CASE REPORT

Confusion and altered behaviour? Cause

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SUMMARY

We describe the case of a 65-year-old man who presented with confusion and change in behaviour, and describe the investigative steps that were taken before a diagnosis was made. This patient was eventually diagnosed with leptomeningeal carcinomatosis secondary to a previously undiagnosed oesophageal carcinoma.

BACKGROUND

Leptomeningeal carcinomatosis (LC) refers to diffuse seeding of the leptomeninges by tumour metastases. It is a rare and often underdiagnosed manifestation of malignancy in adults. We describe the case of a man who presented with a change in behaviour, and describe the investigative steps that were taken before a diagnosis was made. This patient was eventually diagnosed with LC secondary to a previously undiagnosed oesophageal carcinoma. This case highlights the rare disease of leptomeningeal carcinomatosis, which is rarely secondary to oesophageal cancer. It is even rarer for oesophageal cancer to present as leptomeningeal carcinomatosis. This case report also demonstrates the difficulty in diagnosing a patient who presents with aseptic meningitis. This case report highlights the important clinical lesson that large amounts of cerebrospinal fluid (CSF) are required in order to confirm the diagnosis of leptomeningeal carcinomatosis, as the amount of cancer cells present in the CSF are small.

CASE PRESENTATION

Our patient was a 65-year-old gentleman who attended the emergency department (ED) with a history of agitated behaviour. His primary care physician had prescribed sertraline 50 mg once daily and lorazepam 5 mg at night for suspected reactive agitated depression following the death of his wife 2 weeks previously. His daughter noted that since the death of his wife, he had become increasingly vague and had suffered multiple episodes of vacant staring. On the day of admission, the patient had repeated episodes of appearing vacant which were similar to the episodes seen in the previous 2 weeks. He subsequently became acutely agitated and aggressive, which appeared to have been provoked by a visual hallucination. He was an ex-smoker of 14 years with a 30-pack year history. There was no significant history of alcohol consumption. His medical history was unremarkable. He was employed as a secondary school English teacher. His daughter commented that he had lost approximately 3 stone in weight over the previous 6 months.

In the ED, Glasgow Coma Score was 14/15. He was clinically dehydrated and extremely agitated. His tympanic temperature was 36.5°C; pulse rate was 78 beats/min and regular; blood pressure was 108/63 mm Hg. His blood sugar by glucometer was 9.8 mmol/l. Left pupil was initially dilated and unresponsive, but rapidly became responsive, equal and reactive to light. There was no papilloedema. No rash or lymphadenopathy was found. BCG scar on the arm was noted. Cranial and peripheral nerve examinations were limited by agitation. There were no gross abnormalities other than bilateral positive Babinski's sign. Respiratory, cardiovascular and abdominal examinations were all normal. Intravenous diazepam 5 mg was given in the ED for worsening agitation. He settled rapidly and an Abbreviated Mental Test Score was 9/10. Re-examination revealed persistent bilateral positive Babinski's sign only.

INVESTIGATIONS

Initial blood tests performed in the ED revealed normal haemoglobin, white cell count and platelet levels. Erythrocyte sedimentation rate was 28 mm/h (which may be normal for a 65-year-old man). Renal profile, coagulation screen and liver function tests were all within normal limits. Electrocardiograph showed a normal sinus rhythm. Chest radiograph showed left basal atelectasis. The initial differential diagnosis included drug-related seizures/adverse drug reaction (from sertraline or benzodiazepine withdrawal), meningitis or encephalitis.

CT of brain without contrast was done on the night of admission. No gross abnormalities were identified. Ventricle size was normal (figure 1). Lumbar puncture (LP) was then performed. Intravenous efotaxime 2 g and acyclovir 650 mg were administered based on the LP results (table 1). The CSF showed atypical epithelial cells and a sample was sent to a tertiary hospital for cytological analysis. PCR for *Mycobacterium tuberculosis* (TB) complex and herpes simplex virus were requested. The differential diagnosis at this point centred on viral or TB meningitis.

The following day, patient had improved dramatically. He did have subtle defects in both attention and concentration, but was otherwise alert and orientated and able to give a full history. His daughter commented that he was much improved but was 'not quite back to his normal self'. In review of systems, the patient confirmed a 3.5 stone-weight loss over a 6-month period, some of which he claimed was secondary to dieting. Appetite had been poor but improving. He had no history of dysphagia, regurgitation or abdominal pain. Repeat clinical examination demonstrated no objective clinical abnormalities and Babinski's sign was negative bilaterally. Mini-mental state (Folstein) examination was 29/30. Cefotaxime

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Figure 1 Non-contrast CT scan of the brain, the axial slice taken at the level of the lateral ventricles. The scan did not find any abnormalities.

and acyclovir were continued. Further blood culture specimens were taken, as well as serial early morning urine samples for acid-fast bacilli, all of which showed no growth.

