Primary Malignant Melanoma of the Esophagus in A 39-Year-Old Filipino Male: A Case Report

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ABSTRACT

Primary malignant melanoma of the esophagus (PMME) is an exceptionally rare condition, representing a mere 0.1 to 0.2% of esophageal cancers, and accounting for just 0.1 to 0.5% of all melanomas. This case involves a 39 -year-old Filipino male who sought medical attention after an episode of choking. Subsequently, endoscopy with biopsy revealed a mass in the distal third of the esophagus, ultimately diagnosed as PMME based on histopathology and immunohistochemistry. FDG-PET/CT scan revealed a hypermetabolic distal esophageal mass and a confluent upper paratracheal lymphadenopathy. He was initially treated with Pembrolizumab, Nivolumab, and Ipilimumab immunotherapy. However, post-treatment FDG PET/CT scans unveiled metabolic progression of the esophageal mass with new hypermetabolic cervical lymph nodes, necessitating a shift to carboplatin and paclitaxel chemotherapy. After two cycles, there was a notable metabolic regression of the mass and paratracheal node with metabolic resolution of the cervical lymph node. An additional 2 cycles of chemotherapy were given, aimed to further reduce the size of the tumor, however, a succeeding follow-up study revealed metabolic progression of the mass. Surgical resection of both the esophageal mass and paratracheal nodes became imperative. The aggressive characteristics, metastasis at early diagnosis, and lack of effective treatment have contributed to the poor prognosis of PMME. Total esophagectomy is the preferred method of treatment. Chemotherapy and immunotherapy may be used in advanced diseases but with variable efficacy. The utilization of FDG PET/CT scans plays a crucial role in both the initial staging and the ongoing assessment of treatment response in patients diagnosed with PMME. This advanced imaging modality offers valuable insights into the extent of the disease and aids clinicians in evaluating the effectiveness of the chosen therapeutic interventions. Given the rarity and challenges associated with PMME, a multidisciplinary approach integrating surgical, medical, and imaging strategies is essential for comprehensive patient care.

***Keywords**: Primary malignant melanoma of the esophagus, Fluoro-2-deoxyglucose positron emission tomography and computed tomography (FDG-PET/CT), chemotherapy and immunotherapy*

INTRODUCTION

Melanoma is frequently seen in sun-exposed areas, but it can be observed in other sites of the body including the mucosal surface [1,2]. Only 15% of melanomas are encountered in non-cutaneous sites, with 0.1 to 0.5% of these being detected in the esophagus [3]. First described by Baur in 1906, Primary Malignant Melanoma of the Esophagus (PMME) is an extremely rare and aggressive tumor with an incidence of 3.6 in 1 billion, and occurring in 0.1 to 0.2% of all esophageal carcinomas [3,4]. PMME has been reported to have a dismal prognosis and develop multiple metastases even in the early stages of the disease [5]. In patients with esophageal cancer, conventional staging methods include upper endoscopic gastroduodenoscopy and computed tomography (CT). The use of positron emission tomography (PET)/CT with 2-[fluorine 18] fluoro-2-deoxy-d-glucose (FDG) in the evaluation of patients with esophageal carcinoma is increasing and has been reported to be useful in initial staging, assessment of therapeutic response after neoadjuvant therapy and detection of recurrent malignancy [5-15]. However, data are limited regarding the utility of PET-CT in evaluating PMME.

