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Primary Malignant Melanoma of the Esophagus: Prognosis and Therapeutic Challenges

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Abstract Primary malignant melanoma of the esophagus (PMME) is a very rare and highly aggressive tumor, representing <1% of esophageal malignancies. We are reporting a case of PMME in a 54-year-old White, Non-Hispanic male, who presented to the hospital with dysphagia and weight loss. Computed tomography (CT) of the chest revealed a large mid-to-distal esophageal mass with mass effect on adjacent structures, with no evidence of invasion. The patient subsequently underwent esophagogastroduodenoscopy (EGD) with guided biopsy of the esophageal mass. Histopathology and immunohistochemistry of the biopsied specimen were performed and consistent with malignant melanoma. Tumor staging by positron emission tomography and computed tomography (PET/CT) scans revealed extensive, locally advanced disease with lymph node involvement. Subsequently, esophageal ultrasound (EUS) with biopsy of the involved lymph node was performed and was positive for malignant melanoma. The mass was deemed unresectable due to the extensive degree of locally advanced disease. To assist in our therapeutic decision making, the patient was screened for the presence of a BRAF V600 mutation. He was then started on a combination of the BRAF inhibitor (dabrafenib) in combination with the mitogen-activated extracellular kinase (MEK) Inhibitor (trametinib) given the presence of a BRAF V600 mutation.

Keywords: *primary malignant melanoma of the esophagus, Immunohistochemistry, BRAF V600 gene mutation, dabrafenib, and trametinib*

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1. Introduction

Primary malignant melanoma of the esophagus (PMME) is a very rare tumor, which is most commonly seen in male patients aged between 60-70 years old [2,4]. Only a few case reports have been published worldwide. The mean survival time is 10-13.4 months from the time of diagnosis of the disease, while the 5-year survival rate is estimated at 4.2% [1,2,3]. PMME is associated with a poor prognosis due to the aggressive nature of the tumor, late diagnosis, advanced stage of the disease at the time of the diagnosis, and lack of effective therapeutic options [1]. For these reasons, PMME may not be diagnosed until the onset of symptomatic, late-stage disease, or postmortem [1]. Histopathological analysis, as well as positive immunohistochemistry for HMB-45 and S-100 proteins confirm the diagnosis. Generally, surgical resection is the main treatment strategy, however, for those with metastatic or unresectable disease, newer agents, such as targeted therapies, as well as immunologic agents, have become a mainstay of treatment. In the presence of a BRAF V600 mutation, which can be seen in approximately 50% of cutaneous melanomas, BRAF inhibitors in combination with a MEK inhibitor can be used [7,8].

2. Case Presentation

A 54-year-old White, Non-Hispanic man with a past medical history of asthma presented to the hospital with a chief complaint of progressive dysphagia for 2 weeks associated with a 20-pound weight loss within several weeks. He reported a history of tobacco dependence, smoking 1-pack per day for 41 years. He denied any history of gastroesophageal reflux disease, melena,

hematemesis, or alcohol use disorder. Upon arrival, physical examination and routine laboratory workup were unremarkable. CT scan of the chest showed an 8.8 x 8.6 x 10.3 cm esophageal mass, with mass effect on adjacent structures, and no evidence of invasion (Figure 1). Esophagogastroduodenoscopy (EGD) was performed and was revealing an esophageal mass with an ulcerated area. Biopsies of the mucosal lesion, followed by Hematoxylin and Eosin (H&E) staining and immunohistochemical studies were performed. The findings indicated a mucosal melanoma, which was HMB-45 positive, S-100 Protein Positive, and Pancytokeratin negative. (Figure 2 and Figure 3). Based on these results, the patient was diagnosed with PMME. The patient admitted a remote history of atypical appearing nevi that were removed. He denied any personal or family history of cutaneous melanoma. Additionally, a thorough skin exam was performed to rule out metastasis from a cutaneous origin, with no atypical nevi found. For clinical staging, magnetic resonance imaging (MRI) of the brain was performed and did not show any evidence of brain involvement. Carcinoembryonic antigen (CEA) tumor marker was checked as well and was negative.

