

Pearls and Oysters: Tuberculous meningitis

Not a diagnosis of exclusion

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PEARL

- Initiation of antituberculosis therapy and corticosteroids should not wait for definitive diagnosis, but rather should be instated at first suspicion of tuberculous meningitis.

OY-STERS

- Tuberculous meningitis cannot be ruled out by negative CSF culture, smear, or nucleic amplification test. CSF profile may not differ from that of bacterial meningitis.
- Chest radiographs may appear normal in 15% of active tuberculosis cases. Purified protein derivative (PPD) test may be negative.

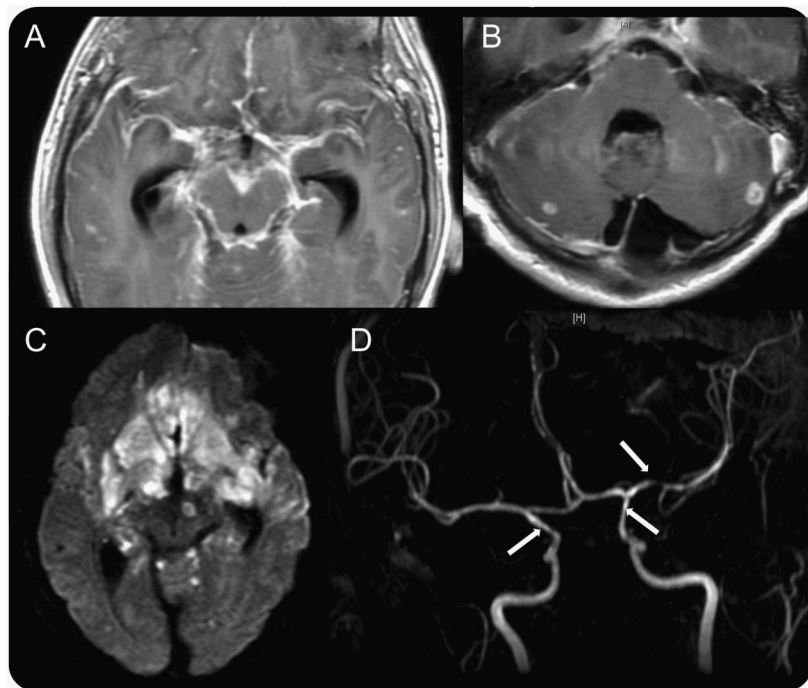
CASE REPORT A 21-year-old man presented to his local emergency department with 5 days of headache, which was dull, occipital, bilateral, nonthrobbing, and progressively worsening. It was associated with mild fever, photophobia, and neck pain and stiffness. He had no history of headache, chronic illness, recent vaccinations, cutaneous rash, cough, diarrhea, arthralgia, or myalgia. He was from Ecuador and had been living in the United States for less than 1 year. He had been incarcerated while in Ecuador. Sublingual temperature on admission was 102.6°F. Other vital signs were within normal limits. On physical examination, he appeared thin but not cachectic. He had meningismus and photophobia, but no papilledema and his mental status was alert and attentive. There were no focal neurologic deficits. CSF contained red blood cells: $24 \times 10^3/\mu\text{L}$; white blood cells: $85/\mu\text{L}$ (lymphocytic predominant); protein: 128 mg/dL; and glucose: 48 mg/dL (CSF/serum glucose ratio = 0.53). CSF Gram stain and cultures, PPD test, and blood and urine cultures were all negative. CT scan of the head on day of admission was entirely normal. MRI without gadolinium contrast showed a single punctate T2 hyperintensity in the left frontal periventricular white matter. Chest radiograph was clear. He received empiric vancomycin, ceftriaxone, and acyclovir. Corticosteroids were not given. The patient did not improve

with antibiotics and continued to be intermittently febrile. On day 5, he became abruptly more somnolent, then comatose, opening eyes only to pain, his pupils were 5 mm and reactive, he had intact brainstem reflexes, withdrawing both arms and legs. Emergent head CT showed development of hydrocephalus and a ventriculoperitoneal shunt was emergently placed. The neurologic examination did not improve after shunt placement, and repeat head CT showed increased hydrocephalus with bilateral cerebral infarcts. On day 11, he was transferred to Columbia University Medical Center for intensive care. He was febrile and comatose. He did not open his eyes to pain, pupils were 7 mm minimally reactive, brainstem reflexes were intact, and he exhibited extensor posturing to pain. Mannitol was given, corticosteroid therapy was started, and an extraventricular drain was placed. The next day, his right pupil was 8 mm and nonreactive. MRI showed diffuse contrast enhancement of the arachnoid, extensive infarction of basal ganglia, midbrain, and pons, and small ring-enhancing lesions in the cerebellum (figure 1, A–D). Repeat lumbar puncture showed red blood cells: $550 \times 10^3/\mu\text{L}$; white blood cells: $250/\mu\text{L}$ (14% neutrophils, 80% lymphocytes, 6% monocytes); protein: 65 mg/dL; and glucose: <10 mg/dL (CSF/serum glucose ratio = 0.08). CSF testing for *Cryptococcus* and toxoplasmosis was negative. CSF acid fast bacilli (AFB) smear was negative $\times 2$, and CSF nucleic acid amplification test was also negative for tuberculosis. Serum HIV test was negative. Not until 14 days after initial presentation and 3 days after transfer to the intensive care unit was antituberculosis therapy finally started, because the pattern of infarcts on the MRI suggested basilar meningitis and he had not improved on broad-spectrum antibiotics. That same day, the first sputum AFB smear was positive, as were all succeeding daily sputum AFB smears. Tuberculosis nucleic acid amplification was positive from the sputum, but persistently negative from the CSF. Daily portable chest radiographs had been normal (read as likely atelectasis), but chest CT showed dense consolidations in the left lung and diffuse micronodular opacities throughout both lungs. Two days later, only 21

