TEST YOURSELF

Pract Neurol 2009; 9: 46–49

Persistent vomiting

Hawraman Ramadan, Alastair Lansbury, Philip Stanley

H Ramadan
Specialist Registrar

A Lansbury
Consultant Neurologist

P Stanley
Consultant in Infectious Disease

Bradford Royal Infirmary, Bradford, UK

Correspondence to:
Dr H Ramadan
Department of Neurology, St Luke's Hospital, Little Horton Lane, Bradford BD5 0NA, UK; Hawraman.Ramadan@bradfordhospitals.nhs.uk

10.1136/jnnp.2008.168203

A 40-year-old right-handed British Asian engineer presented with a four-week history of nausea, persistent vomiting, anorexia and weight loss without abdominal pain or change in bowel habit. During a 10-day hospital admission, his full blood count (FBC), urea and electrolytes (U and E), liver function tests (LFT), C-reactive protein (CRP), calcium and thyroid function tests (TFT) were all normal. Gastroscopy showed *Helicobacter pylori* gastritis and he was discharged home after treatment with amoxicillin, clarithromycin and lansoprazole which resulted in symptomatic improvement.

He returned four weeks later with recurrence of nausea and vomiting, further weight loss (approximately 12 kg in three months) and progressive left leg weakness over 10 weeks which had not been apparent during the previous admission. He also described intermittent, mild, non-disabling headache without cranial nerve symptoms, photophobia, sphincter dysfunction or fever.

He did not have any significant past medical history. He was married with five children, had never smoked and did not drink alcohol. He had had regular contact with a relative treated for pulmonary tuberculosis in the UK five years ago and last travelled abroad three years previously (Saudi Arabia).

On examination he was apyrexial, with a normal systemic examination and no palpable lymphadenopathy. He had normal higher mental functions and cranial nerves with no papilloedema or signs of meningeal irritation, but he did have moderate left-sided pyramidal arm and leg weakness and brisk left-sided reflexes with an up going left plantar response. Sensory and cerebellar examination was normal. He was able to stand and walk with a Zimmer frame.

Normal investigations included FBC with differential, U and E, LFT, calcium, glucose, CRP, mid-stream specimen of urine, ECG and chest *x* ray. However, the CT brain scan with contrast showed hydrocephalus with no focal lesion.

Question 1

What are the presenting neurological problems? What is the differential diagnosis and what further investigations would you suggest?

COMMENT

Progressive haemiparesis, nausea, vomiting and weight loss in a previously fit and well man suggests systemic malignancy with brain metastasis, or chronic meningitis. The hydrocephalus might explain the patient's

intractable nausea and vomiting but not the left-sided weakness. Therefore he had an MR scan of his brain and cervical spinal cord with contrast, to look specifically at the base of brain and cord (fig 1).

Question 2

How would you interpret the MR scan? Suggest a differential diagnosis based on the MR findings and the investigations you would perform next.

COMMENT

The MR brain scan shows hydrocephalus, a small focus of high signal in the right side of the pons compatible with infarction, and meningeal thickening with contrast enhancement in the cervico-medullary region. In the absence of vascular risk factors, the pontine infarction is likely to be due to granulomatous meningitis affecting the small penetrating vessels, the cause of the left haemiparesis. The inflamed thickened meninges in contact with the right medulla and cervical cord may also have been responsible for the gradually increasing weakness.