The hospital course was complicated by the development of atrial fibrillation with a rapid ventricular response, that was controlled with medications. During hospitalization, he tolerated a soft and liquid diet and was stable for discharge. Upon discharge, the patient underwent PET/CT for clinical staging, which re-demonstrated a large, hypermetabolic mass consistent with malignancy extending from the mid-to-distal esophagus (Figure 4) with mediastinal and upper abdomen lymphadenopathy. Biopsy and immunohistochemistry findings of the mediastinal lymph node were similar to those seen in the patient's previous lower esophageal mass biopsy. A melanoma next-generation sequencing panel was ordered and revealed the presence of a BRAF V600 mutation. Because of the locally advanced disease, surgical treatment was not considered. Alternatively, based upon the BRAF V600 mutation, we decided to treat him with dabrafenib/trametinib combination therapy.

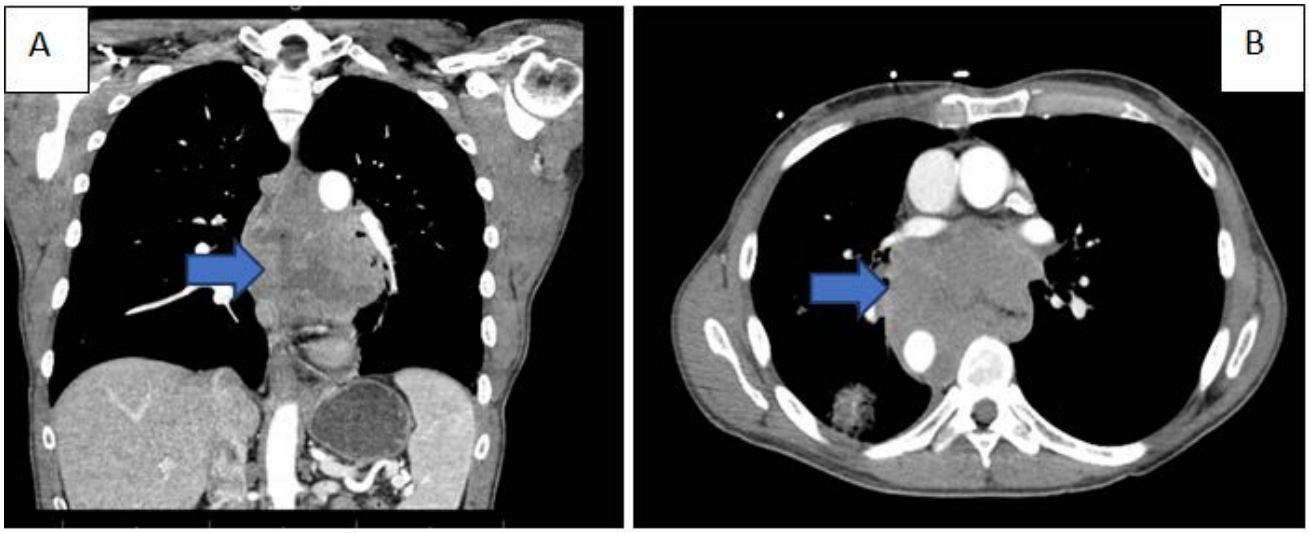

Figure 1. CT scan of the chest showing an 8.8 x 8.6 x 10.3 cm esophageal mass causing a mass effect on adjacent structures without evidence of invasion

