CASE REPORT

From suspected Creutzfeldt-Jakob disease to confirmed histoplasma meningitis

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SUMMARY

A 77-year-old man with chronic obstructive lung disease who was on steroids, presented to the hospital after a fall with subacute headaches and ataxia. During the patient's hospital course, his clinical condition deteriorated with myoclonic jerks, fevers and severe encephalopathy. An extensive workup, including EEG, brain MRI and lumbar puncture, revealed possible Creutzfeldt-Jakob disease. Unfortunately, the patient failed to improve and died 12 days after admission. A brain-only autopsy revealed he had acute histoplasma meningitis with patchy superficial cerebritis.

BACKGROUND

Fungal meningitis is an uncommon cause of encephalopathy, but should always be investigated in patients who are immunosuppressed and have travelled to endemic areas. Histoplasma meningitis should be suspected in patients with meningitis or parenchymal lesions for which results of tests for other causes are negative. Central nervous system involvement might be manifestation of disseminated disease or isolated illness. Creutzfeldt-Jakob disease (CJD) should be suspected in patients with myoclonic jerks and rapidly progressive dementia, and with appropriate EEG (periodic sharp wave complexes (PSWC)), lumbar puncture (elevated 14-3-3 protein) and MRI findings (high signal intensity in caudate nucleus and putamen bilaterally on T2-weighted images).¹⁻³ However, brain biopsy or autopsy is required for definitive diagnosis.

CASE PRESENTATION

A 77-year-old man presented to the hospital after a fall at home secondary to imbalance. He had been experiencing ataxia and occipital headaches for about 3 months prior to presentation. His medical history was notable for chronic obstructive pulmonary disease, coronary artery disease, chronic kidney disease and repaired abdominal aortic aneurysm. He had been hospitalised for emphysema exacerbation a few months before and discharged on supplemental oxygen and steroids. He lived in Maryland, but frequently travelled to a farm in Missouri with his wife. He had a 50-pack-year smoking history, and consumed ethanol on a regular basis. His medications included aspirin, atorvastatin, clopidogrel, montelukast, fluticasone-salmeterol and low-dose prednisone. He did not have any chest pain, dyspnoea, cough, abdominal pain, syncope, aphasia, dysphagia, fevers or memory loss. His vital

signs were normal, and his initial examination was non-focal except for an ataxic gait.

INVESTIGATIONS

His initial laboratory analysis was significant for normocytic anaemia with haemoglobin of 10.9 g/dL and mean corpuscular volume of 87 fL. His white cell count was 8 k/L with 85% neutrophils, 7% lymphocytes and 8% monocytes. His renal panel showed hyponatraemia (132 mmol/L) with a glomerular filtration rate of 52 mL/min/1.73 m². His liver function tests were normal. He had an elevated erythrocyte sedimentation rate (16 mm/hour, reference range is 0–10 mm/hour) and elevated C reactive protein (3 mg/dL, reference range is 0.0–0.5 mg/dL). His admission head CT showed mild central atrophy with no intracranial haemorrhage or displaced skull fracture. His chest CT suggested chronic emphysematous changes with pleural plaques and extensive coronary artery atherosclerosis. During the course of the hospitalisation, the patient developed fevers and myoclonic jerking which prompted lumbar puncture, EEG and brain MRI. His cerebrospinal fluid (CSF) showed an elevated white cell count (53/L, 82% neutrophils, 17% lymphocytes, no red blood cells) with low glucose (4 mg/dL) and elevated protein (292 mg/dL). Cytology of CSF revealed atypical epithelioid cells in the background of acute inflammation and amorphous debris. There were no malignant cells identified on cytology in CSF. CSF cultures were negative for bacteria, viruses, fungi and mycobacteria elements. CSF fungal cultures and complement fixation (CF) were negative on initial CSF studies. CSF was also negative for Herpes simplex virus, Varicella-zoster virus and Enterovirus by PCR testing. The 14-3-3-antigen protein was elevated in the CSF (4.3 ng/mL). Testing for HIV was negative. Serum testing by CF was negative for *Histoplasma* antibody, *Coccidioides* antibody and *Blastomyces* antibody (by CF and immunodiffusion). Urine and serum *Histoplasma* antigen were negative as well. His *Aspergillus* galactomannan (GM) was positive (GM index 0.91). The specificity of the assay for *Aspergillus* spp cannot exclude the involvement of the other fungal pathogens, and false positive results are noted in 10% of the assays. QuantiFERON gold test was negative. A 45 min routine EEG was performed. The EEG showed short run of periodic broad-based sharp waves 1.5 Hz, medium to large amplitude after photic stimulation and low-amplitude delta background 2–3 Hz, consistent with severe encephalopathy. PSWC at 1.5 Hz with medium to large amplitude

