

Isolated hepatobiliary cryptococcosis manifesting as obstructive jaundice in an immunocompetent child: case report and review of the literature

Chi Zhang · Lei Du · Wei Cai · Yeming Wu · Fan Lv

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Abstract The majority of patients with symptomatic cryptococcosis have an underlying immunocompromising condition. In the absence of coexisting immunocompromising condition, *Cryptococcus neoformans* is rarely considered in the differential diagnosis of obstructive jaundice that occurs in children with hilar masslike lesion. Here, we report a 5-year-old boy without immunoglobulin or lymphocyte abnormalities who developed a hepatobiliary infection with *C. neoformans*. Ultrasonography and computed tomography showed dilatation of the bilateral intrahepatic bile ducts and a low-attenuated mass in the hepatic hilum. Microscopic examination of tissue samples revealed abundant numbers of encapsulated yeast cell suggestive of *C. neoformans*. After 4 months of antifungal therapy (liposomal amphotericin B for 2 weeks and oral fluconazole for 3 months), the disease was effectively controlled. Unnecessary operation could be avoided by an early and accurate diagnosis. By sharing our experience, we suggest hepatobiliary surgeons and gastroenterologists should have a suspicion of this unusual entity to make earlier diagnosis and treatment.

Keywords Hepatobiliary cryptococcosis · Obstructive jaundice · Immunocompetent child · Tumorlike lesion

Introduction

Cryptococcus neoformans is an important opportunistic fungal pathogen that is mainly acquired via the respiratory tract. It causes several clinical syndromes and most commonly presents as cryptococcal meningitis [9]. Other clinical manifestations are pulmonary infiltrates, skin lesions, bone involvement, and involvement of other organ (ranging from more to less common) [5, 6]. The establishment of *C. neoformans* infections is generally associated with impaired cellular immunity; the most common conditions include AIDS, prolonged corticosteroid usage, organ transplantation, advanced malignancy, diabetes, and sarcoidosis. The establishment of *C. neoformans* infections in immunocompetent individuals could be owing to increased virulence or dose of the organism. However, even in the context of HIV infection, hepatobiliary complications from cryptococcosis have occasionally been reported and localized involvement of the hepatobiliary system in an immunocompetent individual is exceedingly rare [5, 6]. Up to now, less than 15 cases have been reported in the literature. We herein present an uncommon case of hepatobiliary cryptococcosis in an immunocompetent child presenting with obstructive jaundice. With no evidence of involvement of other organs, we established a diagnosis of *C. neoformans* infection through exploratory laparotomy.

Case report

A 5-year-old boy with a 3-week history of low-grade intermittent fever was admitted to a local hospital. Two weeks after routine antibacterial therapy, he developed painless progressive jaundice, dark urine, and clay-colored stool. Given the results of abdominal ultrasonography, he was referred to our center with a tentative diagnosis of a hepatic tumor. The patient's past medical history and family history were unremarkable.

The first two authors contributed equally to this work and should be considered co-first authors.

C. Zhang · L. Du · W. Cai (✉) · Y. Wu · F. Lv
Department of Pediatric Surgery, Xinhua Hospital, Shanghai Jiao
Tong University School of Medicine, No. 1665, Kongjiang Road,
Shanghai 200092, China
e-mail: caiw1978@163.com

C. Zhang · L. Du · W. Cai · Y. Wu · F. Lv
Shanghai Key Laboratory of Pediatric Gastroenterology and
Nutrition, No. 1665, Kongjiang Road, Shanghai 200092, China

