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CASE REPORT

Tuberculosis-associated hemophagocytic lymphohistiocytosis with subsequent unmasking cryptococcal immune reconstitution inflammatory syndrome (IRIS) in an HIV-negative man

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Abstract
A 22-year-old HIV-negative man from Ghana was diagnosed with severe hemophagocytic lymphohistiocytosis (HLH) induced by multiorgan tuberculosis with peritoneal, hepatic, pericardial, myocardial, pleural, pulmonary, and bone manifestation. His body mass index was 12.9 m^2/kg. Bioptic material of a peritoneal biopsy grew *M. tuberculosis*, sensitive to all first-line antituberculous drugs. HLH resolved with antituberculous therapy, without additional anti-inflammatory therapy being given. The initial CT scan of his brain was normal. After 5 months of antituberculous treatment, he developed a paralysis of the left arm. A cerebral MRT showed ring-enhanced lesions. Blood cultures and lumbar puncture revealed *Cryptococcus neoformans* var. *grubi*. The HIV test was repeatedly negative. Antituberculous treatment was continued for a total of 9 months, and additional treatment with antifungal therapy was established. He recovered fully after 14 months of antifungal treatment.

Keywords Tuberculosis · Hemophagocytic lymphohistiocytosis · HLH · Unmasking IRIS · Cryptococcosis

Introduction

Secondary hemophagocytic lymphohistiocytosis (HLH) can be induced by a number of infections including tuberculosis [1]. The mainstay of treatment is the elimination of the underlying infection, but an additional immunosuppressive therapy may be necessary [2]. Immune reconstitution inflammatory syndrome (IRIS) is a well-known complication after the initiation of antiretroviral therapy in HIV infection [3]. IRIS may manifest as a paradoxical reaction which sees the worsening of symptoms of an infection which has already been treated [such as *Pneumocystis jirovecii* pneumonia or tuberculosis (TB)], or it may unmask an undiscovered opportunistic infection (such as histoplasmosis, TB, or cryptococcosis) [4]. Paradoxical immune reactions are described in up to 25% of HIV-negative patients during TB treatment [5], but the unmasking of hitherto undiagnosed infections in HIV-negative patients after the beginning of antituberculous therapy has not yet been described to our knowledge.

Case report

A 22-year-old man from Ghana presented with fever, fatigue, dyspnea, ascites, and weight loss of 30 kg over a few months. He had immigrated to Germany 4 years earlier and had been healthy until 4 months before admission. He was non-smoker and did not use alcohol or illicit drugs. During the last 4 months, he was treated in several other hospitals for ascites, nodular peritoneal swelling, mesenterial infiltrations, hepatomegaly, osteolytic vertebral lesions, pleural and pericardial effusion, and hemolytic anemia. On several occasions he had self-discharged from hospital after paracentesis or pleurocentesis before the cause of his symptoms could be found. On admission to our department, he was cachectic (44 kg, 1.85 m, body mass index 12.9 kg/m^2), with fever (39.2 °C), tachycardia (113/min), and a discharging wound on the left chest at the site of a previous pleurocentesis. His abdomen was distended, his extremities thin and weak.

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Pathological laboratory tests were: hemoglobin 5.8 mmol/L (normal 8.6–12), platelets 97,000/µL (250–450,000), lactate dehydrogenase 681 U/L (< 250), hyponatremia 129 mmol/L (135–145), hypokalemia 2.6 mmol/L (3.5–5.2), C-reactive protein 103 mg/L (< 5), gamma glutamyltransferase 315 U/L (< 60), alkaline phosphatase 479 U/L (< 126), aspartate aminotransferase 74 U/L (< 50), prothrombin time activity 46% (> 70), ferritin 10,363 µg/L (< 400), soluble interleukin-2 receptor (sIL2-R) 7260 U/mL (< 710), natural killer cells 0.3% (7–31), and albumin 16.2 g/L (> 35). The HIV test and the interferon-gamma-release assay (IGRA, QuantiFERON TB gold in tube®) were negative. Anti-HBc antibodies were positive, HBs antigen and HBs antibodies were negative indicating immunity after previous hepatitis B infection. Hepatitis C serology was negative.

Ultrasound of the abdomen showed ascites, hepatomegaly with nodular lesions infiltrating the lower edge, large nodular lesions of the entire peritoneum, large conglomerated lymph nodes of the mesenterium and omentum majus, and splenomegaly. A chest X-ray revealed a small infiltrate in the left lower lobe and a slight pleural effusion. A CT scan of the brain was normal.

