Reminder of important clinical lesson

Tuberculous meningitis: treat upon suspicion

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Summary

A 58-year-old man from Surinam was referred because of nausea, vomiting, weight loss, ascites and an altered mental state. Tuberculous meningitis was suspected upon examination of the cerebrospinal fluid and antituberculous treatment was initiated. However, the patient did not recover but developed haemiplegia with recurrent aspiration pneumonias. This case illustrates that empiric antituberculous treatment is warranted upon clinical suspicion, since no fast, sensitive diagnostic tests are available to date.

BACKGROUND

Tuberculous meningitis is a devastating disease of the central nervous system, which requires prompt diagnosis and treatment. However, the diagnosis of tuberculous meningitis remains difficult and time consuming.

CASE PRESENTATION

A 58-year-old man from Surinam was referred because of nausea, vomiting, weight loss of 20 kg and gradually increasing abdominal distension over a course of 5 months. He was previously diagnosed with a lacunar infarction after cocaine abuse, from which he recovered without sequelae. Since a week before presentation, he had developed an altered mental state. His sister reported a recent stay in Surinam but no apparent contact with patients with open tuberculosis. On examination the Glasgow Coma Scale score was E3M6V4. No neck stiffness or other signs of meningismus were appreciated. His body temperature was 36.7°C, blood pressure 110/70 mm Hg, pulse 72 bpm. Over the abdomen, shifting dullness was found. Plasma sodium was low at 123 mmol/l, C reactive protein was 77 mg/l and ammonia 10 mmol/l. Chest radiography on admission showed no abnormalities. Ultrasound of the abdomen revealed ascites but no signs of cirrhosis or other pathology.

The altered mental state was initially considered to be caused by the hyponatraemia or intracranial abnormalities including tuberculosis, toxoplasmosis, encephalitis or epilepsy. To distinguish between an infectious and non-infectious cause, the ascites was sampled, showing an elevated albumin level of 30 g/l compared to a serum albumin of 38 g/l and inflammation without malignant cells or acid-fast bacilli. CT of the brain, chest and abdomen demonstrated cerebral atrophy, pre-existent lacunar infarction in the right hemisphere and several small (<1 cm) hilar, mediastinal and para-aortic lymph nodes but no large lymph nodes. A tuberculin skin test (TST) was negative. Serology for HIV, cytomegalovirus (CMV), Epstein-Bar virus and PCR on cerebrospinal fluid (CSF) for HSV, CMV, EBV, varicella-zoster virus; enterovirus; parechovirus and

JC virus were all negative. PCR on CSF, urine and faeces for *Mycobacterium tuberculosis* complex were also negative.

During admission, the patient developed a right-sided pleural effusion that proved to be straw-coloured upon aspiration, with a composition comparable to the ascites: inflammation without malignant cells or acid-fast bacilli. The Interferon Gamma Release Assay (IGRA) came back inconclusive and had to be repeated. The differential diagnosis still included tuberculosis and lymphoma or another malignancy. Both tuberculosis and lymphoma can cause cachexia, ascites and dissemination to the central nervous system, rendering differentiation between these two causes of abdominal lymphadenopathy challenging.¹

Within the course of 1 week, his consciousness remained stable while an extensor plantar response of the right foot developed. CSF was clear and contained elevated white blood cells ($0.4 \times 10^9/l$) and protein (1.96 g/l), and a decreased glucose (1.1 mmol/l).

TREATMENT

We initiated antituberculous treatment comprising isoniazid (300 mg daily orally for 9 months), rifampicin (600 mg daily orally for 9 months), ethambutol (1200 mg daily orally for 2 months) and pyrazinamide (1500 mg daily orally for 2 months); and systemic dexamethasone (28 mg daily intravenously for 1 week, followed by 21 mg, 14 mg and 7 mg daily in week 2, 3 and 4, respectively; followed by 4 mg daily orally, with a reduction schedule of 1 mg each week). Vitamin B6 was added to prevent neuropathy.

