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Case Report

Hemorrhagic Brain Metastasis as the Initial Manifestation of Esophageal Adenocarcinoma

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Abstract

Esophageal carcinoma metastasis to the brain is very rare with less than 300 cases published worldwide. The reported incidence rates of esophageal carcinoma metastases to the brain range from 0.3% to 13%. It is associated with a worse prognosis than brain metastases from other solid tumors. The most common form of metastasis is cystic lesions while hemorrhagic metastasis represents a rare subset of an infrequent entity. It is extremely rare for esophageal carcinoma to present as an isolated brain metastasis with only three cases reported worldwide. These cases were misdiagnosed as meningitis, a pituitary tumor, and glioma. This paper reports the first case of hemorrhagic brain metastasis as the initial and only manifestation of esophageal adenocarcinoma worldwide. Although extensive work up to search for malignancy is a routine procedure in patients with metastatic brain disease, upper gastrointestinal endoscopy, which is rarely done as part of the work up should be included. Esophageal cancer continues to be challenging to manage with very limited therapeutic options. To date, the clinical outcome after treatment is unsatisfactory, and prognosis is poor. Further research is required to identify better treatment approaches and improve the survival of patients. This paper is an urgent call for action to design chemotherapeutic agents that target tumor cells in the blood and different body organs and has the ability to cross the blood–brain barrier with an acceptable side effect profile. This is mainly because metastatic brain disease has become more common in young age group.

Keywords: Brain Hemorrhagic Metastasis; Esophageal Adenocarcinoma; Initial Manifestation.

Introduction

Metastasis is by far the most common type of brain malignancy in adults. Esophageal carcinoma metastasis to the brain is very rare with less than 300 cases published worldwide. The reported incidence rates of esophageal carcinoma metastases to the brain range from 0.3% to 13%. It is associated with a worse prognosis than brain metastases from other solid tumors. The most common form of metastasis is cystic lesions while hemorrhagic metastasis represents a rare subset of an infrequent entity. It is extremely rare for esophageal carcinoma to present as an isolated brain metastasis with only three cases reported worldwide. These cases were misdiagnosed as meningitis, a pituitary tumor, and glioma. In this paper, we report the first case of hemorrhagic brain metastasis as the initial manifestation of esophageal adenocarcinoma. In addition, we are adding upper gastrointestinal tract endoscopy as part of the routine work–up of metastatic brain disease of unknown primary. This report is an urgent call for more research in the field of therapy of esophageal cancer.

Case Report

A 28–year–old previously healthy male presented to the local hospital with a history of headache that started four months ago. The headache was occipital but then became holocephalic with no specific time of occurrence. The headache was progressive, and over the last two days, he became ill which necessitated visiting...
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the emergency department. There was no nausea, vomiting, visual symptoms, ataxia, or weakness. When he went to the emergency department, he was a sick-looking person with a blood pressure of 150/100 mmHg and heart rate of 70 beats per minute. His neurological examination showed right-side hemiplegia with brisk reflexes and right upgoing toe. In the local hospital, a brain computed tomography (CT) scan was done which showed multiple brain hemorrhages, the largest of which is located in the left parietal lobe (Figure 1). He underwent an urgent craniotomy and evacuation of a large left parietal hematoma. The patient was transferred to us post-operatively for further management. In our hospital, a brain CT scan showed multiple acute/subacute hematomas in the brain, namely in the right cerebellum and the left parietal lobe. It was felt that his brain imaging suggests space-occupying lesions and brain metastases. Workup to find the primary malignancy was performed including CT scan of the chest, abdomen, and pelvis which showed a small enhancing necrotic node at the level of the lower esophagus and subtle lower esophageal wall thickness. Other than that, there was no evidence of any other metastases in lungs, liver, or other lymphadenopathy in the body. A magnetic resonance imaging (MRI) of the brain confirmed the presence of multiple hemorrhagic metastatic space-occupying lesions from a distant primary (Figure 2). There was no obvious primary in the thyroid, kidney, or skin on examination or on other imaging. A testicular ultrasound was negative. The patient underwent an esophagogastroduodenoscopy in addition to colonoscopy. The esophagogastroduodenoscopy showed a lower esophageal fungating mass at the gastroesophageal junction measuring around 5 cm that is friable and easy to bleed from which multiple biopsies were taken (Figure 3). Final pathology confirmed the diagnosis of moderately–differentiated adenocarcinoma (stage TX, N1, M1). Immunohistochemistry was strongly positive for CK–7 and negative for CK–20. EMA was strongly positive. Alfa–fetoprotein and beta hCG were negative. HER–2 was equivocal at 2+ (Figure 4). The patient was started on high--dose of dexamethasone 8 mg every 8 hours. He received a whole brain radiotherapy with a dose of 20 Gy in 5 fractions in addition to a concomitant boost to multiple metastatic lesions in the brain to 7 lesions with a dose ranging between 25 to 35 Gy in 5 fractions. The patient responded very nicely to radiotherapy. His dysphasia improved and he was able to speak normally only a few days after completion of radiotherapy. A repeat CT scan of the brain was done in the interim and showed a stable appearance of his hemorrhagic brain lesions.

Figure 1: CT scan of the brain showing multiple brain hemorrhages, the largest of which is located in the left parietal lobe.

