CASE REPORT

Dysphagia and anorexia as presentations of leptomeningeal carcinomatosis

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SUMMARY

A 61-year-old woman presented to the emergency department, with a 4-day history of isolated oropharyngeal dysphagia associated with anorexia and weight loss over the previous 4 weeks. She had no other focal neurological symptoms and no deficits on examination. She had been in a 4-year remission of breast cancer postmastectomy and chemoradiation. Neuroimaging showed enhancement of cranial nerves VII, VIII, cisternal segment of cranial V, dorsal and ventral surfaces of the cervical and thoracic cord as well as enhancement of the cauda equina. Cerebrospinal fluid analysis revealed carcinomatous cells. The patient was diagnosed as having leptomeningeal carcinomatosis secondary to lobular breast cancer and was started on radiation therapy, antihormonal treatments and intrathecal methotrexate.

BACKGROUND

This case is important because it will allow clinicians to appreciate that, typically, a patient with leptomeningeal carcinomatosis (LMC) presents with symptoms such as oropharyngeal dysphagia and anorexia, and is thus diagnosed as having LMC. As will be further discussed later on in this paper, patients with LMC typically present with other focal neurological deficits.

CASE PRESENTATION

We describe a case of a 61-year-old woman with a history of stage IIIc lobular breast cancer (oestrogen/progesterone receptor positive), treated 4 years earlier with a right-sided mastectomy, chemotherapy and radiation therapy, who had since been in remission (confirmed by positron emission tomography scan), presenting with a 4-day history of difficulty swallowing and weight loss. She described initially being unable to swallow solid foods, with subsequent difficulty swallowing liquids a few days later. She had a sensation of dysphagia and odynophagia associated with nausea and retching leading up to her hospitalisation. She also reported anorexia with a 20-pound weight loss over the previous 4 weeks, independent of dysphagia. She denied headaches, weakness, incontinence, dysaesthesias, anaesthesia, gait disturbance and incoordination. She denied chewing abnormalities, dysarthria, dysgeusia and facial asymmetry.

Her vitals in the emergency department were: temperature 100.5°F, blood pressure 113/85, pulse 86, respiratory rate 18 and pulse oximetry measurement 93% on room air.

On physical examination, the patient appeared cachectic with a fever of 100.5°F, but was otherwise in no apparent distress. There was no palpable lymphadenopathy, and lungs were clear to auscultation. There were neither Kernig's nor Brudzinski signs present. Neurologically, the patient was alert and fully oriented. Cranial nerve (CN) testing was intact except for a diminished gag reflex bilaterally. There was no obvious tongue weakness nor were there accessory nerve deficits. No facial asymmetry was noted and the muscles of facial expression were intact. Hearing was within normal limits. Strength and sensory testing were normal and no cerebellar findings were noted in the limbs. Gait assessment revealed a narrow-based gait with slight imbalance on tandem gait but was otherwise normal.

CT with intravenous contrast (Optiray 320) of the chest, abdomen and pelvis were negative for malignancies. MRI (MRI GE, 3 T) of the brain with and without gadolinium (DTPA) contrast revealed abnormal enhancement of CNs VII and VIII within the internal auditory canal with enhancement of the cisternal segment of CN V suspicious for a leptomeningeal process (figure 1). MRI of the cervical and thoracic spine revealed

Figure 1 Brain MRI—axial T1-weighted isotropic three-dimensional fast-spoiled gradient echo (BRAVO) sequence with gadolinium revealing enhancement along the surface of the pons (closed arrows) and cerebellar folia (open arrow) suggestive of leptomeningeal disease.

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enhancement of the dorsal and ventral lower thoracic spinal cord, conus medullaris and nerve roots also suspicious for an underlying leptomeningeal process (figure 2).

Cerebrospinal fluid (CSF) analysis revealed marked cytoalbuminaemic dissociation with protein of 1728.9 mg/dL, with mild pleocytosis and normal glucose. Cytology revealed atypical cells suggestive of carcinoma both singly and in loose aggregates (figure 3). Immunostaining of cytology revealed oestrogen and progesterone receptor positive cells without Her2/neu receptor staining (figures 4–6).