On admission to our center, few positive findings were noted on the physical examination except the patient was visibly icteric and had slight tenderness over the right upper quadrant. No abdominal distension, organomegaly, and palpable lymph nodes were found, and no neurological symptoms or evidence of neurological disturbance were detected. Murphy's sign was negative. The laboratory investigation revealed abnormal liver function tests consistent with obstructive jaundice (alanine aminotransferase 70.0 U/L, reference range 0–75 U/L; aspartate aminotransferase 103.0 U/L, reference range 8–38 U/L; alkaline phosphatase 905.0 U/L, reference range 34–114 U/L; total bilirubin 252.7 $\mu\text{mol/L}$, reference range 3.42–20.52 $\mu\text{mol/L}$; direct bilirubin 201.9 $\mu\text{mol/L}$, reference range 0–6.8 $\mu\text{mol/L}$; albumin 36.4 g/L, reference range 35–50 g/L). The white blood count, coagulation factors, erythrocyte sedimentation rate, and CEA, AFP, and CA125 levels were normal, whereas the carbohydrate antigen 19–9 (CA19-9) level was obviously elevated (361.2 U/mL; normal value <37 U/mL). Anti-hepatitis viruses, anti-HIV, tuberculosis and abnormal autoimmune antibodies, blood culture, and bone marrow culture were all normal or negative.

Abdominal ultrasonography revealed intrahepatic biliary dilatation and an irregular masslike lesion in the hepatic hilum adjacent to the portal vein. No findings suggested bile duct calculi. An abdominal contrast-enhanced computed tomography (CT) scan produced similar findings, with a slight irregular peripheral enhancement and a central area of lower attenuation (Fig. 1a). Combined with poor response to routine antibacterial therapy (ceftriaxone combined with metronidazole) and elevated CA19-9 level, the presence of cholangiocellular carcinoma or other tumor was taken into consideration, and thus, an exploratory laparotomy was done. Intraoperatively, thickened walls of the initial part of the left and right hepatic duct, common hepatic duct, and proximal common bile duct were detected without any perihepatic enlarged lymph nodes. A frozen section of tissue samples from the common hepatic duct wall and masslike lesion showed a granulomatous inflammation with no malignant cells. There was nothing we could do but perform percutaneous transhepatic biliary drainage to treat

the jaundice. Microscopic examination of paraffin sections revealed granulomatous inflammation and multinucleated giant cells in which cuboidal bodies of *C. neoformans* were seen on periodic acid Schiff stains (Fig. 2). Therefore, the diagnosis of biliary cryptococcosis was confirmed.

After operation, the patient was investigated for immunocompromised status. He was HIV-negative with a normal CD4 and CD8 counts (CD4 31.8 %, reference range 24.5–48.8 %; CD8 25.7 %, reference range 18.5–42.1 %). Serum immunoglobulin and complement were as follows: IgG, 12.42 g/L (reference range 7.6–16.6 g/L); IgA, 1.04 g/L (reference range 0.71–3.35 g/L); IgM, 1.24 g/L (reference range 0.48–2.12 g/L); IgE, 0.0042 g/L (reference range 0.001–0.009 g/L); C3, 1.05 g/L (reference range 0.9–1.8 g/L); and C4, 0.47 g/L (reference range 0.1–0.4 g/L). Phagocytic function of the neutrophils was assessed with the nitroblue tetrazolium test, and this was also normal. His chest CT and cranial MRI demonstrated no abnormalities, suggesting that our assumption of “isolated biliary cryptococcosis” was reasonable. Antifungal therapy with intravenous liposomal amphotericin B (5 mg/kg/day for 2 weeks) was used with good clinical and laboratory improvement. He became afebrile and the serum CA19-9 level and liver function tests gradually recovered. Ultrasonography of the liver performed 3 weeks after the initiation of treatment showed a reduction in the size of the masslike lesion. The patient was discharged with oral fluconazole (100 mg/day) for 3 months. Follow-up CT after 4 months showed no masslike lesion in the hepatic hilum (Fig. 1b). Ultimately, he made a complete recovery and no complications were observed during the 8-month follow-up.

