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