Rare disease

Meningeal and brainstem infiltration by a malignant mesothelioma

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Summary

Malignant mesothelioma is an uncommon neoplasia which primarily involves the pleura or peritoneum. Central nervous system involvement is rare. A rare presentation of metastatic pleural mesothelioma, which had infiltrated the meninges and brainstem, is described. The patient presented with diplopia following a 2-week history of malaise, myalgia, mild headache and diarrhoea. Clinical examination found global areflexia, cerebellar ataxia and bilateral sixth nerve palsies. Differential diagnoses included the Miller–Fisher variant of Guillain–Barre syndrome, malignant meningitis and infectious meningitis. The patient was treated with immunoglobulins, plasmapheresis and corticosteroids; however, he deteriorated and died 31 days after admission. Retrospective examination of the MRI of the brain found diffuse low attenuation changes within the pons and cerebral peduncles. Postmortem examination favoured a diagnosis of an early sarcomatoid malignant mesothelioma of pleural origin with leptomeningeal metastatic deposits.

BACKGROUND

Leptomeningeal metastatic disease secondary to a malignant mesothelioma is an extremely rare condition, with only a handful of case reports to date.

The patient presented with a complicated clinical picture due to the multiple areas of neoplastic infiltration over his neuraxis. This led to difficulty in achieving an antemortem diagnosis, with an initial working diagnosis of Miller–Fisher syndrome being made. This difficulty was secondary to multiple factors. First, many of the tests took several weeks to return. Second, the electromyography (EMG) results supported a diagnosis of Guillain–Barre syndrome (GBS) rather than malignant meningitis. Furthermore, no conclusive results were drawn from the lumbar punctures. And finally, the MRI was initially reported as normal, and only found to have leptomeningeal infiltration on retrospective examination following corresponding changes on a CT brain.

All of these issues highlight the importance of continuing to investigate and to re-evaluate results in order to accomplish a diagnosis in a complex clinical case.

CASE PRESENTATION

The patient was a 70-year-old retired Caucasian railway worker, who had been exposed to asbestos 45 years previously. He presented with a 1-day history diplopia, following a 2-week history of malaise, myalgia, mild headache and diarrhoea. He did not give any history of fevers, weight loss, weakness, or nausea or vomiting. He was an ex-smoker with a 10-year pack history. Prior to his presenting illness he had no other significant past medical history and had been fit and well.

Initial clinical examination found an alert afebrile gentleman with a blood pressure of 130/80 mm Hg and a pulse of 80 bpm (regular in rhythm). Cardiovascular, respiratory and abdominal examinations were unremarkable. Neurological examination demonstrated that he had bilateral sixth nerve palsies with other cranial nerves being intact. Tone was normal, sensation was intact and his power was 5/5 in all four limbs. However, he had a global areflexia, and a cerebellar ataxia, particularly in his lower limbs.

INVESTIGATIONS

Initial blood tests including full blood count, renal function tests, electrolytes, liver function tests, coagulation tests, C reactive protein (CRP) and bone profile, were all normal.

Anti-GQ1b and campylobacter serology were negative, as were all other exclusion screens, which included *Borrelia burgdorferi* immunoglobulin G antibodies, Epstein–Barr virus, mycoplasma pneumoniae, angiotensin-converting enzyme (ACE), HIV, serum protein electrophoresis, *Treponema pallidum* antibodies, *Brucella* antibodies, rheumatoid factor, immunoglobulins, acetylcholine receptor antibody, antinuclear antibodies, ribonucleoprotein, Sm, Ro, La, Scl-70, centromere, Jo-1, dsDNA, antimitochondrial antibodies, anti-liver/kidney microsomal antibodies, antigastroparietal cell and antireticulin antibodies.

Three separate lumbar punctures were performed, demonstrating a lymphocytic picture, with an elevated protein count, and a low glucose. No malignant cells were found in the cerebral spinal fluid (CSF).

CSF cultures and PCR for *Mycobacterium tuberculosis* were negative.

Figure 1 MRI scan showing signal change (arrowed) in the leptomeninges.