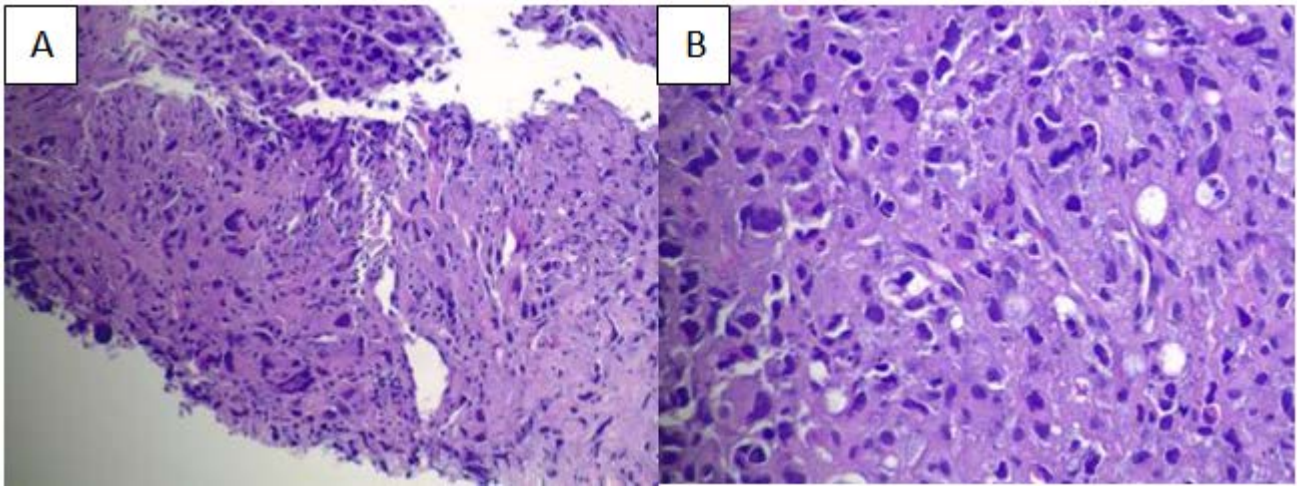

Figure 2. Histological examination showing pleomorphic cells with abundant granular cytoplasm. Hematoxylin and Eosin stain. Magnification of (A) x200, (B) x200

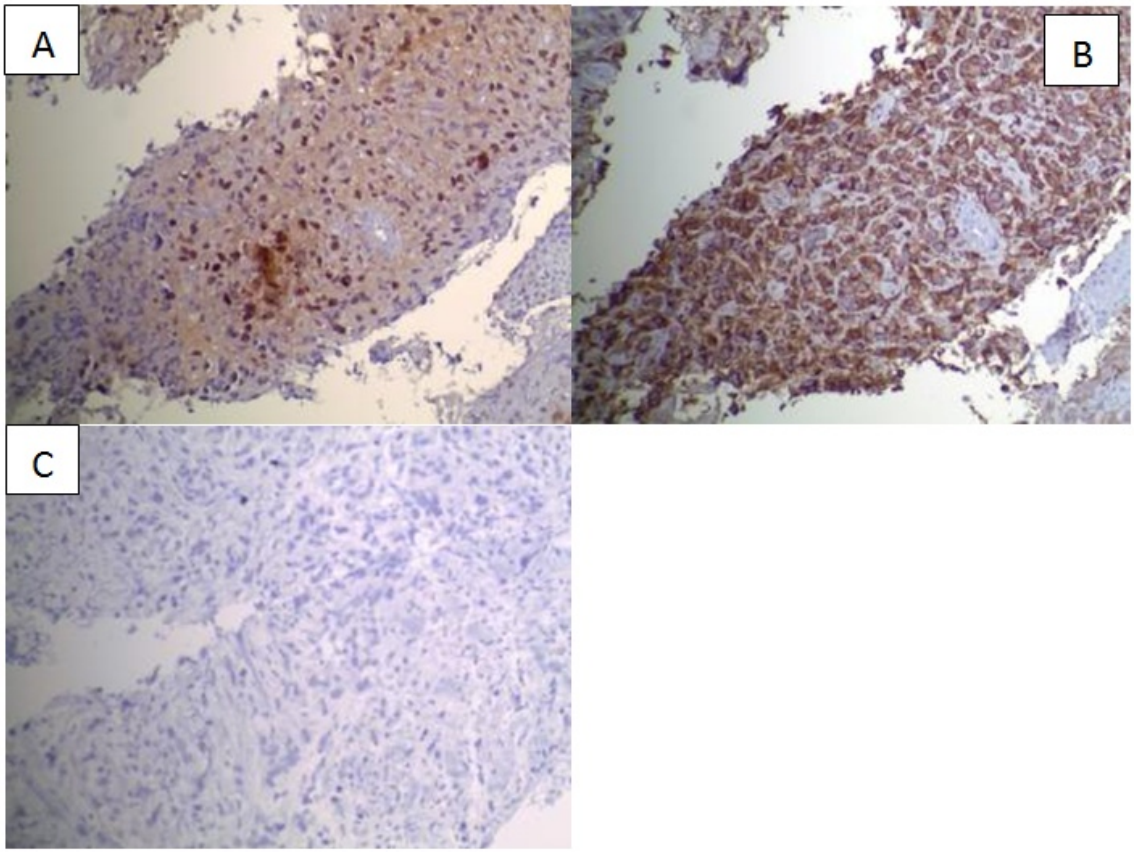

Figure 3. Immunohistochemical staining shows that the neoplastic cells are positive for S-100 immunostain (A) and HMB-45 immunostain (B) and negative for pan cytokeratin immunostain (C), consistent with the diagnosis of malignant Melanoma. (A) x200, (B) x200 (C) x200