Since 6 out of 8 criteria for HLH [2] were positive (fever, splenomegaly, pancytopenia, increased levels of ferritin and soluble interleukin-2-receptor, and low natural killer cells), hemophagocytic lymphohistiocytosis was diagnosed.

A diagnostic laparoscopy revealed infiltration of the parietal and visceral peritoneum with large yellowish nodules, multiple fibrin strands and greenish ascites (Fig. 1). Histology showed granulomatous lesions without caseous necrosis and without acid-fast bacilli. PCR was positive for *M. tuberculosis* complex; the culture grew *M. tuberculosis* with full sensitivity to all first-line antituberculous drugs. Since the patient was very cachectic and barely able to eat, the initial treatment was given intravenously. A weight-adapted i.v. therapy was started consisting of isoniazid 200 mg, rifampin 450 mg, ethambutol 1000 mg, and levofloxacin 500 mg, the latter instead of pyrazinamide which is not available as injection. After 1 month, oral therapy was established with isoniazid 200 mg, rifampin 450 mg, ethambutol 1000 mg, and pyrazinamid 1500 mg. Pyridoxine was added to prevent isoniazid neurotoxicity.

After the beginning of antituberculous therapy, thrombocyte and leukocyte counts slowly normalized, and fever resolved. After 10 days of treatment, ferritin levels had decreased to 5067 µg/L, and sIL2-R levels to 2514 U/L. After 7 weeks of antituberculous treatment, the patient had gained 8 kg in weight (bringing him to 52 kg), and treatment was continued on an out-patient basis.

After 5 months of antituberculous treatment, the patient was readmitted at a body weight of 65 kg complaining of headaches and vomiting. On examination, he was slightly disoriented, febrile (38.0 °C), with reduced strength in his left arm. Cerebral magnetic resonance tomography showed a solitary lesion with ring enhancement in the right parietal parenchyma, central colliquation and focal edema without impairment of cerebrospinal fluid circulation (Fig. 2). Pathological laboratory tests were: hemoglobin 6.9 mmol/L (normal 8.6–12), leucocytes 12,100/µL; fibrinogen 4.5 g/L (1.8–3.5); CRP 24.2 mg/L (< 5). At this point, ferritin was 1850 µg/L, and sIL2-R was normal. Repeat HIV testing was negative. The Quantiferon TB test was now positive.

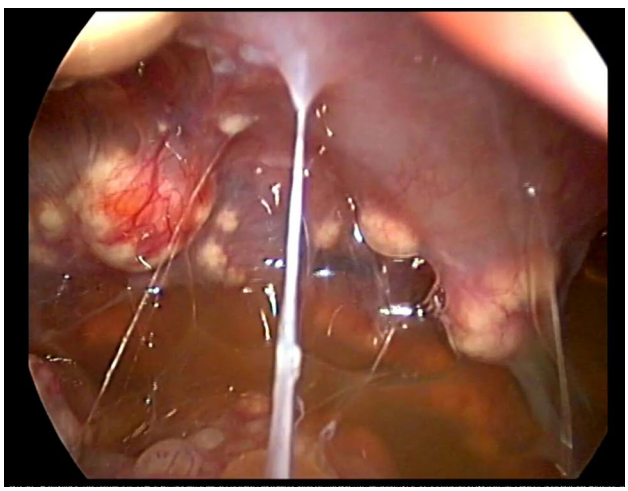

Fig. 1 Laparoscopy. Large peritoneal tuberculomas, ascites, and intraperitoneal fibrin strands

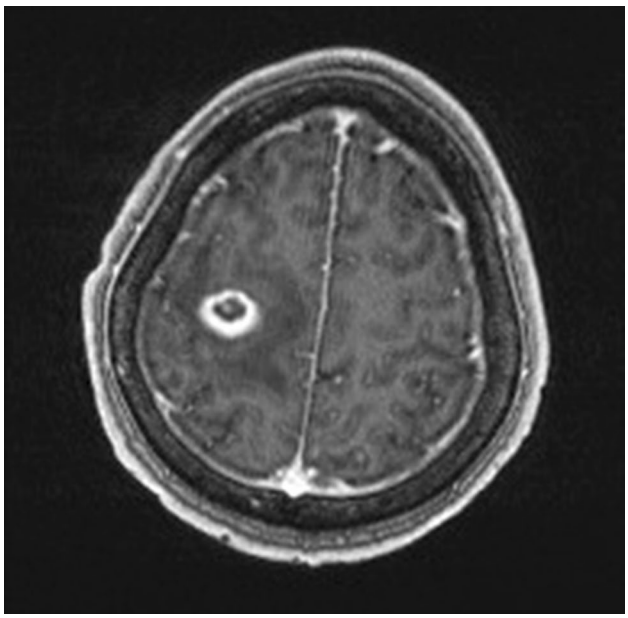

Fig. 2 Cerebral magnetic resonance imaging, T1 MPR with contrast medium, axial ring enhancement with central necrosis and perifocal edema