CSF ACE levels, cultures and virology screens (herpes simplex virus DNA, varicella zoster DNA, enterovirus RNA, cytomegalovirus DNA, Epstein–Barr virus DNA) were negative.

The first lumbar puncture on day 2 found a white cell count (WCC) of $100 \times 10^6/l$ (differential 99% lymphocytes, 1% polymorphs), a raised protein at 1.53 g/l and a low glucose at 2.4 mmol/l. The second lumbar puncture on day 7 found a WCC of $62 \times 10^6/l$ (differential 87% lymphocytes, 13% polymorphs), a raised protein at 1.49 g/l and a low glucose at 1.4 mmol/l. The third lumbar puncture on day 28 found a WCC of $2.0 \times 10^6/l$, a raised protein of 3.98 g/l and a glucose of 0.9 mmol/l.

Two EMGs were performed; the initial EMG on day 3 was reported as a normal study. The second EMG on day 16 found that there was evidence of a proximal demyelinating polyradiculopathy, and also demonstrated that F wave

latency was absent in the upper and lower limbs. These findings were felt to support but not confirm the clinical diagnosis of GBS.

A chest x-ray was unremarkable showing clear lung fields, and a normal cardiac shadow.

A MRI of the brain was performed on day 2 and was initially reported as normal. A MRI of the spine was not done.

A CT scan of the chest, abdomen and pelvis on day 29 was unremarkable with no evidence of a primary or metastatic malignancy.

A CT scan of the brain on day 29 found subtle diffuse low attenuation seen within the pons and cerebral peduncles. At this point the MRI of the brain was retrospectively re-examined and corresponding signal changes were found within these areas (figures 1–4). It was felt that radiologically these changes represented an encephalitis or other inflammatory process.

Figure 2 MRI scan showing signal change (arrowed) in the leptomeninges.

DIFFERENTIAL DIAGNOSIS

The majority of the investigations took several weeks to process; consequently, the initial diagnosis of the Miller–Fisher variant of GBS was based on the patient’s history and clinical findings of areflexia, ataxia and ophthalmoplegia.

Differential diagnoses included a carcinomatous meningitis, an infectious picture (eg, tuberculous meningitis) or a connective tissue disease.

When the anti-GQ1b, campylobacter serology and the majority of the tests returned as negative, efforts were made to investigate other diagnoses, particularly the diagnosis of malignant meningitis.

TREATMENT

The patient was started on a 5-day course of intravenous immunoglobulin, but by day 12 he had developed widespread 4/5 power limb weakness, and his respiratory func-

tion deteriorated with functional vital capacity dropping to 1.3 litre. Consequently, he was transferred to the intensive therapy unit (ITU) for ventilatory support. On the ITU, he underwent further treatment with plasma exchange therapy and high dose methylprednisolone; however, he failed to respond and rapidly became quadriplegic. Following this, he developed a pneumonia and died 31 days after admission.

OUTCOME AND FOLLOW-UP

Throughout the illness, the diagnosis remained equivocal. The presenting history and clinical features suggested Miller–Fisher syndrome, which had been supported by: (i) the initial report of the MRI brain being normal, (ii) the fact that no malignant cells were found in the CSF and (iii) the supportive findings on the EMG. However, the lumbar punctures were out of keeping for a GBS. Once serology for Miller–Fisher returned as negative, and combined with the

Figure 3 CT brain showing subtle diffuse low attenuation changes within the pons and cerebral peduncles.

results of the lumbar punctures, the CT brain and the retrospective analysis of the MRI, a diagnosis of carcinoma seemed more likely. At this point the patient rapidly deteriorated and died, so consequently a formal diagnosis of malignant meningitis was not achieved until postmortem.

PATHOLOGY

On autopsy, the right pleural cavity was obliterated by dense fibrous adhesions, with a focal area of probable plaque formation. However, despite the microscopic findings, there was no macroscopic suggestion of tumour formation, and there was no lung parenchymal tumour. The external brain (1425 g) displayed an area of light brown discolouration over the anterior brainstem, especially around the ponto-medullary junction, although the macroscopic appearance of internal sections was unremarkable.

