CASE REPORT

Headache in a young woman: leptomeningeal metastasis as the first presentation of underlying breast malignancy

Poornima Mohan,¹ Marilina Antonelou,² Ophelia Dadzie,³ Simon Dubrey⁴

¹Department of Acute Medicine, Hillingdon Hospital, Uxbridge, UK

²Department of Medicine, Hillingdon Hospital, Uxbridge, UK

³Department of Histopathology, Hillingdon Hospital, Uxbridge, UK

⁴Department of Cardiology, Hillingdon Hospital, Uxbridge, Middlesex, UK

Correspondence to

Dr Simon William Dubrey,
simon.dubrey@thh.nhs.uk

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SUMMARY

A 37-year-old woman presented with a 2-week history of persistent headache in an occipitotemporal distribution. The patient had experienced prior headaches and migraines, but this presentation was characterised by its intensity and duration. There was associated dizziness and blurring of vision in episodes occurring up to 4–5 times per day. Whole body cross-sectional CT imaging and MRI of neuronal axes were normal. Cerebrospinal fluid cytology demonstrated large abnormal pleomorphic cells expressing the tumour marker CA125. Positron emission tomography-fluorodeoxyglucose revealed bilateral axillary and cervical lymphadenopathy as well as increased uptake in the lateral regions of both breasts. These results correlated with MRI breast and mammography findings. Axillary lymph node biopsy showed poorly differentiated adenocarcinoma making the diagnosis of breast malignancy, the most likely primary site of metastatic leptomeningeal disease. In the 6-week interval between initial presentation and diagnosis, the patient deteriorated significantly with the new onset of facial nerve palsy and partial seizures. The treatment intent was palliative, focusing on symptom control with systemic chemotherapy and whole brain radiotherapy.

BACKGROUND

Leptomeningeal metastasis (LM) is a rare and disabling manifestation of extra-neuronal malignancies, most commonly seen in patients with a primary breast malignancy. It can present with a spectrum of neurological features, the most common being headache (45%).¹ Early diagnosis through cerebrospinal fluid (CSF) cytology and or neuroimaging, followed by treatment, can prolong the mean survival from 4–12 weeks to up to 4–6 months.

CASE PRESENTATION

We present the case of a 37-year-old Caucasian woman presenting with a 2-week history of insidious onset occipital-temporal headache, associated intermittent dizziness and blurred vision. The patient had experienced prior headaches and migraines, but this presentation was characterised by its intensity and duration. Her neurological examination was unremarkable. She had a background of simple migraines and asthma. There was no family history of breast cancer. Inflammatory markers, erythrocyte sedimentation rate and renal and liver function tests were all normal; CT of the head was

unremarkable. A lumbar puncture showed an opening pressure of 24 mm Hg, white cell count 8.9×10^9 (lymphocyte predominant 89%) and mildly raised protein. No organisms were seen on Gram stain and acid-fast bacilli tuberculosis culture, and viral PCR for HIV, herpes simplex virus (HSV), cytomegalovirus and Epstein-Barr virus were negative. However, CSF cytology revealed large abnormal lymphocytes of uncertain origin, resembling blast cells. An initial unenhanced MRI of the head was unremarkable. In the interim, the patient deteriorated further; the intensity of the headache became worse, with new onset neuropathology. She developed facial paraesthesia, nystagmus and right-sided facial nerve palsy. A repeat MRI of the head, this time with gadolinium enhancement, was performed 10 days after the initial scan, and continued to reveal no focal intra-axial or extra-axial abnormality. A CT scan of the thorax, abdomen and pelvis revealed small volume lymphadenopathy, most prominent in the left axillae, but no specific features of primary malignancy or features of a definite lymphoproliferative disorder.

The diagnosis became leptomeningeal disease, as a manifestation of metastatic adenocarcinoma, with the primary tumour originating from the breast. After starting chemotherapy, the patient developed malignancy associated complications of lower limb deep venous thrombosis and partial seizures. These were addressed with low-molecular-weight heparin and levetiracetam (250 mg two times a day), respectively.

INVESTIGATIONS

Further cytological analysis of CSF revealed that the large pleomorphic lymphocytes expressed CK7 and CA125. Serum CA125 was also raised to 896 kU/L (normal range 0–35) with normal carcinoembryonic antigen, β -human chorionic gonadotropin and CA19–9 levels.

