CASE REPORT

Delayed diagnosis of cryptococcal meningoencephalitis due to negative cryptococcal antigen test

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SUMMARY

Cryptococcus spp. commonly causes infection in immunocompromised hosts. Clinical presentation of cryptococcal meningoencephalitis (CM) is variable, but headache, fever and a high intracranial pressure should suggest the diagnosis. The cryptococcal antigen test is a specific and sensitive rapid test that can be performed on blood or cerebrospinal fluid. We report a case of CM in a patient with previously undetected lymphocytopenia. Because cryptococcal antigen test results were negative, diagnosis and treatment were delayed.

BACKGROUND

Cryptococcus spp. commonly causes infection in immunocompromised hosts. However, in 10–30% of HIV-negative patients with cryptococcal meningoencephalitis (CM) or disseminated cryptococcosis, no apparent underlying condition is found.^{1 2} On the other hand, it is possible that an as yet undefined immunodeficiency in these patients was clinically not apparent and/or not detected due to technical limitations. Clinical presentation of CM is variable and, therefore, challenging. Most patients present with subtle signs of meningitis or meningoencephalitis that develop over several weeks, including fever, headache and fatigue. Cryptococcal antigen test and culture of the cerebrospinal fluid (CSF) often establishes the diagnosis. When obtaining CSF, a high opening pressure—as a sign of high intracranial pressure—is a typical feature of CM. The cryptococcal antigen test, a specific and sensitive rapid test, can be performed on blood or CSF.³ Nevertheless, typical signs of a disease should not be overruled by a laboratory test, even when its general performance is very good. We present a case of CM in a previously healthy woman. Lymphocytopenia and high intracranial pressure were evident during the course of disease. Because cryptococcal antigen test results were negative, diagnosis and treatment were delayed.

CASE PRESENTATION

A 41-year-old woman was hospitalised for severe headache. She reported to have dermatomycosis, but otherwise the medical, social and family history was unremarkable. Clinical examination showed vitiligo and slight nuchal rigidity, but no fever. Blood tests revealed normal white cell count (6×10^9 cells/l) though with a lymphocytopenia (0.25×10^9 cells/l). The C reactive protein level was 72 mg/l (normal <5 mg/l).

On the basis of her symptom (severe headache) and the clinical finding (nuchal rigidity), meningitis was suspected. A lumbar puncture was performed and CSF showed 282 cells/ μ l (50% mononuclear cells) and increased protein (0.85 g/l) and lactate levels (3.2 mmol/l). Empirical therapy for meningitis was started, including ceftriaxone and acyclovir. However, PCR assay results were negative for HSV-1/-2 and enterovirus in CSF, as were blood and CSF culture results after 5 days incubation. Serological testing for *Borrelia burgdorferi*, syphilis, tick-borne encephalitis and HIV were negative. Therefore, empirical treatment was stopped. The presumed diagnosis was meningitis due to an undetected virus.

Nine days after admission, the patient developed signs of elevated intracranial pressure, including vomiting, abducens nerve palsy and bradycardia. An MRI of the cerebrum showed an obstructive hydrocephalus with an enlarged ventricular system, compression of the cortex and effacement of the sulci. Because of tonsillar herniation, emergency posterior fossa decompression was performed, and CSF and biopsies of the cerebellum were obtained.

DIFFERENTIAL DIAGNOSIS AND INVESTIGATIONS

Biopsies obtained during surgery were cultured on various media and sent for histopathological analysis. Considering the negative microbiological results from the CSF analysis, the differential diagnosis included severe viral meningoencephalitis, carcinomatous meningitis, granulomatous inflammation and vasculitis.

However, no autoantibodies were found in the serum, and electrophoresis revealed no pathological patterns. Also, PCR assay for HSV-1/-2 and enterovirus in CSF, and serological testing for *B burgdorferi*, syphilis, tick-borne encephalitis and HIV were repeated but remained negative. Also, cryptococcal antigens (Latex-Cryptococcus Antigen Test, Immuno-Mycologics, Norman, Oklahoma, USA) in both CSF and serum were negative.

However, on the same day of emergency posterior fossa decompression, yeasts grew in specimens from the initially obtained CSF. Also, histopathological examination of the samples obtained during craniectomy showed lymphogranulocytic infiltration and round, yeast-like cells (figure 1A,B), identified as *Cryptococcus neoformans* var. *grubii* in culture.

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Figure 1 (A and B) Micrographs of biopsy specimens of the cerebellum (haematoxylin–eosin stain). Infiltrates of lymphocytic and polymorphonuclear cells (arrows) confirm the meningitis (A; original magnification, $\times 100$, inset $\times 400$). Periodic acid/Schiff's reagent stain revealed variably sized spherical yeasts (arrows), consistent with *Cryptococcus* spp. (B; original magnification, $\times 1000$).

TREATMENT

Intravenous liposomal amphotericin B (5 mg/kg per day) and flucytosine (25 mg/kg four times a day) were administered for 1 month. Then, treatment was switched to fluconazole 800 mg daily for 2 months, followed by the 400 mg daily for an additional 9 months.

