Round Granulomatous Lesions in a Young Girl: A Quiz

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A 13-year-old girl presented to the hospital with lesions on her scalp, face, and neck that had developed over the course of 2.5 years, together with fever and cough present for 2 weeks. Physical examination was notable for multiple round granulomatous lesions involving the scalp, face, neck, and upper back area (Fig. 1). The patient had no further history of skin or systemic disease. Initially, she was misdiagnosed with eczema and systemic lupus erythematosus at a local hospital. She then received systemic therapy with glucocorticoids for 2 months, but the lesions were aggravated over time. The patient was transferred to Huashan Hospital in Shanghai for further investigation.

What is your diagnosis? See next page for answer.

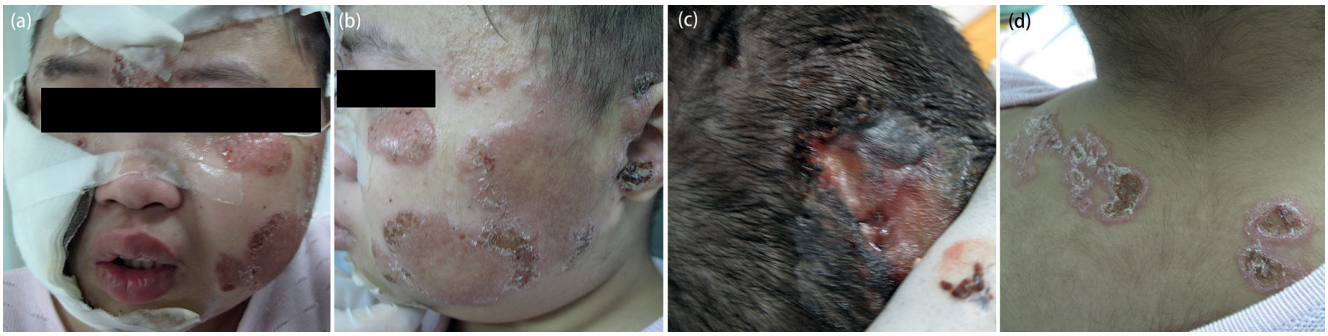

Fig. 1. Lesions before treatment. (a) Face (the patient refused to remove the gauze because it was too painful; (b) left cheek; (c) scalp; (d) upper back.

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ANSWERS TO QUIZ

Round Granulomatous Lesions in a Young Girl: A Commentary

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Diagnosis: **Disseminated cryptococcosis with hepatitis B virus (HBV) infection**

At the outpatient department, microscopic examination of pyogenic fluids from lesions and phlegm revealed many capsulated budding yeast cells with a "halo" around the cells, which were morphologically similar to *Cryptococcus* (Fig. 2). The patient was admitted to the inpatient department. Microscopic examination of pyogenic fluids from the cerebrospinal fluid (CSF) also showed many capsulated budding yeast cells resembling *Cryptococcus*. Fungal culture of pyogenic fluids from lesions, sputum, and blood isolates all revealed creamy yeast colonies. Molecular analysis of these isolates identified them as *C. neoformans*. Latex agglutination test of the CSF and blood showed an elevated titre greater than 1:1,280. Histopathology of a lesion from 2 years previously showed focal neutrophil infiltration multi-cells granuloma of the upper and middle dermis, with many capsulated budding yeast cells (Fig. 3).

Furthermore, hepatitis B tests, for HBsAg, HBeAg, and HBcAb were all positive, and the HBV-DNA count was 3.7 IU/ml. Laboratory tests revealed a red blood cell count of $3*10^9$/l, haemoglobin 97 g/l, C-reactive protein 147 mg/l, albumin 24.9 g/l, $CD3^+$ 42.90%, $CD4^+$ 27.50%, $CD8^+$ 16.20%, $CD16^+56$ 4.07%, $CD19^+$ 53.40%. IgG 1,450 mg/dl, IgA 148 mg/dl, and IgM 135 mg/dl were all elevated.

Initial examination included a chest computed tomography (CT) scan, which revealed bilateral pulmonary infiltration and right pleural effusion. An abdominal ultrasound showed an enlarged liver with echo changes, right liver calcification, and splenomegaly. Bone marrow aspiration suggested proliferative anaemia and infection.

Combining the laboratory examination information with the clinical manifestation, a diagnosis of disseminated cryptococcosis with hepatitis B virus (HBV) infection was made. The patient was started on intravenous amphotericin B (1 mg/kg/day) and flucytosine (100 mg/kg/day). Oral potassium chloride was also given to correct the patient's hypokalaemia. Flucytosine was exchanged for fluconazole (12 mg/kg/day) and the dosage of amphotericin B was decreased (to 0.7 mg/kg/day) after 3 weeks, due to the patient's alleviating blood urea and creatinine. There was also abnormal microglobulinuria, as well as electrocardiogram ST segment changes and Q-T interval delay. To correct this, the dosage of amphotericin B was adjusted (to 0.5 mg/kg/day). A few days later, the patient presented with a loss of appetite, low blood pressure, slowed heart rate, and vomiting. In light of these severe adverse reactions, amphotericin B was changed to AmBisome® (5 mg/kg/day). After the switch, the patient stopped vomiting and her heart rate returned to normal. Meanwhile, lamivudine (100 mg/day) was given for hepatitis. Due to financial reasons, the patient switched back to using amphotericin B. After 2 months of treatment, she reported a marked improvement in her symptoms and lesions. The lesions had mostly healed, with some hyperpigmentation and scarring remaining. The cryptococcal antigen (CrAg) latex agglutination test also became negative. To date, at 10-year follow-up, the patient shows no relapse of symptoms.