Discussion

Although cryptococcosis is considered an opportunistic infection as it affects mainly immunocompromised individuals, it is also observed in patients without signs of immune deficiency [7]. Typical clinical manifestations are meningoencephalitis and pulmonary infiltrates, whereas the involvement of other

Fig. 1 **a** Enhanced computed tomography scan showed intrahepatic bile duct dilatation and an ill-defined low-attenuation mass in the hepatic hilum adjacent to the portal vein (arrow). **b** Enhanced computed tomography scan after 4 months of medical treatment showed no masslike lesion in the hepatic hilum

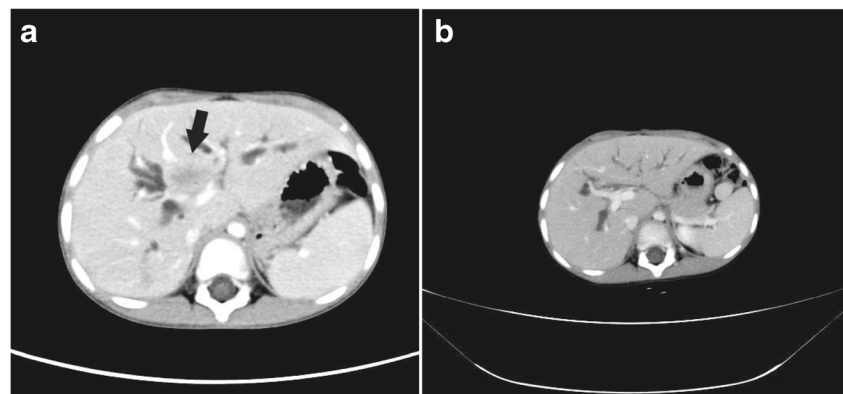
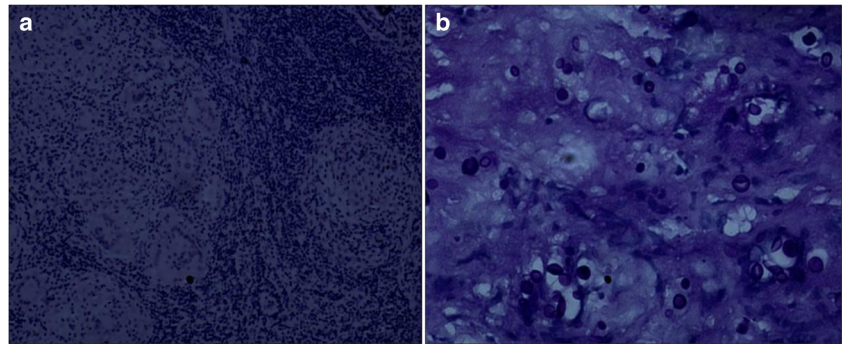


Fig. 2 **a** Hematoxylin and eosin stain revealed granulomatous inflammation. **b** Periodic acid Schiff stain showed encapsulated yeastlike fungi in multinucleated giant cells suggestive of *C. neoformans*



organ is less common [5, 6]. Hepatobiliary cryptococcosis, however, is an exceedingly unusual clinical entity. We sought all studies about *C. neoformans* in PubMed; only nine reports were related with hepatobiliary cryptococcosis manifesting as jaundice in an immunocompetent patient, and three literatures about hepatobiliary cryptococcosis in immunocompetent children were found [1, 2, 4]. Apart from hepatobiliary involvement, two patients had pulmonary infiltrates, two patients had lymphadenopathy, and three patients had central nervous system involvement. Thus, this is a unique report on isolated biliary cryptococcosis in an immunocompetent child. In the present case, neither clinical nor radiological infection findings in the central nervous system or lung were noted. The clinical characteristics of hepatobiliary cryptococcosis in immunocompetent children are shown in Table 1.