OUTCOME AND FOLLOW-UP

On day 9, the patient worsened: his consciousness diminished (E4M5V2) and he developed fever and neck stiffness. The hyponatraemia was considered to be due to cerebral salt wasting. Thoracoscopy showed granulomatous lesions on the parietal pleura. Biopsies of these lesions demonstrated necrotising granulomas. Because of respiratory failure and exhaustion, the patient was mechanically ventilated for 6 days. Ten days after admission, the second IGRA came back positive. Four weeks after admission, the

second PCR of the CSF was found to be positive for *M tuberculosis* and 6 weeks after admission, *M tuberculosis* was cultured from the pleural fluid. This culture also showed good susceptibility of the isolate to isoniazid, rifampicin, ethambutol and pyrazinamide.

The patient did not recover from his disseminated tuberculosis with tuberculous meningitis, pleuritis and peritonitis. He suffered from diminishing spontaneous speech, right-sided haemiplegia and recurrent aspirations with pneumonia. Over a course of 10 months, despite supportive respiratory care and administration of nutrients via a percutaneous gastric catheter, the recurrent pneumonias gradually caused exhaustion and respiratory failure, to which the patient finally succumbed.

DISCUSSION

Tuberculous meningitis, the most severe manifestation of extrapulmonary tuberculosis, is a rare but devastating disease of the central nervous system. It accounts for 1% of all cases of tuberculosis²⁻⁴ and the incidence in high-income countries is low. It has exceptionally high rates of mortality and morbidity: 50% of patients die or remain disabled.³⁻⁵ Predisposing factors include alcoholism, diabetes mellitus, HIV infection, malignancy and immunosuppressive treatment.⁵⁻⁶

In this case, the patient presented with nausea, vomiting, weight loss, ascites and an altered mental state. Although the insidious presentation of tuberculous meningitis often includes non-specific symptoms such as malaise, anorexia and fatigue, it usually presents with various symptoms including headache and fever.²⁻⁵⁻⁷ Tuberculous meningitis should be considered if a patient presents with an unexplained altered mental state combined with headache, fever, neck stiffness, weight loss, ascites or cranial nerve involvement⁶ and CSF should be obtained. Typical findings are mononuclear cell pleiocytosis, low glucose levels—relative to the serum glucose level—and elevated protein levels.⁵⁻⁶ Tubercle bacilli in CSF are required for a definite diagnosis but cultures take several weeks and are only positive in 25–70% of cases, often necessitating multiple CSF sampling. Smear is rapid and inexpensive but has an even lower sensitivity of 0–20%.⁷⁻⁸ TST gives falsely negative results in 50% of cases.⁶⁻⁷ Staining techniques such as Ziehl-Neelsen have a high specificity but again a low sensitivity of 20–80%.⁶⁻⁸ The IGRA has a high specificity but cannot distinguish between latent or active tuberculosis infection and is falsely negative in 50% of cases.⁷

The detection of *M tuberculosis* DNA in CSF samples using single gene PCR is a widely applied assay. However, single gene PCR on *M tuberculosis* in CSF has a low sensitivity of 31.4–56% and a specificity of 98%.⁹ In the future, multiplex PCR, simultaneously assessing different genes specific for *M tuberculosis* complex (ie, IS6110, mpb64, rrs and rpoB), may become available. Since this latter assay has a sensitivity of 95% and a specificity of 97% for diagnosing extra-pulmonary tuberculosis, it might lead to significant improvement and shortening of the diagnostic tract in affected patients.¹⁰

The hallmark pathological features of tuberculous meningitis are meningeal inflammation, fibroglutinous basal exudates, vasculitis and hydrocephalus due to obstruction of CSF flow. Exudates can cause constriction and thrombosis of cerebral vessels, after occlusion leads to infarction

of the underlying tissue, which is common in patients with tuberculous meningitis.⁵

Antituberculous treatment was initiated on day 7 after presentation. In an Australian review of 48 patients, the diagnosis was only considered on the day of presentation in 37% while only 6% was treated with antituberculous treatment on the first day.⁶ Molenaar *et al* described three patients in whom it took several days to reach a diagnosis, antituberculous treatment was initiated at days 4, 11 and 3 after presentation, respectively.⁶