To further investigate the elevated CA125 levels in serum and CSF, imaging of the breasts was carried out. Radiographic X-ray mammography was initially performed and showed no discrete lesion or microcalcification.

Histology of a left axillary nodal biopsy confirmed pleomorphic, poorly differentiated cells. The biopsy cores were extensively infiltrated by files and small nests of poorly cohesive cells with large pleomorphic hyperchromatic nuclei and moderate cytoplasm. Intracytoplasmic vacuoles were seen with overall appearances suggestive of metastatic malignancy and likely adenocarcinoma (figure 1).

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Immunohistochemistry showed these cells to be positive for MNF116, CK and e-cadherin, while being negative for TTF1, ER, PR, Wt-1, S100, HMB45 and CD45. With the differential now indicating possible primary sites of upper gastrointestinal (GI) tract, pancreatobiliary tract and the genital tract, a second immunochemistry panel was requested. This showed the tumour to be strongly and diffusely positive for CA125, CEA, CDX2 and CK20. Staining with alcian blue/periodic acid-Schiff showed focal cytoplasmic mucin. In addition, the Her-2 receptor status was negative. The potential primary sites now suggested included ovary, pancreatobiliary tract and, possibly, breast ductal carcinoma.

A subsequent MRI (performed in the context of having established the presence of adenocarcinoma in an axillary node biopsy) demonstrated abnormal enhancement in the left and right upper outer quadrants of both breasts. Positron emission tomography-fluorodeoxyglucose demonstrated extensive bilateral 1.5 cm axillary nodal disease, deep cervical lymphadenopathy, with areas of increased uptake in the lateral aspect of both breasts, which could represent a primary tumour. A gynaecology review of scans, including transvaginal ultrasound of the ovaries and examination of the cervix, adnexae and pelvis, were normal. Colonoscopy and upper GI endoscopy were also normal.

These findings supported the diagnosis of leptomeningeal disease, as a manifestation of metastatic adenocarcinoma, with the primary tumour originating from the breast.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of persistent headache with normal brain imaging and lymphocyte predominance on the CSF, includes viral and tuberculous meningitis,¹ as well as lymphoproliferative disorders. Central nervous system lymphoma is a likely differential diagnosis in the context of CSF lymphocytosis. Flow cytometry was used in our patient in an attempt to identify/exclude lymphoid cell lines indicative of haematological malignancies. CSF flow cytometry studies were performed on two different sample occasions and were negative for B and T cell lineage markers. Two lymphocyte populations were identified including around 45% of mature T cells with a CD4:CD8 ratio of four and a second population of abnormal large cells (around 43%) weakly expressing CD45 and CD14.

Mollaret's syndrome is a diagnosis of exclusion in persistent headaches. It is a form of benign, recurrent, aseptic meningitis. Attacks tend to be separated by symptom-free periods and they

resolve with no residual defects. CSF analysis reveals pleocytosis with large lymphocytes. There has been increasing evidence to implicate the HSV-2 in many such cases.²

TREATMENT

The patient was treated with a palliative combination of anthracycline, platinum and fluoropyrimidine chemotherapy.^{3 4}

Subsequently, and following development of partial seizures, the patient completed a course of palliative whole brain radiotherapy (20 Gy in 5 sessions), with the addition of a higher dose dexamethasone (16 mg and tapering according to response).

OUTCOME AND FOLLOW-UP

Unfortunately, the patient progressively deteriorated with new development of partial seizures that occurred 2–3 times a day. She was started on levetiracetam and dexamethasone in combination with whole brain radiotherapy. The case was discussed at the hospital multidisciplinary team, and in view of the presence of leptomeningeal disease, the treatment intent was decided to be palliative with anthracycline, platinum and fluoropyrimidine combination chemotherapy. Community palliative care was organised with regular oncology follow-up. The patient subsequently died 5 months after the initial presentation.

DISCUSSION

LM is a devastating manifestation of extra-neuronal malignancies, most commonly breast (35%), lung (25%) and haematological malignancies (19%). It is estimated that leptomeningeal metastases, for malignancies in general, comprise approximately 4–7% of central nervous system (CNS) metastases,^{5–7} and in breast cancer, represent between 5% and 20% of CNS metastases.^{6 8 9} In patients with breast cancer in whom their metastatic disease is confined to the leptomeninges without parenchymal brain involvement, the prevalence is up to 3.5%.¹⁰

In the literature, most cases describe LM carcinomatosis as the result of a solid primary tumour seeding into the arachnoid and pia maters, via haematogenous spread or direct dissemination of malignant lesions via cerebrospinal fluid.^{11 12} As a result, the entirety of the neuroaxonal system can be affected. Presenting features can range from headaches to seizures and cranial nerve palsies, depending on the main domains of the neuroaxis affected.