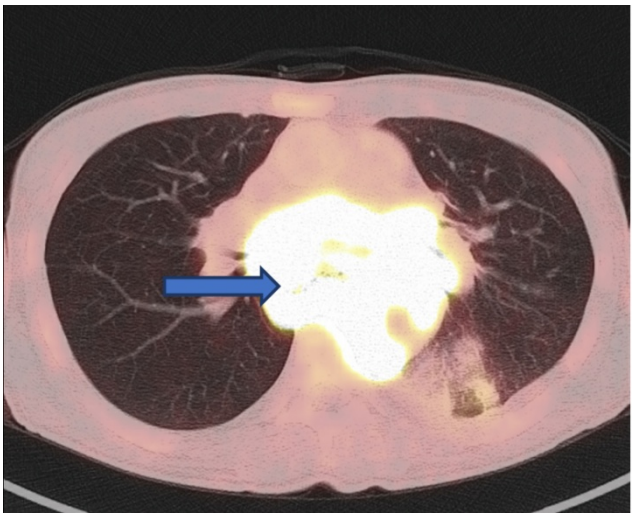

Figure 4. PET/CT scan that showing a large hypermetabolic mass in the mid to distal esophagus consistent with malignancy

3. Discussion

Primary malignant melanoma can originate from different sites where there are melanocytes, however, skin is the most frequent site [3]. Primary malignant melanoma of the gastrointestinal tract is extremely rare. PMME represents 0.1-0.5% with male to female prevalence ratio of 2:1 [1,3,5]. PMME commonly occurs in the 6th to 7th decades of life and is associated with a mean survival time of 13.4 months [1,2,3]. In the presence of extracutaneous melanoma, with no prior history of cutaneous melanoma or evidence of new melanoma on the physical examination, the diagnosis of primary esophageal melanoma can be made [4]. According to the literature, almost half of the patients with PMME have been found to have metastasis at the time of diagnosis. While the most common site of metastasis is the liver (39.3%), it can also involve the lung, regional lymph nodes, brain, bone, kidney, and adrenals through both hematologic and lymphatic spread [1,4].

While studies demonstrate that genes such as CDKN2A, BRAF, and PTEN may be involved in the carcinogenesis of cutaneous melanoma, their role in the pathogenesis of PMME has not yet been studied [3].

PMME patients may present with symptoms such as dysphagia, weight loss, retrosternal chest pain, hematemesis, and melena. Approximately 90% of PMME arise from the middle to the distal third of the esophagus, where the greatest concentration of melanocytes are found [4,5,6]. On endoscopic exam, lesions often present as polypoid, darkly-pigmented masses, however, 10-25% may have variable colors depending on the amount of melanin pigment they possess [4,5,6]. It is important to note that while the histological exam typically reveals melanin granules, occasionally lesions may lack pigment (i.e. amelanotic). The absence of pigment in the amelanotic variant may render diagnostic difficulty and misdiagnosis for other tumors, such as undifferentiated small cell carcinomas and carcinosarcomas. Immunohistochemistry is necessary to confirm the diagnosis by demonstrating the presence of melanocyte markers such as HMB-45 and S-100 proteins and the absence of pan cytokeratin. Imaging modalities, such as CT chest or upper abdomen, PET, and EUS, assist with tumor staging. Surgical resection remains the standard

treatment strategy with the greatest survival in PMME patients. Other treatment modalities such as chemotherapy, radiotherapy, chemoradiotherapy, endocrine therapy, or immunotherapy are alternative tools in the palliative management of nonsurgical cases. Recently, the introduction of molecular analysis for driver mutations such as BRAF and KIT gene mutations has increased the availability of agents used to treat melanoma [5]. The combination of BRAF/ MEK inhibitors is now the standard of care in patients with BRAF V600-mutated advanced melanoma. It decreases mitogen-activated protein kinase (MAPK) resistance and therefore improves the tumor response rate [7].

4. Conclusion

Primary malignant melanoma is a rare and aggressive malignant tumor that typically occurs in the distal two-thirds of the esophagus. Histological analysis and immunohistochemistry staining with S100 and HMB-45 are used to confirm the diagnosis. Early recognition and treatment are essential to improve survival. The mean survival time is 10-13.4 months from the time of diagnosis of the disease. Surgical resection is the modality associated with the best chance for cure. In those who are not surgical candidates, immunotherapy and targeted treatment for those who harbor BRAF V600 mutation remain the main therapeutic options.

Conflict of Interest

None of the authors have any conflict of interest to declare.

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