Standard antituberculous treatment (rifampicin, isoniazid, ethambutol and pyrazinamide) should be initiated as quickly as possible.²⁻⁵⁻⁶⁻¹¹⁻¹² The WHO guidelines recommend a treatment duration of 6 months, with 9–12 months of treatment in severely affected patients. Adjuvant treatment with dexamethasone has been shown to significantly reduce mortality rates, although the exact mechanism remains unclear.²⁻⁵⁻¹¹⁻¹³ Despite antituberculous treatment, mortality and morbidity rates in tuberculous meningitis remain high. A Danish review of 50 patients described a death rate of 19% and 48% neurological sequelae,² while Garg⁵ report death or disability in more than 50% despite antituberculous treatment. Common neurological sequelae are haemiplegia or paraplegia, aphasia and vision loss.⁵

Early, often empiric, treatment is fundamental to improve clinical outcome of tuberculous meningitis but prompt diagnosis remains problematic due to a non-specific presentation and time-consuming diagnostic tests with low sensitivity, as illustrated by our case.²⁻⁵⁻⁷⁻⁸⁻¹²

Learning points

- ▶ Tuberculous meningitis is often overlooked as possible diagnosis in high-income countries, leading to delays in initiation of appropriate therapy which further contributes to the high morbidity and mortality of the infection.
- ▶ Consider tuberculous meningitis as a cause of unexplained altered mental state combined with headache, fever, neck stiffness, weight loss, ascites or cranial nerve involvement.
- ▶ The diagnosis of tuberculous meningitis remains a problematic and time-consuming process.
- ▶ Antituberculous treatment with adjuvant dexamethasone should be initiated as quickly as possible.
- ▶ Multiplex PCR may be helpful in rapidly diagnosing tuberculous meningitis.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. Shao H, Yang ZG, Deng W, *et al*. Tuberculosis versus lymphoma in the abdominal lymph nodes: a comparative study using contrast-enhanced MRI. *Eur J Radiol*. Published Online First: 20 June 2012. doi:10.1016/j.ejrad.2011.11.004.
2. Christensen AS, Andersen AB, Thomsen VO, *et al*. Tuberculous meningitis in Denmark: a review of 50 cases. *BMC Infect Dis* 2011;**11**:47.
3. Shao Y, Xia P, Zhu T, *et al*. Sensitivity and specificity of immunocytochemical staining of mycobacterial antigens in the cytoplasm of cerebrospinal fluid

- macrophages for diagnosing tuberculous meningitis. *J Clin Microbiol* 2011;**49**:3388–91.
4. **Xu HB**, Jiang RH, Li L, *et al*. Diagnostic value of adenosine deaminase in cerebrospinal fluid for tuberculous meningitis: a meta-analysis. *Int J Tuberc Lung Dis* 2010;**14**:1382–7.
  5. **Garg RK**. Tuberculous meningitis. *Acta Neurol Scand* 2010;**122**:75–90.
  6. **Molenaar RP**, Jansen CL, Taphoorn MJ. Three patients with tuberculous meningitis: treatment started at tentative diagnosis. *Ned Tijdschr Geneeskde* 2008;**152**:593–8.
  7. **Cherian A**, Thomas SV. Central nervous system tuberculosis. *Afr Health Sci* 2011;**11**:116–27.
  8. **Kusum S**, Aman S, Pallab R, *et al*. Multiplex PCR for rapid diagnosis of tuberculous meningitis. *J Neurol* 2011;**258**:1781–7.
  9. **Cheng VC**, Yew WW, Yuen KY. Molecular diagnostics in tuberculosis. *Eur J Clin Microbiol Infect Dis* 2005;**24**:711–20.
  10. **Vadwai V**, Shetty A, Rodrigues C. Using likelihood ratios to estimate diagnostic accuracy of a novel multiplex nested PCR in extra-pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2012;**16**:240–7.
  11. **Green JA**, Tran CT, Farrar JJ, *et al*. Dexamethasone, cerebrospinal fluid matrix metalloproteinase concentrations and clinical outcomes in tuberculous meningitis. *PLoS One* 2009;**4**:e7277.
  12. **Thwaites G**, Chau TT, Mai NT, *et al*. Tuberculous meningitis. *J Neurol Neurosurg Psychiatry* 2000;**68**:289–99.
  13. **World Health Organization**. *Treatment of Tuberculosis Guidelines*. 2010. http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf

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