Chronic lymphocytic meningitis with low CSF sugar, pulmonary infiltrate, and hilar lymphadenopathies in an immunocompetent patient

Raquel Vázquez-Picón, MD
Marian Gómez-Beldarrain, MD
Iñigo Vicente-Olabarria, MD
Aida Rodríguez-Sainz, MD
Juan Carlos García-Moncó, MD

Practical Implications

Cryptococcal meningitis should be kept high in the differential diagnosis of chronic lymphocytic meningitis with low glucose and pulmonary involvement, even in healthy individuals.

The combination of chronic meningitis with low CSF glucose, lung infiltrates, and hilar lymphadenopathies in an immunocompetent individual is highly suggestive of tuberculosis but encompasses other treatable disorders.

We describe a patient who presented with the aforementioned combination and in whom a final diagnosis of widespread cryptococcosis was made.

Patient description

A 23-year-old woman in prior good health was admitted for progressive headache of 4 weeks' duration with low-grade fever, weight loss, occasional vomiting, and malaise. She lived in an urban setting and denied the use of illicit drugs, contact with contagious persons, or any other relevant antecedent. One week before, she had been brought to the emergency department for a transient state of agitation that required neuroleptics. A noncontrast brain CT scan was normal, and she was discharged.

Physical examination was normal except for mild neck stiffness. A lumbar puncture showed lymphocytic pleocytosis (412 cells/mm³), low glucose (17 mg/dL), and increased protein (126.5 mg/dL) (table). Immunoglobulin G index was normal. Gram and Ziehl-Neelsen stains did not reveal organisms, and aerobic cultures were negative. Immunophenotyping of the CSF cells showed a predominance of polyclonal T lymphocytes, consistent with infection and not with lymphoma.

Department of Neurology (RV-P, MG-B, AR-S, JCG-M) and Magnetic Resonance Imaging Unit (IV-O), OSATEK, Hospital de Galdakao-Usansolo, Galdakao, Spain.

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Correspondence to: hospit05@sarenet.es

Table CSF parameters over time

	Admission	Week 1 after admission	Week 2	Week 5	Week 8
Cells/mm³ (normal <5 cells/mm³, 100% lymphocytes)	412 (98% lymphocytes)	398	309	54	53
Cell phenotyping	Monocytes (14%), neutrophils (5%), lymphocytes (80%); 89% of lymphocytes were T cells, with CD4 (43%), CD8 (35%), and CD4/CD8 ratio (11%)				
Protein, mg/dL (normal <45 mg/dL)	126.5	113	117	44.5	42.1
Glucose, mg/dL (normal >45 mg/dL)	17	28	33	51	4
Immunoglobulin G index (normal <0.7)	0.57	ND	ND	ND	ND
Adenosine deaminase, IU/L (normal <5 IU/L)	10	8.3	7.6	4.2	3.3
Fungal culture	<i>Cryptococcus neoformans</i>	ND	Negative	Negative	Negative

Abbreviation: ND = not done.

Blood chemistries, complete blood count with differential, lymphocyte count, complement, serum gamma globulins, and C-reactive protein were within normal limits. HIV serology was negative and there was no other evidence of immunosuppression. Blood cultures were negative.

During admission, she presented with another episode of agitation. A brain MRI showed several small contrast-enhancing lesions in the white matter of the frontal and parietal lobes (figure 1) without meningeal enhancement. Antituberculous therapy was started empirically.

A chest x-ray showed a right middle lobe infiltrate, confirmed by CT scan, as well as several enlarged lymph nodes in the mediastinum (figure 2). An interferon- γ release assay (Quantiferon) test was positive, and a subsequent tuberculin skin test was negative.

Figure 1 Brain MRI findings

Brain MRI showing several subcortical white matter lesions (arrowheads) involving frontal areas (A, axial fluid-attenuated inversion recovery sequence). The most prominent lesion involves the left superior frontal circumvolution. After gadolinium administration some of the lesions enhanced, and there was also a linear enhancement corresponding to perivascular regions (B, axial T1-weighted sequence). Another small focus of enhancement was present next to the right occipital horn and parietal lobe (not shown).

Figure 2 Thoracic CT scan findings

The thoracic CT scan showed an infiltrate on the left upper lobe (red arrowhead) as well as prominent lymph nodes involving the mediastinum, the aortopulmonary window, both hila, and the subcarinal region (yellow arrows).

A bronchoscopy showed an inflammatory infiltrate involving the lingula, and a lymph node biopsy was performed.

One week after admission, growth of *Cryptococcus neoformans* in the CSF and lymph node biopsy was detected. Cryptococcal antigen detection in serum and CSF was repeatedly negative, and the patient denied contact with bird droppings. Therapy with liposomal amphotericin B was administered for 6 weeks, and consolidation therapy with fluconazole was administered for 10 months.¹

Lumbar puncture was repeated on several occasions (table), showing a progressive normalization of the different parameters. Fungal culture of the CSF was negative 1 week after therapy.

She improved rapidly and has remained asymptomatic thereafter. Follow-up thoracic CT scan and brain MRI were normal. One year after admission, QuantiFERON test was negative.

DISCUSSION

In addition to tuberculosis, the differential diagnosis in this patient initially encompassed other bacterial and viral infections and noninfectious conditions such as sarcoidosis and vasculitis, among others, but there was no evidence for their inclusion.²

The presence of chronic (>4 weeks) lymphocytic meningitis with low CSF glucose with concurrent pulmonary involvement and mediastinal lymph nodes in an immunocompetent individual suggests tuberculosis, but this patient proved to have cryptococcosis. Both infections share a similar pathophysiology—they are acquired by inhalation, with subsequent lung colonization and systemic dissemination with granuloma formation. The clinical presentation of meningitis may also be similar,³ with a prodromal phase of low-grade fever and malaise followed by progressive headache, vomiting, seizures, focal deficits, and papilledema, among others. The neuroimaging findings present in this patient were also consistent with tuberculous or cryptococcal granulomas.

The diagnosis of tuberculous meningitis is challenging^{4,5} because CSF cultures take a long time and are positive in less than two-thirds of patients. *C. neoformans* can grow on most bacterial and fungal media in 3–7 days. The serologic tests for detection of cryptococcal antigen in serum and CSF are extremely accurate for the diagnosis of invasive disease but were negative in this patient. To further complicate matters, an interferon- γ release assay was positive in blood. The tuberculin skin test, however, was negative. Since there is no known crossed immunity between *Mycobacterium tuberculosis* and *Cryptococcus* spp, a false-positive was more likely.⁶

C neoformans, once a rare human pathogen, became a common worldwide opportunistic pathogen, particularly in HIV-infected individuals, but remains uncommon in immunocompetent individuals. Meningoencephalitis represents the primary life-threatening infection for this fungal pathogen, with a mortality rate of 10%–25%.⁷ The prognosis in immunocompetent patients, as well as in those with normal sensorium and early therapy, is excellent.

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