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Figure 1 Brain MRI consistent with tuberculous meningitis



(A and B) With gadolinium contrast showing arachnoid enhancement and cerebellar ring-enhancing foci compatible with small abscesses. (C) Restricted diffusion in the bilateral frontal lobes, basal ganglia, and pontomesencephalon compatible with widespread infarction. (D) Magnetic resonance angiography using 3-dimensional time-of-flight imaging shows narrowing of the distal internal carotid arteries and proximal left middle cerebral artery (arrows), as well as distal anterior and middle and cerebral artery branches compatible with vasculitis.

days after the onset of his headache, the patient died of cardiopulmonary arrest secondary to transtentorial cerebral herniation. Thirteen days later, the CSF culture became positive for *Mycobacterium tuberculosis* sensitive to streptomycin, isoniazid, ethambutol, rifampin, and pyrazinamide.

Limited autopsy of brain and lungs confirmed primary progressive tuberculosis involving both lungs extensively and tuberculous meningitis. Innumerable miliary granulomas were identified bilaterally in both lungs, and there were also extensive adhesions of the right pleura to the pericardium, diaphragm, and chest wall indicating a pulmonary infection of some duration, likely months. The left lung showed necrotizing pneumonia with pulmonary edema. Examination of the brain demonstrated basilar meningitis, with extensive thickening and cream-white discoloration of the basal leptomeninges extending from the basilar and vertebral arteries and upper cervical spinal cord to the optic chiasm. Many of the cerebral vessels showed adventitial destruction by inflammatory infiltrate, and some showed both medial and even intimal involvement, often with fibrinoid and/or caseating necrosis completely occluding the vascular lumen. Several cranial nerves were infiltrated by inflammatory cells

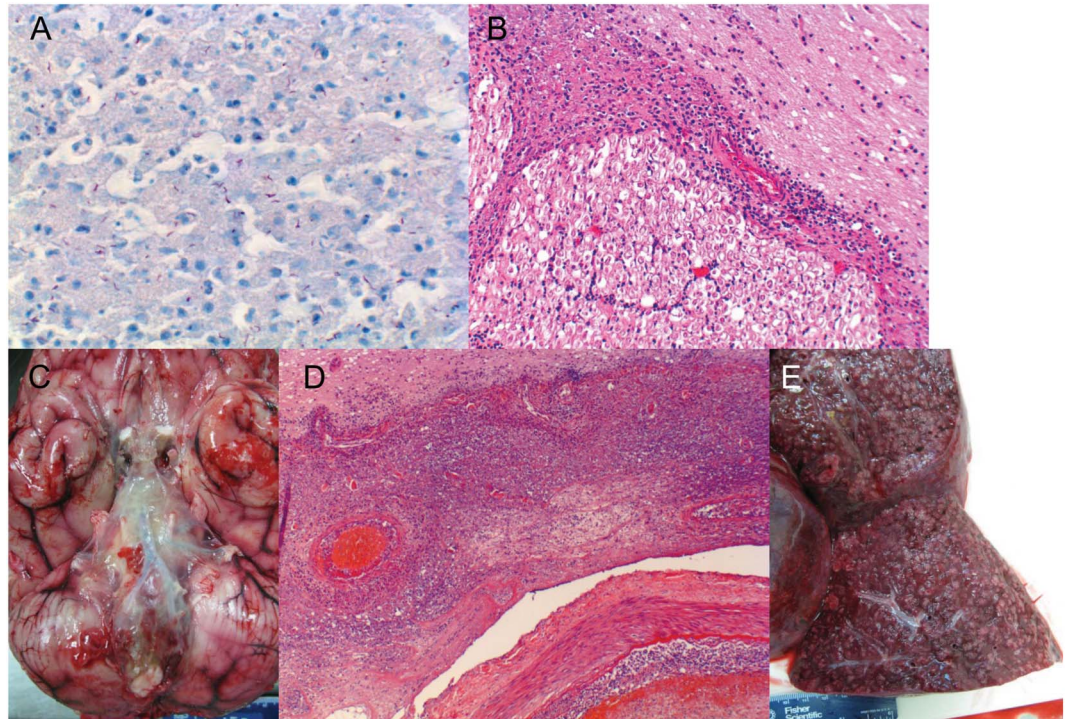
with involvement of both the perineurium and endoneurium. A stain for AFB revealed numerous bright pink, thin, spindle-shaped bacilli consistent with *M tuberculosis*, present predominantly within the basal leptomeninges, but also seen in the leptomeninges of the superior frontal cortex, within the endoneurium of bilateral cranial nerves, and tracking into the subpial parenchyma of the pons (figure 2, A–E).