To our knowledge, almost all patients in the literature have a delayed diagnosis and our case is no exception. As delays in antifungal therapy are associated with poorer clinical outcomes including increased mortality, an early diagnosis and prompt treatment are essential to cure cryptococcosis [10]. There are several reasons for delayed diagnosis of hepatobiliary cryptococcosis in patients without apparent immunodeficiency: First, a lack of clinical awareness of this entity combined with underutilization of specific diagnostic testing; second, the absence of characteristic local or systemic symptoms; and third, the absence of specific radiological features. According to previous reports, the radiological appearance of hepatobiliary cryptococcosis can be diverse. In most cases, hepatobiliary cryptococcosis manifests as a tumorlike lesion in the liver, mimicking the manifestation of cholangiocellular carcinoma,

Table 1 The clinical characteristics of hepatobiliary cryptococcosis in immunocompetent children

Reference, patient age/sex	Symptoms	Other sites of infection	Results of cryptococcal antigen testing	Way of establishment of diagnosis	Antifungal therapy/outcome
Bucavalas et al. [1], 15/male	Right upper quadrant pain, jaundice, signs of portal hypertension	None	ND	Exploratory laparotomy	Amphotericin B (0.6 mg/kg/day, 7 weeks), discharge on oral fluconazole (200 mg/day, 7 weeks)/cured
Das et al. [2], 5/male	Fever, jaundice, erythematous rash	Cervical and bilateral axillary lymph nodes	ND	Fine-needle aspiration cytology	Amphotericin B (0.7 mg/kg/day, 10 weeks), discharge on oral fluconazole (dosage and duration ND)/cured
Goenka et al. [4], 7/male	Fever, jaundice, coughing, breathlessness, streaky hemoptysis, generalized lymphadenopathy, multiple cutaneous ulcers, splenomegaly	Lymph nodes, skin, spleen, lungs	1:65,532	Liver biopsy; smear examination from lymph node aspirate, sputum, skin scrapings and urine	Amphotericin B (0.3 mg/kg/day, duration ND)+oral 5-flucytosin (150 mg/kg/day, duration ND)/cured
Our patient, 5/male	Jaundice, low-grade fever	None	nd	Exploratory laparotomy	Liposomal amphotericin B (5 mg/kg/day, 2 weeks), discharge on oral fluconazole (100 mg/day, 12 weeks)/cured

ND not documented, nd not done

primary sclerosing cholangitis, lymphoma, etc. In fact, low-attenuation masslike lesion on contrast-enhanced CT has been described as characteristic of granulomatous infections including fungal infection, although they may also be noted in other in other disease such as metastasis, lymphoma, and Whipple's disease [3]. Thus, it was regretful that we failed to have a suspicion for this nonspecific biliary inflammation when we found a low-attenuation lesion in the liver on CT. Since the patient had persistent low-grade fever, elevated CA19-9 level, and routine antibacterial therapy was not effective, it was considered to be of cholangiocellular carcinoma or other tumor until excision biopsy was done.

Specific testing for cryptococcal antigen in the serum is a simple, safe and convenient diagnostic tool for patients with *C. neoformans* infection [7, 8]. If we had tested for cryptococcal antigen in the serum of our patient during the early stage of treatment, correct diagnosis could have been achieved much more quickly and unnecessary exploratory laparotomy could have been avoided. In patients with cryptococcosis, serum cryptococcal antigen is frequently positive with titers ranging from 1:8 to 1:65,532 and can be very helpful for diagnosis [7, 8]. Exact diagnosis can be established by biopsy or bile or blood examination using special stains and cultures. For culture-negative disease, ultrasound-guided puncture biopsy is more recommended compared with exploratory surgery.

In conclusion, we present a unique case of isolated hepatobiliary cryptococcosis in an immunocompetent child whose initial manifestation was obstructive jaundice. It is relatively difficult to reach a precise decision because the clinical and radiological manifestations are not specific. Reports of cryptococcal liver infection are too rare to elucidate characteristic clinical and radiological features. Hence, for immunocompetent individuals with obstructive jaundice and low-attenuation masslike lesion of unknown cause, surgeons and gastroenterologists should have a suspicion for *C. neoformans* infection and an early investigation of cryptococcal antigen in

serum sample should be suggested. Awareness of this entity may help to avoid delayed diagnosis and unnecessary operation.

Conflict of interest We declare no conflict of interest.

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