Primary Malignant Melanoma of the Gastroesophageal Junction Treated With Immunotherapy: A Case Report

Nabil Attlassy, BS; Abiye Agbeh, BS; Rohan Patnaik, BS; James Miller, MD, MPH; James McCarthy, MD

ABSTRACT

Introduction: Primary malignant melanoma of the esophagus constitutes 0.1% to 0.5% of all primary malignant esophageal neoplasms. Melanocytes are present within the squamous epithelium of the esophagus in the stratum basale layer with melanocytosis rare within the esophagus. Primary esophageal melanoma is aggressive and has a poor survival rate; 80% of patients have metastatic disease at diagnosis. Resection surgery is usually first-line treatment for localized primary malignant esophageal melanoma, but recurrence rates remain high. Tumor-specific immunotherapy has shown promising results. We report a case of primary malignant esophageal melanoma with metastasis to the liver treated with immunotherapy.

Case Presentation: A 66-year-old woman presented with 2 months of progressive dysphagia and 3 episodes of hematemesis the previous night. Endoscopic examination showed a hypervascular distal esophageal mass. Biopsy was positive for S-100, SOX-10, and HMB-45 and showed rare mitotic figures with scattered pigment, consistent with melanoma. She was scheduled for esophagectomy initially, but instead pursued immunotherapy after liver metastasis was diagnosed during preop magnetic resonance imaging. Immunotherapy consisted of 8 cycles of pembrolizumab, followed by 4 months nivolumab and ipilimumab. The patient remains in remission 3 years after completing immunotherapy.

Discussion/Conclusions: Our patient was diagnosed with primary malignant esophageal melanoma of the distal esophagus with metastasis to the liver, a presentation that typically has a poor prognosis. Despite this, remission was achieved with immunotherapy without surgical intervention. Only a small number of cases of primary esophageal melanoma treated with immunotherapy have been reported—one showcasing tumor stabilization following several cycles of therapy with eventual metastasis, while our patient had a stable response to treatment. Further exploration of medical management with immunotherapy should be conducted, as it represents an alternative treatment for patients who do not have the option of surgical management.

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INTRODUCTION

Primary malignant melanoma of the esophagus (PMME) is a rare cancer that constitutes 0.1% to 0.5% of all primary malignant esophageal neoplasms.[1] The primary nature of melanoma within the esophagus had long been debated in the 20th century, but 2 findings have clarified its origin. First, melanocytes are typically not found within the esophagus. Aberrant migration during embryogenesis, however, can allow for translocation of melanocytes to the stratum basale within the squamous epithelium of the esophagus. This is seen on pathologic biopsy as increased numbers of dendritic melanocytes and increased deposition of the melanin pigment within the squamous epithelium of the esophagus. Second, esophageal melanocytosis is rare, occurring at rates between 0.07% to 2.1% and can only be seen endoscopically once significant concentrations of melanocytes are present to allow for gross observation.[1]

PMME is highly malignant and confers a poor survival rate. Median survival is typically 8 to 34.5 months following diagnosis, with an overall 5-year survival rate of less than 20%.[2] Hematogenous and lymphatic metastasis of PMME is common, with liver metastasis being the most common at 31%, followed by the mediastinum, lungs, brain, and pancreas.[3] Treatment for PMME is not yet standardized but regimens include surgery, chemotherapy, and immunotherapy.[4] First-line therapy typically includes en blocresection, but this has been associated with high rates of recurrence. Adjuvant chemotherapy

Figure 1. Esophagogastroduodenoscopy Showing 2 cm Lobulated Mass at Squamocolumnar Junction From Esophageal View (left) and Gastric View (right)