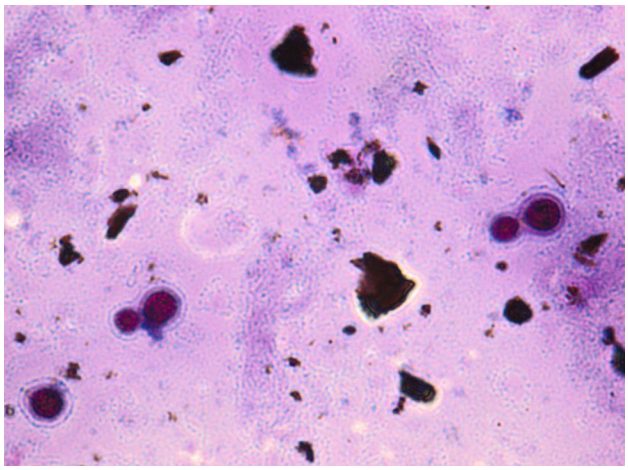

Fig. 3 Direct Gram-preparation of the first positive blood culture (magnification ×1000). Gram-positive, spherical yeast cells surrounded by a thin, capsule-like structure are visualized. Single budding can be observed as well

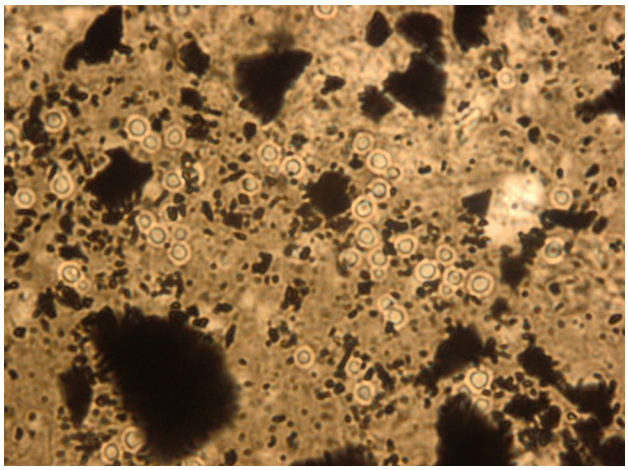

Fig. 4 India Ink preparation of the first positive blood culture (magnification ×200)

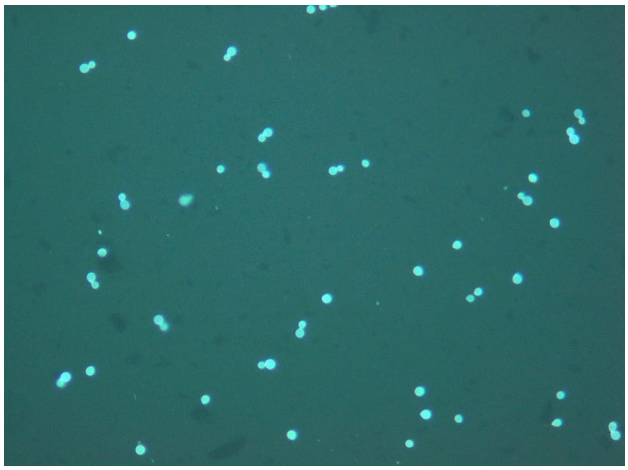

Fig. 5 Calcofluor white preparation of the first positive blood culture (magnification ×200)

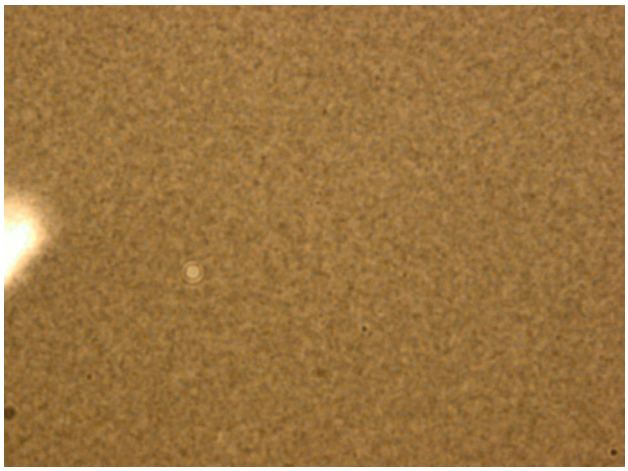

Fig. 6 India Ink preparation of CSF (magnification ×200)

