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Oesophageal adenocarcinoma presenting with synchronous brain metastases

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SUMMARY

Brain metastases are rare and poorly understood complications of oesophageal carcinoma. This report describes a case of brain metastasis as the initial presentation of oesophageal adenocarcinoma. The rarity and the lack of prospective clinical trials of brain metastasis in oesophageal cancer result in the absence of treatment guidelines. Common treatments for brain metastases, regardless of tumour of origin, are applicable to oesophageal brain metastases and include surgical resection, whole brain radiation therapy, stereotactic radiosurgery, chemotherapy/immunotherapy and/or symptomatic control with steroids and anticonvulsants.

BACKGROUND

Oesophageal carcinoma is a common malignancy worldwide and carries an unfavourable prognosis. The median survival is less than 1 year, and a 5 year survival rate is around 10% in Western countries for advanced stages.[1 2] Oesophageal cancer commonly metastasises to the liver, lungs and bones, whereas brain metastases are extremely rare. Three large retrospective studies evaluating thousands of cases of oesophageal carcinoma found the rate of brain metastasis to be between 1.61% and 2.2%.[1 3 4] The median survival time for this patient population was found to be between 3.8 and 8.7 months, with 1 year survival rates between 5.8% and 35% across the three studies. An analysis of the US Surveillance Epidemiology and End Results (SEER) database (2010–2018) similarly found the rate of brain metastasis from oesophageal carcinoma to be 1.8%, with a median survival of 5 months.[5]

Due to the rarity of brain metastases from oesophageal carcinoma, no firm treatment guidelines have been established. In the aforementioned studies, various treatments such as whole brain radiation therapy (WBRT), surgical resection, stereotactic radiosurgery (SRS), chemotherapy/immunotherapy or some combination of these were discussed for the treatment of brain metastases.

CASE PRESENTATION

A man in his mid-50s with a history of gastro-oesophageal reflux disease, previous heavy alcohol use, and a 40-pack-year smoking history presented to the emergency department with dysphagia, hiccups, headache and a 30 pound weight loss. He endorsed that the headaches were diffuse, global and dull in nature and had started approximately a month prior with increasing frequency and intensity. The physical examination revealed left hemiparesis, moderate dysmetria on finger-to-nose testing on the left and flat affect.

INVESTIGATIONS

A contrast-enhanced MRI of the brain was performed, which showed a heterogeneously enhancing 6.2 cm right frontal lobe mass with significant vasogenic oedema and local mass effect, including effacement of the supratentorial ventricles and a 17 mm leftward midline shift. Numerous additional supratentorial and infratentorial small enhancing lesions were also identified, compatible with multifocal intracranial metastases (figure 1).

A contrast-enhanced CT scan of the chest, abdomen and pelvis identified circumferential oesophageal wall thickening with near-complete obliteration of the lumen at the gastro-oesophageal junction. The CT was also notable for distal para-oesophageal and left supraclavicular lymphadenopathy, bilateral scattered pulmonary nodules, multiple hepatic lesions measuring up to 4.1 cm and multiple aortocaval lymph nodes. Laboratory results were notable for significantly elevated tumour markers, CA 19-9 (456 U/mL) and CEA (225.4 ng/mL).

The patient underwent craniotomy and resection of the right frontal lobe mass with significant improvement in his neurological symptoms. Oesophagogastroduodenoscopy (OGD) during

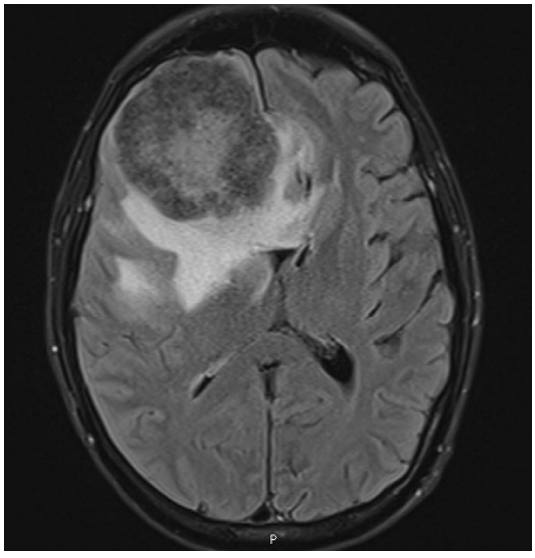

Figure 1 Contrast-enhanced MRI demonstrates a heterogeneously enhancing 6.2 cm right frontal mass with vasogenic oedema and local mass effect, including effacement of the supratentorial ventricles and 17 mm leftward midline shift.

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the same hospital admission showed a partially obstructing, malignant-appearing, large and friable oesophageal tumour in the lower third of the oesophagus, extending into the proximal stomach. An oesophageal stent was sutured in place during this OGD, which allowed the patient to resume eating by mouth.