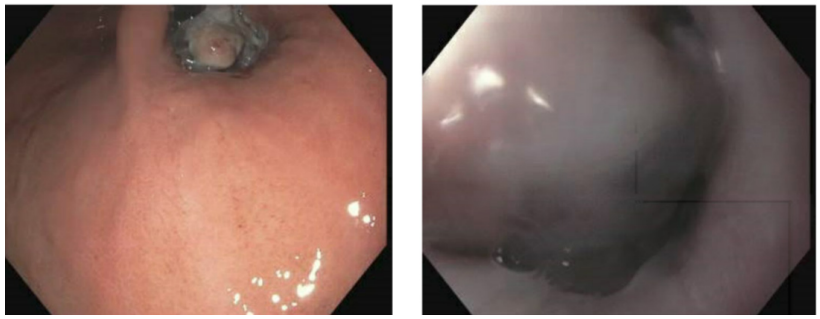
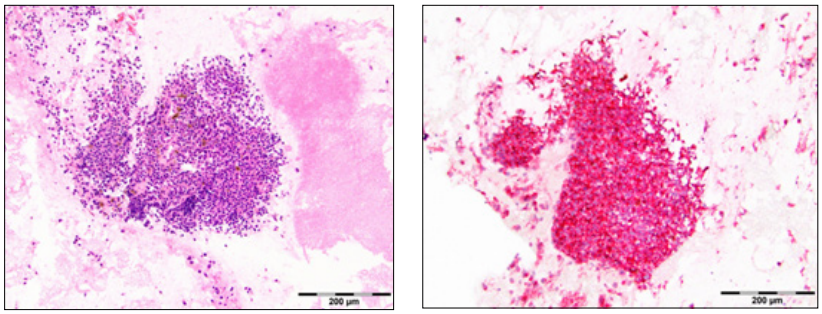


Figure 2. Esophageal Biopsy Hematoxylin and Eosin Stain (left) and Immunostain (right) at 200 x Magnification



Immunostaining was done with a melanoma cocktail consisting of HMB-45, MART-1/Melan-A, and tyrosinase.

and tumor-specific immunotherapy also have shown promise for patients; however, the low prevalence of PMME makes it difficult to provide comprehensive evidence-based therapies.[5]

CASE REPORT

A 66-year-old White woman with a history of hypertension, anemia, and hyperlipidemia was admitted with 2 months of progressive dysphagia, 2 days of fatigue, and 3 episodes of hematemesis the previous night. Endoscopy and computed tomography scan showed a 2 cm mass in the distal esophagus (Figure 1).

Repeat endoscopy confirmed the 2 cm mass at the esophageal squamocolumnar junction without ulceration or bleeding, and endoscopic ultrasound further characterized the mass as submucosal and hypervascular. Fine needle aspiration biopsy revealed sheets of malignant cells consisting of epithelioid cells with amphiphlic cytoplasm, prominent nucleoli, mild nuclear atypia, and occasional melanin pigment with no obvious lymphoid infiltrate. Immunostaining was positive for S-100, Sox-10, and HMB-45, which confirmed diagnosis of esophageal melanoma (Figure 2). Molecular analysis was negative for pathologic mutations, including BRAF and CKIT. Brain magnetic resonance imaging (MRI) showed no evidence of acute intracranial abnormality and positron emission tomography (PET) scan was negative for evidence of distant metastasis consistent with a diagnosis of primary melanoma. The patient had no prior history of melanoma—cutaneous or otherwise.

Cardiothoracic surgery initially recommended an esophagectomy with adjuvant chemotherapy as the lesion appeared primary and localized. However, a preoperative outpatient abdominal MRI revealed a 1 cm hepatic right lobe lesion (Figure 3), with biopsy confirming metastatic melanoma negative for PD-L1 (Figure 4). Surgery was canceled and treatment options were discussed.

Initially, the patient received microwave ablation therapy for the liver metastasis. She then underwent 8 cycles of pembrolizumab followed by 4 months of combined therapy of nivolumab and ipilimumab. She developed allergic interstitial nephritis due to the checkpoint inhibitors and was given a 6-month steroid taper. As of 2019, she continued to be seen for her chronic kidney disease secondary to therapy, but her PET scans were reassuring for no new or progressing melanoma.

DISCUSSION

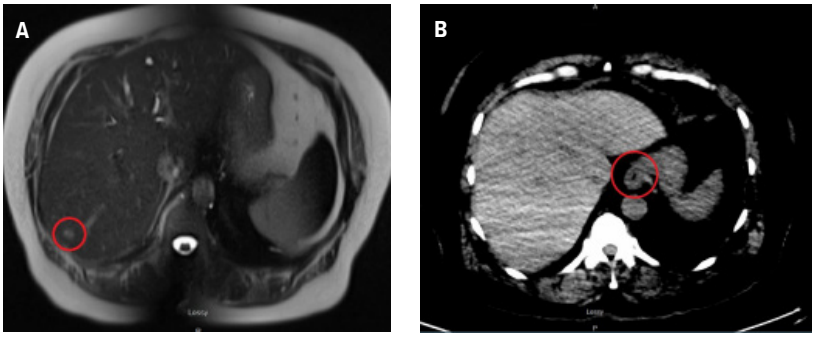
PMME is a rare tumor that accounts for less than 0.2% of esophageal malignancies.[6] Prognosis for these tumors is poor, with past literature reporting 5-year survival rates between 4% and 37%.[7] It mainly arises in the distal esophagus during the sixth or seventh decade of life, as with the patient described in this report.[8] PMME is found around the world but has an increased incidence in Asian populations—especially Japan—with a rate of mucosal melanomas 21.7% to 33.5% of total melanomas compared to 2% in the western world.[9] PMME generally presents late in its course with symptoms of dysphagia, odynophagia, and weight loss similar to other malignancies of the esophagus.[8] However, even with presumptive diagnosis of PMME following positive immunohistochemistry staining, it is important to rule out other potential primary sites, as well as assess the patient for distant metastasis. As was the case for our patient, this includes a full body PET scan, brain MRI, and a dermatologic exam.