DISCUSSION Tuberculous meningitis, an uncommon diagnosis in the United States, is one of the most common causes of subacute and chronic meningitis in developing countries. In the United States between 1993 and 2006, there were 253,299 cases of tuberculosis reported, of which 1.2% were tuberculous meningitis. Of these patients with tuberculous meningitis, 61% were foreign born, the mean age was 42 years, and 20% were HIV positive.¹

Acute tuberculous meningitis develops when old focal lesions in communication with the meninges (known as Rich foci) rupture, releasing massive numbers of mycobacteria, triggering a robust T-cell response and catastrophic immune reaction in and around the meninges and associated vasculature. Hydrocephalus occurs with the development of an adhesive inflammatory exudate that affects the Sylvian fissures, basal cisterns, brainstem, and cerebellum, resulting in CSF obstruction. Vasculitis with ensuing infarction is likely caused by several mechanisms: strangulation of the vessels in the thick exudate at the base of the brain, T-cell-mediated inflammation of the adventitia leading to vessel wall necrosis and thrombosis, stretching of vessels by rapidly enlarging ventricles in the setting of acute hydrocephalus, and midbrain and frontal lobe infarction as the brain herniates.²

Diagnosis of tuberculous meningitis is not always straightforward, as demonstrated by this case. However, there are a few distinguishing features that should trigger suspicion. Patients with tuberculous meningitis typically present with a subacute course. They are more likely to have cranial nerve palsies. They will not usually have a blood leukocytosis. CSF is typically clear with moderate numbers of lymphocytes and neutrophils, elevated protein, and a low CSF/serum glucose ratio. However, neutrophils can predominate, especially early in the course of CNS infection, and the CSF/serum glucose ratio can be normal.^{3,4} CSF nucleic acid amplification tests and smears are often negative. CSF cultures cannot be relied on because they take weeks to grow and success depends on acquisition of a large volume (>5 mL) of CSF. A recent study reported that AFB ultimately were cultured from only 71% of patients.⁴ Chest radiographs are actually very useful and cost-effective for diagnosing active tuberculosis, with sensitivities varying from 68% to 97%. However, as many as 15% of hospitalized patients

Figure 2 Gross and microscopic evidence of devastating mycobacterial infection



(A) 400 \times view of acid fast stain in the leptomeninges adjacent to the basilar artery with multiple acid fast bacilli. (B) Involvement of cranial nerve III by the exuberant inflammatory process. (C) Ventral aspect of the brain showing extensive basilar meningitis with clouding of the leptomeninges by pus. Note encasement of the cranial nerves and vasculature. (D) 400 \times view of the basilar artery (lower right), leptomeninges, and ventral pons with acute and chronic inflammation. (E) Gross picture of miliary tuberculous nodules in the lung.

may have a negative chest radiograph with active pulmonary tuberculosis.⁵ Factors that interfere with the sensitivity of the chest radiograph include the quality of the image (the image quality of portable radiographs is poor) and whether the patient is immune compromised.⁶ The PPD test is 80% to 90% sensitive in most cases of active tuberculosis; however, caution should be exercised in interpretation of the PPD test because several factors can lead to a false-negative result. These include recent vaccination with a live virus vaccine, recent corticosteroid use, recent tuberculosis, concurrent HIV infection, cancer, and very severe tuberculosis to the point whereby the immune system can no longer mount an appropriate response (the likely scenario in this case). A negative PPD test in a patient coming from an endemic area warrants consideration of the possibility of immunosuppression. On MRI, basal meningeal enhancement, tuberculomas, and infarction (particularly of the basal ganglia) all support a diagnosis of tuberculous meningitis, but cannot exclude cryptococcal meningitis, sarcoidosis, or lymphoma.²

In this case, the diagnosis of tuberculous meningitis should have been suspected given the history and presentation, but appropriate treatment was delayed because of an atypical CSF profile, negative chest radiograph, and

negative PPD test. The mortality rate for untreated tuberculous meningitis is 100%.⁷ Even if adequately treated, the mortality rate is still very high when treatment is initiated after patients have progressed to coma.⁸ Initiation of antituberculosis therapy should not wait for definitive diagnosis, but rather be instated at the first suspicion of tuberculous meningitis.⁹ The patient should also be rapid-tested for HIV and started on high-dose corticosteroids, which are strongly associated with a reduced risk of death.¹⁰ In addition to antituberculosis and corticosteroid therapy, development of obstructive hydrocephalus should be anticipated and immediately managed by ventricular drainage.

AUTHOR CONTRIBUTIONS

Amy C. Jongeling: drafted and revised the manuscript and provided figure 1. David Pispapia: provided description of pathology findings and figure 2.

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DISCLOSURE

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