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were seen after photic stimulation, which are typical for middle and late stage CJD. EEG image shows PSWC, (figure 1). The MRI showed extensive symmetrical diffusion restriction and fluid attenuated inversion recovery (FLAIR) hyperintensity in the cingulate gyrus and paramedian frontal cortex, the left and right perisylvian cortex, the mesial and anterior temporal lobe cortex, medial occipital lobe cortex, cortex in the lateral and superior portions of the cerebellum, and the posterior cortex of the midbrain. There was a 2 mm lacunar infarction adjacent to the left tectum, and diffusion restriction in the cortical surface of the medulla near the craniocervical junction. The patient has unusual symmetrical diffusion restriction and FLAIR hyperintensity in the cingulate gyrus in the cortex of the perisylvian cortex, in the limbic system, including anterior temporal lobe, medial temporal lobe, and the medial occipital lobe on the left and right side, as well as the cortical surface of the tectum, medulla, dorsal lateral thalamus, and left and right basal ganglia including the caudate nucleus and putamen (figure 2A–C). The differential diagnosis of these findings includes prion disease such as acquired CJD and viral cerebritis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes bacterial, viral, fungal meningitis, CJD, autoimmune and toxic/metabolic causes. The CSF

protein of 14-3-3 and EEG findings are typically seen in CJD. However, the CSF studies with low glucose, high protein, no malignant cells on cytology, subacute presentation, travel to endemic area and immunosuppressed status with no signs of dementia point towards fungal meningitis. The time frame of presentation, and low glucose are not consistent with CJD. The patient's clinical condition continued to deteriorate in spite of supportive treatment, and he died 12 days after his initial presentation to the hospital. His wife consented to an autopsy.

TREATMENT

The patient was treated with vancomycin, cefepime, ampicillin and acyclovir. Though *Aspergillus* GM antigen was positive, the test has to be considered in conjunction with microbiological cultures and histological examination of biopsy specimens. False positive results are reported in 10% of assays. For all positive results, two consecutive positive results should be obtained from separately drawn specimens before the patient is considered to have positive *Aspergillus* antigen test. The authors discussed the above findings with the infectious disease consultant; since no fungal elements were seen on initial CSF studies, and tests for *Histoplasma* antibody, *Coccidioides* antibody, and *Blastomyces* antibody were negative, empiric antifungal agents were not recommended as empiric therapy.

Figure 1 EEG image showing periodic sharp wave complexes.

Figure 2 MRI fluid attenuated inversion recovery (FLAIR) (A), diffusion (B), T2 (C) weighted image showing unusual symmetrical diffusion restriction and FLAIR hyperintensity in the cingulate gyrus in the cortex of the perisylvian cortex, in the limbic system, including anterior temporal lobe, medial temporal lobe and the medial occipital lobe on the left and right side, as well as the cortical surface of the tectum, medulla, dorsal lateral thalamus, left and right basal ganglia including the caudate nucleus and putamen.

Figure 3 Leptomeninges stained with Grocott methenamine silver stain. There are numerous yeast cells (size 2–4 μm) with budding and with no evidence of hyphae (original magnification, $\times 600$).

OUTCOME AND FOLLOW-UP

A brain-only autopsy was performed using precautions for prion diseases. External examination of the brain revealed softening of inferior temporal lobes and cloudy meninges. Examination of internal structures showed softening of the temporal lobes and also of the deep nuclei bilaterally. Microscopic examination of the brain showed multiple areas of acute meningitis with yeast-like organisms that stained positive with the Grocott methenamine silver stain (figure 3) and negative with the Fontana-Masson, mucicarmine and pneumocystis stains. The underlying brain parenchyma showed superficial acute cerebritis underlying some of the areas with meningitis. In addition, there was more widespread but still patchy acute ischaemic damage. These findings support a diagnosis of fungal meningitis that eventually led to acute ischaemic brain damage.