Disseminated cryptococcosis is very rare in children, especially presenting with skin lesions as the primary manifestation. Disseminated cryptococcosis usually starts in the lungs and central nervous system, and then spreads to other organs. When pulmonary cryptococcosis is symptomatic, its manifestation may range from fever to subacute respiratory illness, asymptomatic pulmonary infiltrates, subpleural masses, solitary nodules, or effusions. In the current case, the systemic symptoms were fever and coughing. Signs

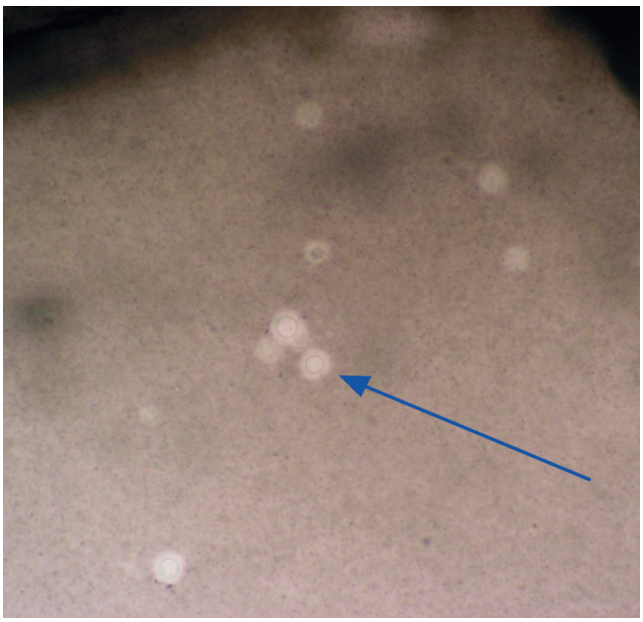

Fig. 2. Indian ink staining of pyogenic fluids from lesions shows capsulated budding yeast cells with a "halo" around the cells (original magnification ×400).

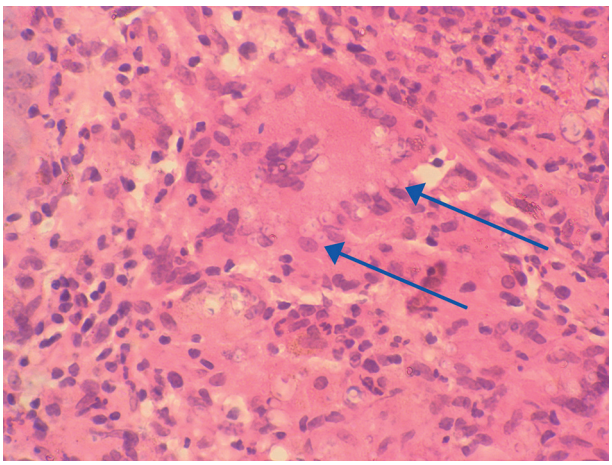

Fig. 3. Periodic acid-Schiff (PAS) staining from 2 years previously shows capsulated budding yeast cells with a "halo" around the cells (original magnification ×400).

of pulmonary infiltration were also seen in the patient's chest CT scan. Manifestations of cutaneous cryptococcosis are quite diverse, including abscess, infectious verrucous rashes, papules, nodules, granulomas, and ulcerations, occasionally resembling cellulitis, bullous erysipelas, or whitlow (1). In this patient, it presented as multiple round granulomatous lesions. Cutaneous cryptococcosis is more often secondary than primary. In the present case, it was the primary manifestation. The histopathology of a lesion from 2 years previously already showed *Cryptococcus* structures. At that time, the patient received a glucocorticoid treatment, which may have induced spreading of *Cryptococcus*.

In patients with hepatic dysfunction or other liver diseases, cryptococcosis has been reported to manifest mainly as peritonitis or disseminated disease (2). Disseminated cryptococcosis is observed mostly in immunocompromised patients, which can lead to misdiagnosis if it presents in immunocompetent children. This patient was also misdiagnosed at the previous hospital, where she was treated with glucocorticoids for 2 months. Incorrect treatment did not alleviate the disease, but aggravated her illness. The insidious onset and presentation with non-specific symptoms often leads to delay in obtaining a correct diagnosis. With the radiological presentation of pulmonary cryptococcosis mimicking miliary tuberculosis, it often leads to misdiagnosis.

The more traditional diagnosis of *Cryptococcus* is based on the observation of capsulated yeasts by direct microscopic examination and histopathology, isolation of *Cryptococcus* in culture, and by the demonstration of capsular antigen in the supernatant of various fluids, including serum and CSF by latex particle agglutination or enzyme-linked immunosorbent assays (3, 4). With the advancement of molecular diagnostics, there are now more ways to identify pathogenic *Cryptococcus* species. PCR fingerprinting and multi-locus microsatellite typing were used in the current case for more accurate species identification.

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