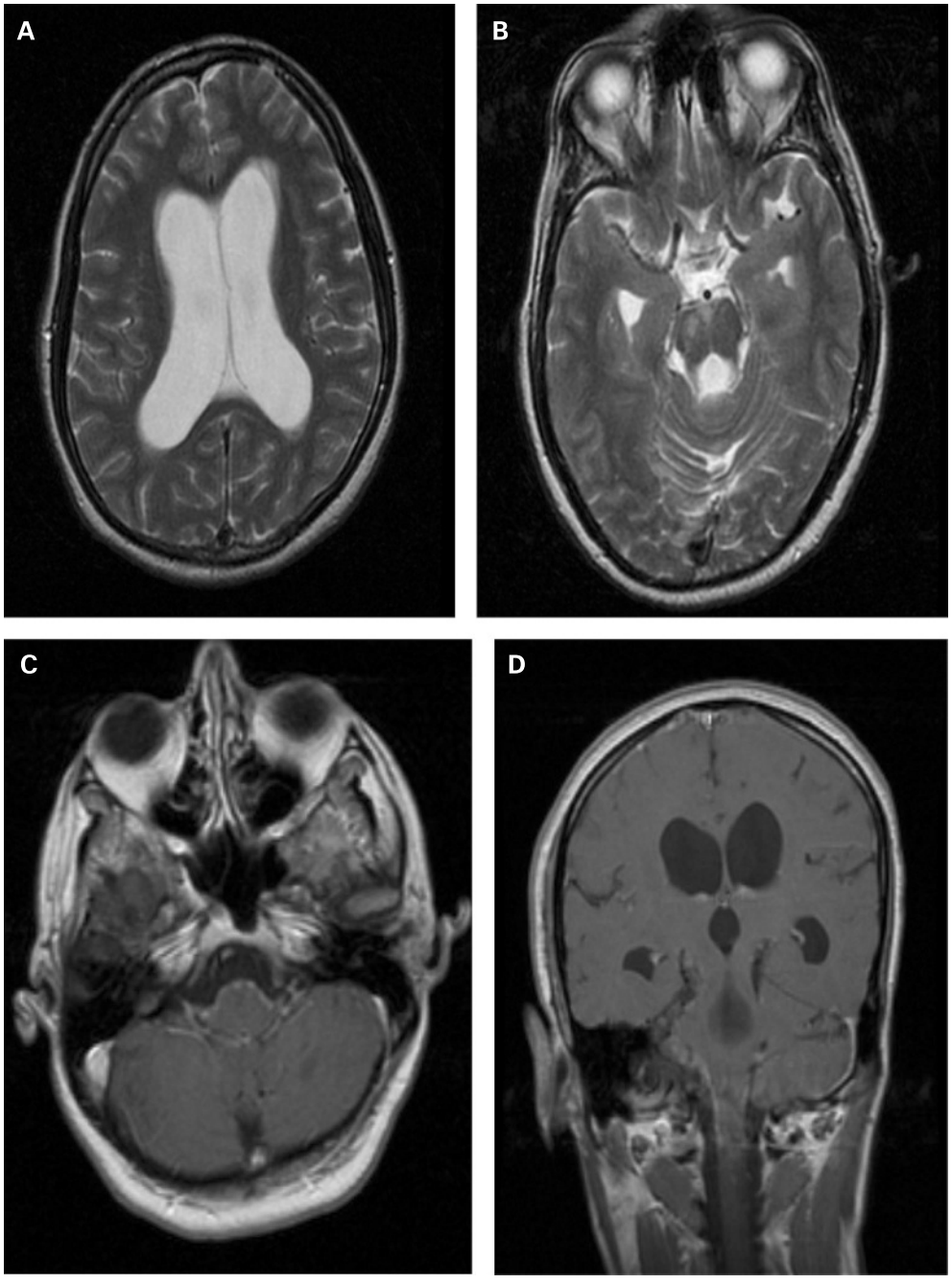

Figure 1
Brain MR scan: axial T2-weighted (A, B) enhanced axial (C) and coronal (D) T1-weighted.

Based on the MRI findings the differential diagnosis became malignant meningeal infiltration, tuberculous meningitis (TBM), cryptococcal meningitis or sarcoidosis.