During her hospitalisation, the patient developed bilateral lower extremity weakness and was found to have additional areas of metastatic disease in the sacrum. Lumbar radiotherapy was recommended for treatment of additional areas of disease in addition to radiographic evidence of cauda equina involvement with LMC. Radiation therapy of the lower back was given at 2300 cGy over 7 days. The patient received dexamethasone, letrozole and capecitabine. An Ommaya (Integra) reservoir with ventricular shunt was placed and intrathecal methotrexate initiated.

INVESTIGATIONS

- ▶ MRI of the brain
- ▶ MRI of the lumbar spine
- ▶ MRI of the thoracic spine
- ▶ MRI of the cervical spine
- ▶ Lumbar puncture

DIFFERENTIAL DIAGNOSIS

- ▶ Viral meningitis
- ▶ Bacterial meningitis
- ▶ Fungal meningitis
- ▶ Tuberculosis meningitis
- ▶ Infectious encephalitis
- ▶ Autoimmune encephalitis
- ▶ Hashimoto's encephalitis
- ▶ Rasmussen encephalitis
- ▶ HIV encephalitis
- ▶ Limbic encephalitis

Figure 2 Brain MRI—axial T1-weighted isotropic three-dimensional fast-spoiled gradient echo (BRAVO) sequence with gadolinium revealing enhancement along bilateral vestibulocochlear nerves.

Figure 3 MRI of the lumbosacral spine—sagittal T1-weighted sequence with gadolinium revealing enhancement along the surface of the conus medullaris with clumping of the cauda equine.

TREATMENT

- ▶ Radiation therapy
- ▶ Intrathecal methotrexate chemotherapy
- ▶ Systemic chemotherapy
- ▶ Antihormonal treatment
- ▶ Corticosteroids

OUTCOME AND FOLLOW-UP

The patient was managed through a multidisciplinary approach involving neurology, oncology, radiation oncology and neurosurgery. An Ommaya reservoir was placed for administration of intrathecal chemotherapy. The patient received 7 days of radiation therapy for a total of 2300 cGy to the lumbar spine, 2 weeks before the start of intrathecal methotrexate chemotherapy. She received a daily dose of dexamethasone, as well as a one-time

Figure 4 Cerebrospinal fluid, tumour cells, light microscope (Papanicolaou stain, ×400). Tumour cells are discohesive, with hyperchromatic nuclei and high nuclear-cytoplasmic ratio, consistent with metastatic breast carcinoma. The picture was taken with a Nikon eclipse Ni microscope using an iDS-5i2 camera.

Figure 5 Immunostaining—cerebrospinal fluid, cell block, tumour cell cytoplasm are strongly expressing pan-keratin (left) and mammaglobin (right; $\times 400$). The picture was taken with a Nikon eclipse Ni microscope using an isDS-5i2 camera.

injection of letrozole in the hospital. Her next dose of letrozole was scheduled for 2 weeks later at her outpatient appointment, along with capecitabine.

DISCUSSION

LMC is defined as infiltration of the pia mater and arachnoid membrane by malignant cells. LMC can be limited to the meninges but can also occur in association with parenchymal invasion of the central nervous system (CNS) with or without dissemination into the ventricles. The incidence in the cancer population ranges from 5% to 8%.¹ Specifically, 2–5% of patients with breast cancer may develop LMC.² It is the most common solid tumour to exhibit leptomeningeal metastases.³ Lobular breast cancer is more likely to lead to LMC compared with other breast cancer subtypes. This increased risk could be due to a cell size or shape with physical properties that favour certain areas with microanatomy that is more conducive to trapping these types of cells.⁴ There is evidence in the literature that differences in the expression of E-cadherin, tenascin, vitronectin and thrombospondin expression have been noted in lobular cancer, which may be a reason for the increased incidence.⁵

It is not uncommon for most patients to have intraparenchymal brain metastases concurrent with LMC and widely disseminated cancer.⁶ LMC can occur months to years after the diagnosis; in one study, duration from initial diagnosis to LMC was approximately 25 months.⁷

Unlike other cancers that affect the CNS, the clinical signs and symptoms of leptomeningeal metastasis are highly variable because they affect the entire neuraxis. Tumour cells reach the leptomeninges by direct extension or haematogenous spread and disseminate throughout the neuraxis by the flow of the

CSF.⁶ Nevertheless, the most common initial symptoms include headache, nausea, vomiting, backache, polyradiculopathies, incontinence, confusional state, lower motor neuron weakness and sensory abnormalities.⁸ Focal neurological signs and seizures may be seen, and about half the patients develop hydrocephalus.⁹