Figure 2: MRI of the brain showing multiple hemorrhagic metastatic space-occupying lesions from a distant primary.

Figure 3: Esophagogastroduodenoscopy showing a lower esophageal fungating mass at the gastroesophageal junction measuring around 5 cm that is friable and easy to bleed.
His neurological examination still shows complete loss of power on the right side of the body in addition to left-sided homonymous hemianopsia. The rest of his cranial nerve examination was unremarkable. The patient requested to be transferred to another country for further treatment that could be as well experimental.

**Discussion**

Acute bleeding into a metastasis represents less than 1% of hematomas in neurosurgical series and 5.5% in autopsy studies. Intratumoral hemorrhage can be a significant factor in the management of some types of brain metastasis. Hemorrhage may be confined to the metastatic brain tumor itself, exist as intracerebral hematoma intermixed with scattered tumor fragment, or occur in the area immediately adjacent to the tumor. The mechanism of intratumoral hemorrhage could be related to loss of vessel integrity, necrosis of parts of the tumor, and neovascularization. Tumor type rather than lesion size appears to be related to bleeding tendency. Hemorrhagic metastatic tumor range in size from microscopic tumor deposits to several centimeters in diameter. Hemorrhagic metastatic is most common in patients with malignant melanoma and germ cells tumor. The imaging characteristics of our patient were suggestive of hemorrhagic metastasis. These include the presence of several non—contiguous enhancing lesions, hemorrhage occurrence in the vascular border zone regions and white matter junctions with no occurrence in the basal ganglia region, and enhancement adjacent to the blood clot. In addition, the neoplastic lesions do not display the usual pattern of hematoma resolution on serial imaging studies.

Esophageal cancer is the third most common gastrointestinal cancer and the seventh most common cause of cancer—related mortality internationally. Its onset is typically characterized by local infiltrative growth and lymph node invasion. It affects men four times more than women and carries poor prognosis with a 5—year survival rate of 17—23%. Unfortunately, 50% of patients with esophageal cancer have metastatic disease at the time of diagnosis. With local disease progression, metastases can develop in lymph node, liver, lung, bone, adrenal, peritoneum, and brain tissues via hematogenous spread.

Brain metastasis has been reported in 0.3% to 13% of patients with esophageal cancer. The incidence of brain metastasis from a known primary cancer is almost equal to that of brain metastasis where the initial cancer is unknown. Brain metastasis in metastatic esophageal cancer mostly occurs via arterial circulation. Tumor cells seed in small arterial vessels or capillaries in the white—matter—cortex border zone, especially in the watershed areas. Metastasis is more frequent in deep and midline structures including the basal ganglia and cerebellum. In western countries, the most common histology in both primary tumor and brain metastasis is adenocarcinoma. However, the most common pathology for east Asia is squamous cell carcinoma. The most common symptoms of brain metastasis from esophageal cancer include fatigue, headaches, seizures, cerebellar dysfunction, and mental changes. Rapid mental deterioration, cerebellar signs, and hydrocephalus suggest posterior fossa lesions, while cranial nerve lesions indicate brainstem metastasis.

Brain metastasis usually occurs in patients with a known malignancy or could be discovered during the routine workup of such patients. Unfortunately, most of patients with cancer of unknown primary origin will remain unknown for a period of time despite extensive investigations. Patients with brain lesions suspicious of metastasis and no history of other tumors typically have extensive and expensive diagnostic investigations to identify the primary cancer. Routine cancer screenings including a whole—body positron emission tomography scan and conventional diagnostic modalities such as CT and/or MRI are important in detecting unknown primary tumors.

Treatment options for brain metastases from esophageal cancer include surgical resection, whole brain radiation therapy, and stereotactic radiosurgery. Whole brain radiation therapy improves the neurological symptoms and prevents the development of new metastatic lesions in the short term. However, it does not significantly improve the long—term survival. With new targeted therapeutics in esophageal carcinoma and more effective control of systemic disease, more cases of brain metastasis from this lethal disease may occur. Therapies that cross the blood—brain barrier and reach the brain targeting brain lesions are highly needed. Temozolomide
is an orally administered alkylating prodrug that is locally metabolized to its active form. It showed promise in metastatic brain lesions from solid tumors with an acceptable toxicity profile. Prognostic indicators in brain metastases from esophageal cancer include primary tumor stage and extent of systemic disease, functional status, and age. The survival of patients ranges from 2 weeks to 2 years after the diagnosis of brain metastasis\(^1\).

**Conclusion**

This paper reports the first case of hemorrhagic brain metastasis as the initial and only manifestation of esophageal adenocarcinoma worldwide. Although extensive work up to search for malignancy is a routine procedure in patients with metastatic brain disease, upper gastrointestinal endoscopy, which is rarely done as part of the work up should be included. Esophageal cancer continues to be challenging to manage with very limited therapeutic options. To date, the clinical outcome after treatment is unsatisfactory, and prognosis is poor. Further research is required to identify better treatment approaches and improve the survival of patients. This paper is an urgent call for action to design chemotherapeutic agents that target tumor cells in the blood and different body organs and has the ability to cross the blood–brain barrier with an acceptable side effect profile. This is mainly because metastatic brain disease has become more common in young age group.

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