OUTCOME AND FOLLOW-UP

The further clinical course was favourable and without development of neurological sequelae.

Initially, the lymphocytopenia found at admission was interpreted as an immune response to a viral infection or an unspecific reaction to a severe inflammation. Interestingly, although the total lymphocyte counts increased during hospitalisation, it did not reach normal values and remained below 1.0×10^9 cells/l.

Considering this unexplained and persistent lymphocytopenia together with the diagnosis of CM (notably, a diagnosis that is significantly more frequently found in immunosuppressed than in immunocompetent patients), specific investigations with respect to immunodeficiency were performed 15 days after admission. The total lymphocyte count was 0.58, and the CD4-count 0.417×10^9 cells/l (normal range 1.2–2.8, and 0.41 – 1.59×10^9 cells/l, respectively). However, decreased CD8 T-cell (0.08 , normal range 0.19 – 1.14×10^9 cells/l) and natural killer cell counts (0.02 , normal range 0.09 – 0.59×10^9 cells/l) were found. Nevertheless, no specific immunodeficiency syndrome was identified.

Six months after decompression, the calotte defect was covered with a polymethylmethacrylate (Palacos) implant. At follow-up 1 year after the admission, the patient is in good health but complains about fatigue.

DISCUSSION

Most patients with CM are immunosuppressed (eg, HIV infection, glucocorticoid or chemotherapy, solid organ transplantation recipients). In so-called ‘not immunosuppressed’ patients, it is possible that—in some cases—an undefined immunodeficiency is clinically not apparent and/or not detected due to technical limitations. In our patient, neither an immunodeficiency syndrome was known, nor was there a disease history that could have suggested an immunosuppressed status. HIV was ruled out via repeated serology testing. At admission, lymphocytopenia was misinterpreted as a transient immune response to viral infection causing meningitis. Finally, the diagnosis of CM together with persistent lymphocytopenia during the whole course of disease suggested that this patient is not firmly immunocompetent.

We do not know whether or not the lymphocytopenia was pre-existing. Also, the cause of the CD8 T-cell and NK cell

deficiency is unknown. Given the uneventful patient history of infectious diseases, it is possible that this deficiency is acquired via an unidentified trigger. Finally, we do not know whether the reported association of lymphocytopenia and vitiligo played a role in this case.⁴ Nevertheless, there are other cases described in literature, reporting a subtle immunodeficiency, such as decreased antibody levels, that were only identified after the patient presented with CM.⁵

As explained in the introduction, the clinical manifestation of CM can be variable. In this case, initial clinical signs were subtle, no underlying disease was apparent, no yeasts were seen in India ink staining and cryptococcal antigen test results were negative in serum and CSF. Furthermore, yeast colonies were not detected in specimens from lumbar CSF until the ninth day of culture. However, during the course of the disease, the patient developed signs of high intracranial pressure (eg, vomiting, abducens nerve palsy, bradycardia), which were evident in the imaging also. Of note, when obtaining CSF, a high opening pressure—as a sign of high intracranial pressure—is a typical feature of CM. In this case, the antifungal treatment was delayed, because cryptococcal antigen test results were negative.

The cryptococcal antigen test is an important tool for rapid diagnosis of CM. Most assays have a sensitivity of 93–100% and a specificity of 93–98%.^{1–6} In HIV-negative and non-immunosuppressed patients, however, sensitivity appears to be lower.^{7–8} In clinical practice, this constellation of a lower sensitivity should be taken into account. The reason for a higher sensitivity of the antigen test in severely immunosuppressed patients is not known. It is possible that due to a weaker immune response, the cytotoxic interactions between host and fungi is less prominent, and that the replication of the organisms is less hindered. Consequently, there are fewer products from the host cells that could interfere with the antigen, and a stronger antigen shedding is occurring. In the same line of reasoning is the hypothesised association of high fungal load and antigen positivity.⁸ However, up-to-date, these arguments are speculative. In our patient, cryptococci grew relatively late (day 9) indicating a low fungal load. On the other hand, cryptococci were clearly visible in histopathological examination, making the estimate of fungal load difficult.

This case demonstrates the difficulty of timely diagnosis of CM in a patient with no apparent underlying disease, negative cryptococcal antigen test results and no microorganism growth during the first days of CSF culture. It also suggests lymphocytopenia (irrespective of etiology) as a potential risk factor for CM and, last but not least, the precariousness of relying on test results with high sensitivity.

Learning points

- ▶ Severe headache, fever and a high intracranial pressure suggest the diagnosis of cryptococcal meningoencephalitis (CM) even in the so-called immunocompetent patient.
- ▶ The occurrence of CM in a previously healthy patient should alert the possibility of an immunodeficiency syndrome.
- ▶ Even high-sensitivity tests such as the cryptococcal antigen test should not rule out the diagnosis of CM when clinical findings are suggestive.

Competing interests None.

Patient consent Obtained.

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