Subclassification of fungal organisms on microscopic examination can be challenging. The organisms seen in this case were entirely yeast forms with no hyphae identified. On the basis of this finding and the size of the organisms, the differential diagnosis included small unencapsulated *Cryptococcus*, *Histoplasma* and *Pneumocystis*. Fontana-Masson stain was negative, which most likely ruled against *Cryptococcus*. Additionally, the CSF and serum cryptococcal antigen tests prior to death were negative, further arguing against this as the diagnosis. *Pneumocystis* was also a possibility, but immunohistochemistry for the organism was negative at autopsy. Stored CSF was, therefore, tested for β D-glucan, a marker to confirm the presence of fungus. The results came back positive (>500 pg/mL). The remaining CSF was then sent to an outside laboratory to test for histoplasmosis antigen, and the results were highly positive (>19 ng/mL: above the limit of quantification). In addition, *Histoplasma* antibodies were positive in stored serum and CSF samples tested by enzyme immunoassay: serum IgG strong positive (>80 units) and IgM weak positive (10.3 units); CSF IgG strong positive (>80 units) and IgM negative (4 units). The stored serum and CSF studies were sent to a reference laboratory in Indiana, USA, for repeat testing, which were positive for *Histoplasma* as noted above. The initial testing of CSF *Histoplasma* was carried out at a local laboratory.

In summary, the patient presented with a fall and a 3-week history of ataxia and headache. In the hospital, he had myoclonus and a rapid decline in his mental status. Clinical workup did not yield a definitive cause of his symptoms, although CJD and viral encephalitis were high in the differential diagnosis. At autopsy, he was found to have acute fungal meningitis with subsequent testing identifying histoplasmosis. He ultimately died due to complications from the disease.

DISCUSSION

Histoplasmosis is endemic in central and eastern USA, particularly areas around the Ohio and Mississippi River Valleys, as well parts of Central and South America, Africa, Asia and Australia.⁴ The initial infection generally affects the lungs. While many infections remain asymptomatic, disseminated infections develop in ~ 1 in 2000 of infected individuals.⁵ Of those with a disseminated infection, 5–20% will develop central nervous symptoms.^{6–7} Risk factors for disseminated infection include an immunocompromised state and extremes of age.⁸ Clinical symptoms are generally non-specific, but do include meningitis and encephalitis. The meningitis is usually characterised as granulomatous inflammation rather than the acute inflammation found in this patient. Establishing a diagnosis of histoplasmosis infection is difficult.⁹ Cultures and antigen testing in serum, urine and CSF are the most useful measures for arriving at an accurate diagnosis.^{10–12} Hypoglycorrhachia (low glucose level in CSF) is seen in bacterial, fungal, tubercular meningitis, malignancy, hypoglycaemia, subarachnoid haemorrhage and inflammatory conditions. Elevated CSF protein is notable in a variety of conditions, including infections, multiple sclerosis, intracranial haemorrhage, Guillain-Barré syndrome, malignancies, endocrine abnormalities, inflammatory conditions and certain medication use. CJD encephalopathy has elevated CSF protein (14-3-3), but normal glucose in CSF. Histoplasma meningitis typically has high protein and low glucose in CSF, as noted in our case. Detection of 14-3-3 protein in CSF should be considered an adjunctive rather than absolute test for the diagnosis of prion diseases. A systematic review sponsored by the American Academy of Neurology reported an overall

Learning points

- ▶ Fungal meningitis is a rare cause of encephalopathy, and should be considered in patients who are immunosuppressed and reside or have travelled to endemic areas.
- ▶ Cerebrospinal fluid (CSF) studies which show low glucose, high protein and are negative for malignant cells need further specialised fungal stains and brain tissue to make a diagnosis of fungal meningitis.
- ▶ Fungal CSF and serum studies should be sent to reference laboratories for testing.
- ▶ Definitive diagnosis of rare causes of encephalopathy is with brain biopsy or autopsy.
- ▶ In complex neurology cases where CSF studies, EEG and MRI are non-diagnostic at first glance, consultation with neuropathologist, microbiologist, neurologist and infectious disease consultant is essential to clinch a rare diagnosis. Referral to tertiary care centres should be considered as well.

sensitivity of 92% and a specificity of 80% in diagnosing sporadic CJD. In one large case series, tau had superior accuracy and specificity when compared to 14-3-3 protein as a diagnostic test for CJD; however, both tests produced a significant number of false negative and false positive results. In our case, we did not send CSF for PrP(Sc) and τ analysis. Treatment options include an array of antifungal medications that are generally prescribed for a prolonged period.¹³ To avoid missing the diagnosis, fungal testing should be sent to the reference laboratory. Consultation with neuropathologist, microbiologist, neurologist, infectious disease physicians and referral to tertiary care centres is essential in complex cases. Risk factors for fungal meningitis include immunosuppressed or immunocompromised status, along with exposure to fungal spores in the environment while living or travelling to endemic areas. Untreated disseminated infection is often fatal, with a clinical course ranging from 2–12 weeks.

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