The patient then had two lumbar punctures (LP) three weeks apart. On both occasions the opening pressure was normal and the cerebrospinal fluid (CSF) was clear and colourless. The first LP showed a low glucose 1.4 mmol/l (plasma glucose 5.3 mmol/l), CSF protein 1.56 g/l (normal 0.2–0.4 g/l), 10×10^6/l white cells—6 lymphocytes and 4 neutrophils. Protein electrophoresis showed a positive monoclonal band on an oligoclonal background present in CSF although not in serum. The second LP showed glucose 2.0 mmol/l (plasma 6.3 mmol/l), protein 1.1 g/l and 5×10^6/l white blood cells. On both occasions, CSF cytology showed no abnormal cells, negative Gram stain and growth, negative India ink stain, no acid fast bacilli on auramine staining and negative TB culture and TB PCR.

The following further investigations were normal or negative: lactate dehydrogenase, clotting profile, thrombophilia screen, cholesterol, triglycerides, antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, rheumatoid factor, angiotensin converting enzyme, Quantiferon-TB gold test (an in vitro test of gamma interferon production from lymphocytes after challenge with *M tuberculosis* specific antigen), urine for Bence Jones protein, serology for brucella, syphilis, HIV and Lyme disease.

His erythrocyte sedimentation rate ranged between 22 and 29 mm in the first hour and serum immunoglobulin electrophoresis showed a polyclonal increase in IgG and IgA. Contrast CT of his chest, abdomen and pelvis was normal apart from a 12 mm lymph node in the upper mediastinum and a 15 mm soft tissue density at the right hilum.

Question 3

What would you do next?

COMMENT

He was started on anti-tuberculous therapy (rifampicin, isoniazid, pyrazinamide and ethambutol) together with prednisolone 40 mg daily after the first LP result, pending further investigation and based on the history of TB contact, low glucose and high protein in the CSF, and basal meningeal enhancement on the brain MRI. Four weeks after admission there was no change in his clinical status and repeat brain CT did not show worsening of the hydrocephalus. He then had a PET (positron emission tomography) scan to determine the extent of any subclinical malignancy or inflammatory condition. It showed a widespread hyper-metabolic process involving cervical, mediastinal and abdominal lymph nodes. There was no liver or lung involvement. The conclusion was likely lymphoma or metastatic malignancy, with TB or sarcoidosis less likely. Cervical lymph node biopsy showed granulomatous lymphadenitis most likely due to TB with no evidence of malignancy. But TB culture of the gland was negative (albeit five weeks after the start of TB treatment).

Following this he made a gradual recovery, started to eat and drink, gained weight, generally felt better with some improvement in his mobility. Three weeks after initiation, the steroids were gradually tapered and stopped four weeks later, but the TB therapy was continued. Ten months following initial presentation, he was symptom-free apart from mild residual spastic weakness of the left leg necessitating occasional use of a walking stick.

TB meningitis is the most likely diagnosis given the CSF picture, history of a TB contact and sustained improvement on anti-tuberculous therapy, despite negative TB-PCR and culture of his cerebrospinal fluid and negative Quantiferon-TB gold test. Sarcoidosis is less likely on epidemiological grounds, normal serum angiotensin converting enzyme levels and sustained clinical response with only a short course of steroids. Unlike primary central nervous system lymphoma, metastatic lymphoma can involve the leptomeninges without parenchymal invasion; however, this is unlikely given the clinical improvement and lack of evidence on the lymph node biopsy.

Tuberculous meningitis (TBM) is a subacute, debilitating disease with a high morbidity and mortality in spite of treatment. There has been a steady increase in the number of TB cases in the UK; in 2004 around 7000 cases were reported in England and Wales. Improved case notification, a rise in the elderly population, TB among new immigrants, homelessness and

10.1136/jnnp.2008.168203

HIV disease may be contributing to this rise. TBM accounts for 1.5% of all TB cases[1] and can present in various forms, which often makes early diagnosis difficult. The presence of extrameningeal TB or a TB contact may be helpful. The prodrome is usually non-specific with no one symptom predominating: 28% report headache, 25% vomiting and 13% fever.[2]