Histological examination of the pleura and the brainstem revealed malignant spindle cell neoplasms exhibiting similar features, namely of an atypical spindle cell proliferation in a collagenous stroma with marked atypical mitotic activity. Further sections from the brainstem revealed superficial parenchymal invasion and infiltration of perivascular, perineural and intraneural (abducens nerve) areas. The differential diagnosis at this point included a primary pleural tumour with metastatic meningeal deposits, a meningeal tumour with metastatic pleural deposits, or a primary visceral tumour with pleural and meningeal deposits.

Immunohistochemical studies of atypical spindle cells from the pleural lesion showed diffuse strong positivity for pancytokeratin and patchy positivity for p53, and negativity for epithelial membrane antigen (EMA), S100, calretinin, CK5 and desmin. The proliferation activity (Ki65) was low (under 10%). The tumour cells in the brainstem showed a

Figure 4 CT brain showing subtle diffuse low attenuation changes within the pons and cerebral peduncles.

similar immunoprofile with diffuse strong positivity for pancytokeratin and p53, weak cytoplasmic staining for EMA and negative for S100 and GFAP. Ki67 was low (10–15%).

The morphological similarities between the two malignancies, the immunoprofile of these tumour cells and the clinical history (absence of other visceral or intracranial tumours) favoured a diagnosis of an (early) sarcomatoid malignant mesothelioma of pleural origin with leptomeningeal metastatic deposits ('malignant meningitis') (figures 5–9).

DISCUSSION

Metastatic malignant mesothelioma is an uncommon neoplasia which arises from the pleura or peritoneum, presenting around 40 years after exposure to asbestos. It is associated with occupational asbestos exposure.¹

Pleural mesotheliomas typically present with shortness of breath, cough, chest pain and associated weight loss. Metastases usually spread to the lung, liver, adrenal glands and kidneys.²

Central nervous system involvement is rare but cerebral metastases are described, with the majority being dis-

Figure 5 Pleura, showing focally hypocoelular collagenous thickening with underlying hypercellular areas; zonation corresponding to the tumour (H&E, $\times 40$ magnification).

Figure 6 Pleura, showing malignant spindle cell proliferation in the collagenous stroma (H&E, $\times 200$ magnification).

Figure 7 Pleura, malignant spindle cell proliferation, showing strong positivity for pancytokeratin (immunoperoxidase staining for pancytokeratin, $\times 200$ magnification).

Figure 8 Brainstem, showing malignant spindle cell proliferation infiltrating into the brain parenchyma (H&E, $\times 200$ magnification).

Figure 9 Brainstem, including malignant spindle cell proliferation infiltrating around blood vessels of the meninges, showing strong positivity for pancytokeratin (immunoperoxidase staining for pancytokeratin, $\times 200$ magnification).

covered postmortem.^{2–5} The histopathology in intracranial metastases is often found to be comparable to glioblastoma multiforme. For example, Falconieri *et al*² describe three cases of a spindle cell tumour that focally exhibited pseudopalisading, necrosis and vascular buds.

Meningeal or brainstem involvement is extremely rare. MRI results of leptomeningeal infiltration by a malignant mesothelioma have been reported in the literature. One case showed diffuse leptomeningeal infiltration, bilateral frontal and left temporal haemorrhages and oedema,⁶ and in another case leptomeningeal metastases with contrast enhancement, more prominent in the cerebellar sulci, and changes consistent with acute hydrocephalus.⁷

Leptomeningeal metastases present with a myriad of symptoms and signs which correspond with neurological dysfunction at multiple levels of the neuraxis.^{8–9} Presenting symptoms commonly comprise headache, ataxia, nausea, mental change and lower motor neuron type weakness. Prognosis is poor, with a median survival of 4 months from diagnosis.¹⁰

Learning points

- ▶ Leptomeningeal metastasis secondary to a malignant mesothelioma is extremely rare.
- ▶ A comprehensive history including questioning regarding asbestos exposure, may help in guiding differential diagnosis in certain complex clinical presentations.
- ▶ MRI is an important tool in achieving a diagnosis antemortem.

Competing interests None.

Patient consent Obtained.

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