Four days post admission, patient was conversing well but remained intermittently vague. A repeat LP was performed on day 5 (table 1). A moderate lymphocyte count, a high protein and a very low glucose was again noted. Further CSF was sent for cytology. It was subsequently felt by the cytopathology department that there were abnormal meningeal cells present in the CSF, but there was insufficient sample to identify them definitively as malignant cells. A larger sample of CSF was requested for repeat analysis. Additional serum tests performed included human HIV, enterovirus, adenovirus, mycoplasma, herpes simplex, syphilis and cryptococcal serology, all of which were negative. CSF was also sent for cryptococcal antigens, culture and sensitivity, as well as viral culture, which were all negative.

Table 1 Cerebrospinal fluid analysis breakdown on Day 1 and Day 5 post-admission.

	Day 1	Day 5
CSF		
Appearance	Clear and colourless	Clear and colourless
WCC	33	14
WCC Differential	95% Lymphocytes; 5% Neutrophils	99% Lymphocytes; 1% Neutrophils
Gram stain	No organisms	No organisms
Protein	1.7	2.3
Glucose	1.2	0.7
Ziehl-Neelsen stain	Negative	Negative
Culture	Negative	Negative
Cytology	Atypical epithelial cells	Abnormal meningeal cells

CSF, cerebrospinal fluid; WCC, white cell count.

Psychiatric consultation was requested, 1 week postadmission, in view of his recent mood change. After psychiatric evaluation, it became apparent that he had been having word-finding difficulties and deteriorating short-term memory for 3–4 months. He admitted to visual hallucinations for the last 4 months, specifically an ill-defined image in his left visual field that he thought was a threatening individual. He felt that some of his weight loss had been unintentional. He was concerned about his performance as a school teacher during this period.

The cytology report, the low CSF glucose and the history of significant weight loss led to suspicions of an occult malignancy. CT scan of thorax, abdomen and pelvis was performed.

On day 7 of admission, 6 h after the CT thorax, abdomen and pelvis scan, he had a clonic seizure lasting 2 min, which was aborted by 5 mg intravenous diazepam. Postictally, he became severely agitated and restless. His daughter, at the time, commented that this behaviour was similar to that witnessed on the day of admission. Further per-rectal diazepam was given and sodium valproate 300 mg twice a day was also started. In view of the clinical deterioration and lack of a definitive diagnosis, rifampin, isoniazid and pyrazinamide were started to cover for *M tuberculosis*. In total, 15 mg intravenous diazepam and 10 mg/rectal diazepam were administered. Despite this, he remained extremely agitated, restless and confused, pulling out repeated intravenous cannulae and urinary catheters. He was then transferred to the intensive care unit to be intubated and sedated.

The CT scan of thorax, abdomen and pelvis with oral and intravenous contrast demonstrated a circumferential soft tissue mass at the distal oesophagus (figure 2) which was associated with lesser curvature, coeliac axis and para-aortic lymphadenopathy. The remainder of the examination was unremarkable.

The patient was ventilated and sedated for 2 days. Following extubation, he remained confused but less agitated. Repeat lumbar puncture was performed. Immunocytological analysis identified abnormal cells in the CSF which were weakly positive for the anti-cytokeratin (CAM 5.2) immunohistochemical stain (which is a marker used to identify secretory epithelia) (figure 3). There were, however, insufficient cells to give a definitive diagnosis. An upper gastrointestinal endoscopy confirmed an occlusive

Figure 2 Contrast-enhanced CT of the lower thorax demonstrating circumferential lower oesophageal thickening (arrowed) consistent with tumour.

Figure 3 High-power photomicrograph of cerebrospinal fluid. Immunocytochemical staining weak positive for cytokeratin CAM 5.2.

mass at the oesophago-gastric junction (figure 4). Biopsies that were taken revealed a poorly differentiated malignant tumour probably of squamous cell origin (figure 5) and carcinoma was confirmed by positive immunohistochemical staining for the CAM 5.2 epithelial marker (figure 6).

An MRI of brain with contrast was performed. This confirmed diffuse leptomeningeal enhancement with some deep sulcal nodular enhancement (figures 7 and 8). A diagnosis of primary oesophageal squamous carcinoma with leptomeningeal metastases was made. In addition, the CSF PCR for *M tuberculosis* complex had returned as negative. At this point, the anti-TB medications were stopped.