Isolated oropharyngeal dysphagia with anorexia as the presenting symptom of LMC is unusual since most cases are associated with prominent neurological deficits. This type of presentation is primarily seen in isolated gastrointestinal malignancies with LMC in 0.14% of patients with gastric adenocarcinoma and 0.16% of patients with oesophageal adenocarcinoma.¹⁰

Only 5% of patients with LMC present with dysphagia, typically in addition to other neurological symptoms including hearing or vision changes, weakness and loss of facial sensation. Other manifestations such as vertigo, nausea, vomiting, headache and encephalopathy can occur as a consequence of direct intraparenchymal involvement or subsequent development of obstructive hydrocephalus. Spinal root involvement can lead to radicular symptoms and drop metastases can lead to cauda equina syndrome, resulting in bladder and bowel dysfunction.¹⁰

Lumbar puncture in patients with LMC typically reveals increased opening pressure >20 cm H₂O, usually ranging between 20 and 40 cm H₂O. CSF pleocytosis is typically lymphocyte predominant and ranges between 10 and 202 WCC/mm³. CSF protein concentration is also elevated (>45 mg/dL) and can be as high as 8.0 g/L. Hypoglycorrhachia ($<60\%$ of serum glucose) is also seen in about 50% of patients with LMC.¹¹ A definitive diagnosis of LMC can only be confirmed by the presence of malignant cells in the CSF. CSF

Figure 6 Immunostaining—cerebrospinal fluid, cell block, tumour cell nuclei are expressing ER (left) and PR (right; $\times 400$). The picture was taken with a Nikon eclipse Ni microscope using an isDS-5i2 camera.

cytology remains the gold standard for diagnosis of leptomeningeal metastasis with high specificity (>95%) and low sensitivity (<50%).¹⁰

Overall, the prognosis of LMC is poor. The median survival in untreated patients is 4–6 weeks, which may increase to 4–6 months with aggressive treatment.¹¹ Treatment options in patients with leptomeningeal metastases include intrathecal treatment with intraventricular methotrexate given twice weekly via an Ommaya reservoir.¹² Cytarabine and thiopeta can be given intrathecally and are used principally in haematological malignancies. Radiation therapy is recommended as a treatment measure to reduce symptoms, or when combined with intrathecal chemotherapy, to reduce CSF flow disturbances. Focused beam radiation is applied locally to sites of bulky disease. If intraparenchymal metastases are also present, treatment should consist of whole brain radiation therapy followed by radiation therapy.¹³

There are several ongoing studies for treatment of LMC. Topoisomerase inhibitors are as effective as traditionally used intrathecal agents, and both etoposide and topotecan hydrochloride have little toxicity, which may be useful as an adjunct to other agents or as a prophylactic treatment. Mafosfamide may be useful in childhood CNS malignancies to help delay or avoid radiation exposure. Since there is almost no toxicity and some efficacy, sodium iodide I 131 (¹³¹I) is also presently being studied in clinical trials.¹⁴

LMC is a devastating manifestation of cancer recurrence and it is therefore imperative to have a high level of suspicion in patients with presumptive oncological remission. LMC can present with a variety of clinical symptoms ranging from isolated dysphagia and anorexia, to full-blown meningitis and cranial neuropathies. It is imperative to remain vigilant in managing patients presumptively in cancer remission since aggressive treatment needs to be initiated in cases of LMC.

Patient's perspective

- After arriving at the hospital's emergency room, I had to submit to many tests. Of course after finding out the diagnosis, I was devastated to hear I had stage 4 brain and spine cancer. Within a 3-week period I was very happy to see a treatment plan set up for radiation and chemo. I was very pleased to get the proper care and treatment for my cancer as we did not want it to move forward. I have kept myself in very high spirits and plan to remain the same throughout my stay and my recovery at home.

Learning points

- Minor symptoms such as dysphagia with anorexia can be a presenting symptom for patients with underlying leptomeningeal carcinomatosis, despite the absence of other presenting symptoms.
- Time after remission for leptomeningeal carcinomatosis can occur years after treatment for initial malignancy.
- The importance of cerebrospinal fluid cytology in diagnosis cannot be overstressed.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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