The tumour marker CA125, commonly associated with ovarian cancer, was elevated in our patient and is recognised as also being a marker for advanced breast cancer, often pleural involvement and a poor prognosis.^{12–15}

The measurement of levels of CA125 in CSF has a role in the early diagnosis of meningeal carcinomatosis and appears highly sensitive.¹⁶ Levels of tumour markers, including CA125, may also help in predicting a response to therapy and outcome.^{10 15} CSF tumour marker levels may help in the selection of patients who may benefit from further treatment or in withholding treatment from those not responding.

When to order imaging studies on patients presenting with headache +/- additional symptoms is an important part of their initial assessment; guidelines from National Institute for Health and Care Excellence () and the American College of Emergency Physicians provide an excellent reference.^{17 18} The National Comprehensive Cancer Network (NCCN) recommends CSF cytology for direct visualisation of tumour cells as the gold standard diagnostic test. This is followed by extensive neuroaxonal imaging using gadolinium-enhanced MR scanning (gad-MRI) to identify deposits along the neuroaxis and to detect leptomeningeal, dural or cranial nerve enhancement.^{11 19}

Figure 1 Histology from left axillary node biopsy. Lymph node cores densely infiltrated by poorly cohesive pleomorphic cells, exhibiting intracytoplasmic vacuoles (H&E at $\times 20$).

MRI has resolution limitations in the detection of microscopic disease,⁵ with a reported sensitivity for the detection of leptomeningeal disease lying between 65% and 71%.^{20–21} In addition, it is estimated that up to 1/3 of cases with leptomeningeal disease may be asymptomatic.²²

This condition entails a devastating prognosis, and in untreated groups the survival can be as short as 4–12 weeks, due to rapid onset debilitating neurological symptoms, resulting in a terminal event.³ It is of prime importance to perform appropriate investigations to confirm the diagnosis and promptly refer for specialist input. The aims of treatment with chemotherapy or radiotherapy is primarily to maintain the patient's quality of life, provide neurostabilisation of symptoms and improve survival.^{11–23–24} Treatment options include radiation therapy and chemotherapy (either systemic or intrathecal), and, in some cases, surgical intervention for the management of hydrocephalus. Management is guided by the results of advanced imaging studies, tumour markers (CSF levels may help) and the patient's functional status and willingness to undergo such therapies.²² Radiotherapy is likely to be used for bulky disease or that causing obstruction to CSF flow, in such contexts it is largely in a palliative role.

Surgical procedures are used for relief of CSF outflow, and in such circumstances are usually addressed with insertion of a ventricular-peritoneal shunt. Intrathecal chemotherapy carries the advantage of gaining access across the blood–brain barrier and is likely to include liposomal cytarabine, methotrexate or thiotepa. A major disadvantage of intrathecal chemotherapy is the possibility of inducing a chemical meningitis and, more rarely, leucoencephalopathy. The results of comparative trials between these various agents and combinations thereof are summarised elsewhere,^{22–25–26} but have shown little difference in survival rates between the different agents. A recognised pathway in responsive patients might include radiation to bulky tumours and symptomatic sites (+/– placement of a ventricular catheter/shunt to allow drug administration and cerebro spinal fluid pressure relief, respectively), followed by intrathecal chemotherapy.²⁶ A recent review summarises the latest advances in the management of leptomeningeal cancers.²⁷

Learning points

- ▶ When assessing persistent headaches, metastatic disease is an important differential even in the absence of systemic symptoms.
- ▶ Thorough investigation of persistent headaches with cerebrospinal fluid cytology is important in making the diagnosis, as MR and cross-sectional imaging may be normal.
- ▶ In light of the advances made in the therapy of breast and other solid tumour malignancies, prompt diagnosis can prevent progression of disease and improve quality of life.
- ▶ This case highlights the difficulties in investigating any malignant scenario with an apparently unknown primary site.⁸
- ▶ Guidelines on when to order imaging studies in young and adult patients presenting with acute headaches are useful resources for management.^{17–18}

Competing interests None declared.

Patient consent Obtained.

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