The microscopic examination of the surgically resected frontal lobe brain tumour demonstrated a moderately differentiated glandular neoplasm with highly pleomorphic, mitotically active and cytologically atypical cells with glandular formation. The tumour demonstrated strong, nuclear CDX2 staining (caudal type homeobox transcription factor 2) and positive SATB2 nuclear staining (special AT-rich sequence-binding protein 2); CK20 (cytokeratin 20) was focally positive, and CK7 (cytokeratin 7) was negative. Given the histological and immunohistochemical findings, in the context of the concurrent oesophageal mass seen endoscopically, the frontal tumour was confirmed as a metastatic oesophageal adenocarcinoma. Immunohistochemistry staining of the tumour additionally demonstrated PD-L1 (programmed death ligand 1) positivity (combined positive score: 3), HER2 (human epidermal growth factor 2) positivity (3+) and claudin-18 negativity. Next-generation sequencing of the tumour sample detected a SMAD4 (mothers against decapentaplegic homolog 4) deletion, an MYC amplification and microsatellite stable status.

TREATMENT

The patient was treated with WBRT with hippocampal avoidance. As an attempt to decrease the risk of cognitive impairment from WBRT, the patient was started on oral daily memantine.[6] He responded favourably to the frontotemporal surgical resection and the ensuing WBRT. The patient went on to receive modified FOLFOX (folinic acide, fluorouracil, oxaliplatin) plus nivolumab and trastuzumab, with a partial response according to RECIST (response evaluation criteria in solid tumors) criteria, including near resolution of the liver metastases and no progression of any of the brain metastases.

OUTCOME AND FOLLOW-UP

The patient completed 11 cycles of FOLFOX plus nivolumab and trastuzumab to date. Repeat brain MRI at 3 and 6 months following resection and WBRT showed a dramatic decrease in the size of the primary frontotemporal brain lesion. He continues to live independently and enjoys several prediagnosis pastimes.

DISCUSSION

Brain metastasis is an uncommon and poorly understood complication of oesophageal carcinoma. This is the first report of a synchronous diagnosis of oesophageal cancer with brain metastases. No prior retrospective studies evaluating brain metastasis from oesophageal carcinoma list data on synchronous metastases.[1–5] Brain imaging in the workup for oesophageal carcinoma is rarely performed, so the detection of synchronous brain metastases is naturally difficult.[7]

There is difficulty in predicting outcomes for oesophageal brain metastases. An early study found the 1 year survival rate of oesophageal brain metastases to be 5.8%, and a more recent study found a rate of 35%.[1 4] The median survival times remain less than 1 year in many studies.[1 3–5] Modern treatment approaches such as SRS, hippocampal avoidance and memantine are becoming available to patients with brain metastasis, seemingly improving prognosis at least in oligometastatic disease.[6 8] Advances in SRS may also allow for treatment of brain metastases with lower risks of neurocognitive decline when compared with WBRT.[4] Preoperative planning and surgical techniques are improving across brain metastases from all solid tumours, allowing for increased preservation of normal brain parenchyma during resections.[7] Patients with multiple brain metastases currently remain poor surgical candidates, but they may qualify for SRS if less than 12 parenchymal lesions exist. Overall, the outcomes and prognosis remain guarded despite these improvements.

Some factors correlated with a worse prognosis for oesophageal brain metastases include poor performance status, numerous (≥4) brain metastases, liver metastases and higher recursive partitioning analysis scores.[3 4 9] Some factors associated with better prognosis include solitary brain lesions, good performance status, surgical treatment and treatment with a combination of surgery and radiotherapy.[1 3 4 6] There is also emerging data to suggest that oesophageal tumours driven by p53 loss, P16 INK/ARF loss, IGF1R activation or Notch pathway upregulation might indicate aggressive phenotypes of oesophageal cancer that could generate early metastatic manifestations.[10]

The immune phenotype of oesophageal cancer is also important for prognosis and treatment. Systemic chemoimmunotherapy likely has some impact on the control of brain metastases. For example, checkpoint inhibitor (CPI) immunotherapy, a standard first-line treatment for metastatic oesophageal cancer, is suggested by the authors of the only review article on the topic.[11] By extension from similar solid tumour studies, it is presumed that CPI therapy may have activity in oesophageal cancer; studies in melanoma, non-small cell lung cancer and colon cancer show control of brain metastases by CPI.[12–15] To date, there is only one case report of CPI use in oesophageal cancer with brain metastasis, and it showed that CPI therapy with toripalimab successfully controlled asymptomatic brain metastasis in oesophageal squamous cell carcinoma.[16]

A meta-analysis of 48 studies representing 136 patients with brain metastases from oesophageal carcinoma suggests that the cause of death in these patients was often independent of brain metastasis.[17] This underscores that there is still much to uncover, and further studies on detecting and treating oesophageal cancer are needed. Prospective clinical trials evaluating oesophageal cancer with brain metastases are lacking, given their rarity in this population and associated short survival times; as a result, no treatment guidelines have been established. Therefore, we recommend the use of existing treatments for brain metastases, regardless of tumour origin, including surgical resection when possible, radiation therapy with either WBRT or SRS, chemotherapy/immunotherapy and symptomatic control with steroids and anticonvulsants.

Learning points

- Brain metastases are rare and poorly understood complications of oesophageal carcinoma.
- Brain metastases from oesophageal cancer can be treated with a combination of surgery, radiation and systemic therapies.
- Median survival times for oesophageal brain metastases remain low at less than 1 year, but the prognosis seems to have slightly improved over the last several years.
- Improvements in survival are owed to advances in stereotactic radiosurgery and systemic therapies. Checkpoint inhibitors might have activity in oesophageal brain metastases.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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