Two peripheral blood cultures became positive after 3 days of incubation. Gram staining revealed spherical, yeast-like fungal cells surrounded by a thin capsule-like structure and with a single bud, suggesting cryptococcosis (Fig. 3). Subsequent India Ink staining (Fig. 4) and Calcofluor White staining (Fig. 5) were positive, too. India Ink staining of a cerebrospinal fluid (CSF) sample (Fig. 6) also yielded yeast cells, and cryptococcal capsule antigen was detected by immunochromatography (titer 1:20). CSF culture showed growth of white-to-cream-colored colonies within 72 h. The species of *Cryptococcus neoformans* was confirmed by MALDI Biotyper system (VITEK MS, bioMérieux, Germany), API® ID-strip (API ID 32C yeast identification system, bioMérieux, Germany), and by DNA sequencing of the 18S rDNA PCR product. Further subtyping performed by the National Reference Laboratory for Cryptococcosis (Robert Koch Institute, Berlin) revealed *C. neoformans* var. *grubii*.

Induction therapy was started with intravenous liposomal amphotericin B 200 mg OD, flucytosine 250 mg QID and fluconazole 200 mg BID. The symptoms resolved quickly, the patient left the hospital on the 12th day against medical advice. Consolidation therapy was continued with oral fluconazole 200 mg BID for 8 weeks, followed by maintenance therapy 200 mg once daily for another 12 months [6]. Antituberculous treatment was continued for a total of 9 months due to vertebral tuberculosis. At the end of treatment, the patient had no neurological sequelae, his body weight had increased to 95 kg (BMI 27.7 kg/m^2), and laboratory parameters were normal.

Discussion

Hemophagocytic lymphohistiocytosis in adults is often difficult to diagnose [7], approximatively one third of HLH is infection-associated. Tuberculosis is a known cause of secondary HLH [8, 9]. Treatment of HLH sometimes necessitates immunosuppressive therapy. A Taiwanese patient developed HLH 4 weeks after the beginning of antituberculous treatment, which was interpreted as a form of TB-IRIS. He was successfully treated with additional methylprednisolone and tofacitinib [10]. However, immunosuppressive therapy may be fatal in tuberculosis: a 34-year-old patient died 2 weeks after the initiation of steroids, etoposide, and cyclosporine per HLH 2004 protocol [2] in addition to modified antituberculous treatment [11]. Our patient recovered from HLH while receiving antituberculous treatment without additional immunosuppressants.

The immune reconstitution inflammatory syndrome (IRIS) is caused by the overwhelming inflammatory response launched by a recovering, formerly impaired immune system [12]. In our patient, the mechanism underlying IRIS unmasking a cryptococcal infection seems to be the immune reconstitution after severe multi-organ tuberculosis. We suspect that the latent infection with *Cryptococcus neoformans* had occurred already in Ghana, since, at least in HIV-positive patients, a high percentage of meningitis in sub-Saharan Africa is due to this pathogen [13]. Immunosuppression at the time of TB diagnosis was indicated in our patient by the negative interferon-gamma-release assay (IGRA). The IGRA is false negative in up to 14% of patients with active tuberculosis [14], either indicating the migration of TB-antigen reactive lymphocytes from the blood to the infected site, or indicating a disturbed immune response [15]. In our patient, the IGRA became positive during effective antituberculous treatment [16].

However, not all patients with false-negative IGRA develop IRIS after immune reconstitution. Paradoxical IRIS during established cryptococcal meningitis has been described both in HIV-positive [17] and HIV-negative patients [18]. Unmasking cryptococcal IRIS in HIV-positive patients after the establishment of ART is well-known [19–21]. To our knowledge, however, this is the first report of unmasking cryptococcal IRIS in an HIV-negative TB patient.

Summary

Treatment of tuberculosis may be sufficient to treat TB-associated HLH. After reversion of TB-induced immunosuppression, immune reconstitution inflammatory syndrome (IRIS) may occur in HIV-negative patients not only as paradoxical reaction with increase of tuberculosis-associated symptoms, but also as IRIS unmasking a hitherto unknown infection such as cryptococcosis.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare. The patient gave written consent for publication.

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