For newly diagnosed PMME, surgical resection is currently the most common treatment method.[10] In an analysis of surgical outcomes among 17 patients with PMME, Gao et al showed an overall complication rate of 35.3% among patients who under-

went subtotal esophagectomy and esophagogastrostomy with dissection of mediastinal and abdominal lymph nodes. The median survival time was 18.1 months, with 1-year and 5-year survival rates being 51% and 10%, respectively.[7] Although surgical resection is the most common first-line treatment, the rarity of PMME combined with lack of data has meant a lack of true standardized treatment regimen. For our patient, surgery was not an option due to liver metastasis. She instead started therapy with pembrolizumab, in addition to microwave ablation of 4 hepatic metastases. Her therapy then continued with combination of nivolumab and ipilimumab for 4 months and was complicated by interstitial nephritis. PET scans 4 year after completing treatment were reassuring for no new or progressing melanoma.

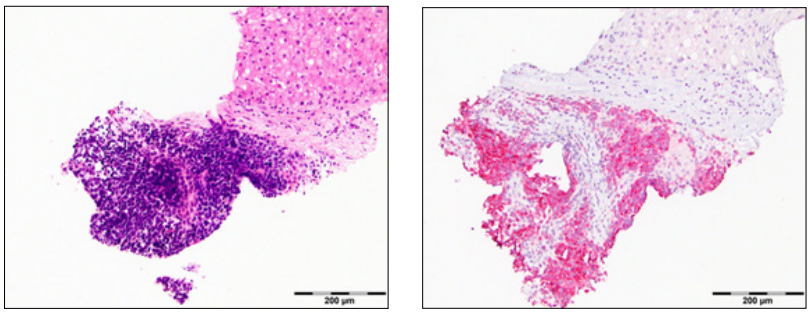
To our knowledge, this is one of the first gastroesophageal junction PMME cases documented in the United States. A minority of cases of PMME treated with immunotherapy have been reported, and our patient has had a remarkable response to treatment. Many treatments in case series in the literature, including Gao et al, involved surgical resection as the primary treatment, with very few involving neoadjuvant therapy. In the case described by Rochefort et al, PMME was treated with nivolumab, with the team reporting knowledge of only 1 other case using checkpoint inhibitor therapy in which the patient passed away 7 months after initiation of treatment.[11] The lack of data on this treatment method should encourage further investigation of PMME in order to develop a better perspective on standardizing treatment. We hope that the rarity of PMME combined with our patient's successful treatment with novel immunotherapy will spur further literature into immunotherapy treatment of PMME.

Figure 3. Magnetic Resonance Imaging Abdomen and Positron Emission Tomography Scan



A. Magnetic resonance imaging abdomen showing lesion suspicious for liver metastases.
B. Positron emission tomography scan showing distal esophageal mucosal thickening consistent with esophagogastroduodenoscopy.

Figure 4. Liver Biopsy Hematoxylin and Eosin Stain (left) and Immunostain (right) at 200 x Magnification Confirming Metastatic Melanoma



CONCLUSIONS

PMME is an extremely rare and aggressive tumor consisting of less than 1% of all primary esophageal neoplasms, especially at the gastroesophageal junction. Surgical resection via esophagectomy with the addition of chemotherapy or immunotherapy remains the most common method of management, although evidence is limited due to the rarity of PMME. Our patient's PMME with minimal metastases provides a data point for the timeline of PMME treated with immunotherapy. Although prognosis remains poor and risk factors poorly understood, further investigation into optimal treatments combined with early diagnosis can elicit better outcomes for patients.

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