Diagnosis is confirmed on lumbar puncture and CSF examination. A raised CSF protein occurs in most, and CSF glucose is reduced in 70%.[3] Acid fast bacilli are seen in CSF smears in about 10–20% of patients.[4] However, depressed cell mediated immunity may lead to atypical findings in the CSF,[5] and even an acellular CSF in elderly and HIV positive patients.[6] The role of PCR has not yet been evaluated for the diagnosis of TBM; sensitivities vary from 33% to 90%, specificities from 88% to 100%.[3] Indirect tests such as the Mantoux or assays of gamma-interferon production from lymphocytes stimulated by *M tuberculosis* specific antigen may be helpful to show the presence of tuberculous disease but do not confirm a diagnosis of TBM. The Quantiferon-TB gold test used in this case has a reported sensitivity of around 80%.[7] But despite all this, the diagnosis is still often difficult and it is not uncommon to fail to identify the bacteria. In these cases the diagnosis depends on the clinical pattern of disease, CSF findings, and response to treatment—as it was thought to in this case.

Various neurological complications may occur including cranial nerve palsies (particularly II, III, IV, VI, VII and VIII), brain infarction, commonly in the internal capsule and basal ganglia, and obstruction of CSF flow leading hydrocephalus. Both CT and MRI of the brain may reveal hydrocephalus, basal meningeal thickening, brain infarction, oedema and tuberculomas. The radiological differential diagnosis includes cryptococcal meningitis, cytomegalovirus encephalitis, sarcoidosis, meningeal metastases and lymphoma.[3]

The National Institute for Health and Clinical Excellence (UK) (NICE) guidelines on the management of TBM recommend a treatment regimen initially lasting for 12 months comprising: isoniazid, rifampicin, pyrazinamide and a fourth drug (for example, ethambutol) for the first two months, followed by isoniazid and rifampicin for the rest of the treatment period for drug-sensitive disease.[8] A systematic review suggests that corticosteroids should be routinely used in HIV negative people with TBM to reduce death and disabling residual neurological deficit among survivors.[9]

PRACTICE POINTS

- Tuberculous meningitis may present insidiously with non-specific symptoms.
- Diagnosis may be difficult when it is not possible to identify the mycobacteria with PCR or culture, despite clinical and radiological features that support the diagnosis and a good response to treatment.
- The incidence of TB is steadily increasing in the UK, possibly as a result of an aging population, high rates of immigration and human immunodeficiency virus infection.

REFERENCES

1. Department of Health. Green Book. DH, 2006. Available at http://www.dh.gov.uk/en/Publichealth/Healthprotection/Immunisation/Greenbook (accessed September 2008).
2. Illingworth RS. Miliary and meningeal tuberculosis. *Lancet* 1956;**ii**:646–9.
3. Jeren T, Beus I. Characteristics of cerebrospinal fluid in tuberculous meningitis. *Acta Cytol* 1982;**26**:678–80.
4. Hopewell PC. Overview of clinical tuberculosis. In: BR Bloom, *Tuberculosis: pathogenesis, protection, and control*. Washington, DC: ASM, 1994.
5. Thwaites G, Chau TTH, Mai NTH, *et al*. Tuberculous meningitis. *J Neurol Neurosurg Psychiatry* 2000;**68**:289–99.
6. Karstaedt AS, Valtchanova S, Barriere R, *et al*. Tuberculous meningitis in South African urban adults. *Q J Med* 1988;**91**:743–7.
7. Mazurek GH, Jereb J, Lobue P, *et al*. Guidelines for using the QuantiFERON-TB Gold test for detecting Mycobacterium tuberculosis infection, United States. *MMWR Morb Mortal Wkly Rep* 2005;(RR15):49–54.
8. National Institute for Health and Clinical Excellence. Tuberculosis. Clinical diagnosis and management of tuberculosis, and measures for its prevention and control. NICE, 2006. Available at http://www.nice.org.uk/Guidance/CG33 (accessed August 2008).
9. Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. *Cochrane Database Syst Rev* 2008;**1**:CD002244.