DIFFERENTIAL DIAGNOSIS

This report describes a case of aseptic meningitis which was later found to be caused by LC from a previously undiagnosed oesophageal primary. Aseptic meningitis is an illness characterised by inflammation of the meninges, usually with an accompanying mononuclear pleocytosis. Clinical symptomatology is varied, including headaches, visual disturbances, altered mental status and seizures. The differential diagnosis in the adult is broad including viral, bacterial, spirochaetal, amoebic, sarcoid, fungal, metabolic, vasculitic, drug-induced and malignant causes. TB meningitis, however, was always considered in this case. The presentation and CSF findings were consistent with a diagnosis of TB meningitis in an immune-competent individual. Although Ziehl-Neelson staining and CSF PCR were negative, it

Figure 4 Endoscopic photograph showing a mass at the oesophago-gastric junction.

Figure 5 High-power photomicrograph of oesophageal mucosal biopsy demonstrating multiple nests and clusters of poorly differentiated malignant epithelial cells (H&E).

did not exclude the diagnosis. In the absence of an alternative diagnosis, empirical treatment for TB was given. However, repeated CSF culture remained negative for TB and once the diagnosis of LC was made, the anti-TB therapy was discontinued. Cryptococcal meningitis in an immune-competent individual was unlikely. HIV test was negative as were CSF and serum cryptococcal antigens.

OUTCOME AND FOLLOW-UP

The patient was palliated on a combination of dexamethasone, phenytoin and haloperidol. He was transferred to the local hospice where he died peacefully 2 weeks later.

DISCUSSION

LC is a rare and often underdiagnosed manifestation of malignancy in adults.¹ Metastatic malignancy presenting as LC is equally uncommon.² The most common causes are solid tumours such as breast, lung (small cell), melanoma, non-Hodgkin's lymphoma and primary brain tumours. LC occurs very rarely in oesophageal carcinoma. It is even rarer for oesophageal carcinoma to present as LC. A search on PubMed revealed only two previous cases^{3 4} of oesophageal carcinoma in which LC was the presentation.

Figure 6 High-power photomicrograph of oesophageal mucosal biopsy. Positive immunohistochemical staining for cytokeratin CAM 5.2.

Figure 7 Postcontrast T1-weighted MRI brain. Diffuse linear leptomeningeal enhancement consistent with malignant infiltration. No intraparenchymal lesion.

With reference to imaging, a non-contrast CT of brain is the most widely used initial brain imaging in emergency settings to exclude gross lesions. It is relatively insensitive compared to

Figure 8 Postcontrast T1-weighted MRI brain. Diffuse linear leptomeningeal enhancement consistent with malignant infiltration, some nodularity deep in the cerebellar sulci (arrowed). No intraparenchymal lesion noted.

MRI. Even a contrast-enhanced CT may give a false-negative in up to one-third of cases.⁵ Contrast-enhanced MRI is the investigation of choice in LC as it is the most sensitive and specific technique for visualising LC. However, a negative MRI scan does not exclude the diagnosis. A study by Gomori *et al*⁶ found that 12% of patients with LC diagnosed by positive CSF cytology had a negative MRI exam. They also found that MRI was positive in 60% of LC patients with negative CSF cytology.⁶ This would suggest that CSF cytology and MRI are complementary examinations; where if one test is negative, the other should be performed.

Malignancy associated with leptomeningeal disease generally confers a poor prognosis, particularly when associated with solid tumours. Giglio *et al*⁷ reported a case series of 21 patients with LC secondary to gastrointestinal malignancy. In their cohort, eight patients had gastric adenocarcinoma and seven patients had oesophageal carcinoma. The median survival after diagnosis of LC was 7 weeks. Abdo *et al*⁴ reported four cases of LC from oesophageal cancer and all these patients died within 20 days of diagnosis. Treatment goals include symptom palliation, improving or stabilising neurological function and prolonging survival.⁸ Depending on performance status, degree of fixed neurological deficits and cancer burden, treatments can range from radiation therapy, high-dose systemic chemotherapy and intrathecal chemotherapy to symptom palliation only.^{8,9}

Learning points

- ▶ Be suspicious of elderly patients with apparently no medical history who present with altered behaviour and confusion. Do not assume it is secondary to a psychological disorder until an organic cause has been ruled out.
- ▶ If there is a clinical suspicion of leptomeningeal carcinomatosis, multiple, large volumes of cerebrospinal fluid samples are required to make a definitive diagnosis.

Competing interests None.

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