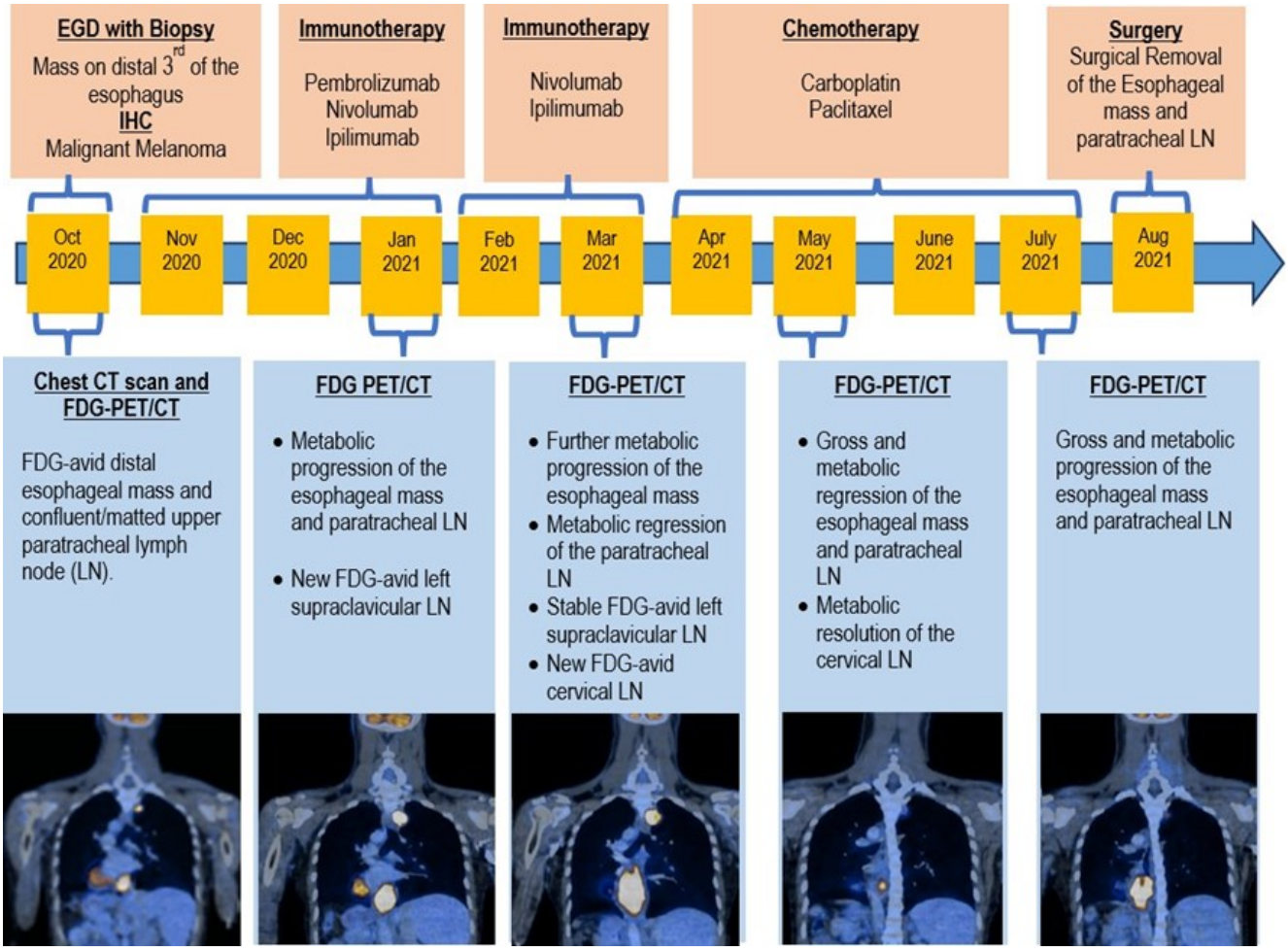
This paper will describe a case of a patient diagnosed with primary malignant melanoma of the esophagus who underwent an FDG PET/CT scan for initial staging and evaluation of treatment response after chemotherapy and immunotherapy.

CASE STUDY

Patient Information

A 39-year-old Filipino male had one episode of choking incident following a consumption of meat, without any associated symptoms of dysphagia, heartburn, retrosternal pain, hematemesis, melena, and weight loss. The patient's past medical history is unremarkable however, there is a family history of bone cancer on his maternal side. He is a previous 6-pack smoker and an occasional alcoholic beverage drinker. There were no significant skin lesions and lymph node swelling found during physical examination .

Timeline



Diagnostic, Treatment and Outcome

Esophagogastrostomy with biopsy was done which showed a mass at the distal third of the esophagus. Final histopathology revealed malignant neoplasm with the following primary considerations: small cell neuroendocrine carcinoma, malignant melanoma, poorly differentiated carcinoma, and large cell lymphoma. Immunohistochemistry was done on a biopsy specimen with a report compatible with malignant melanoma: wherein the specimen was positive for human melanoma black (HMB)-45, and negative for CK and CD20. A chest CT scan revealed an enhancing soft tissue density in the right paratracheal region measuring 3.8 x 3.2 cm, which mildly compresses the trachea, and an enhancing soft tissue lesion in the distal region of the esophagus near the gastroesophageal junction measuring 4.9 x 3.1 x 3.6 cm. Based on histologic and immune-histochemical studies, the diagnosis of Primary Malignant Melanoma was made.

FDG-PET/CT scan was requested for initial staging and a pre-treatment scan for the patient. FDG PET/CT findings revealed an intensely FDG-avid (SUVmax 16.7) enhancing soft tissue mass at the distal esophagus with associated irregular circumferential wall thickening from the mass down the gastroesophageal junction and, an intensely FDG-avid (SUVmax 17.1) enlarged and matted right upper paratracheal lymph node (Figure 1).

The patient underwent evaluation by surgeons to explore the possibility of surgical resection for the esophageal mass. However, surgical intervention was deemed unfeasible as it would result in incomplete resection of both the esophageal mass and the paratracheal lymph nodes. Consequently, the patient was initiated on adjuvant therapy, receiving 1 cycle of Pembrolizumab followed by 2 cycles of Nivolumab and Ipilimumab. An FDG PET/CT scan was requested after 2-month interval to assess treatment response, which revealed interval metabolic progression with no significant change in the size of the distal esophageal mass (SUVmax 19.8) and right upper paratracheal lymphadenopathies (SUVmax 19.7); and interval appearance of an intensely FDG-avid (SUVmax 7.6) unenlarged left supraclavicular lymph node which is likely a new nodal metastasis. Considering the possibility of pseudoprogression, a follow-up PET/CT scan was recommended, and in the interim, the patient was advised to continue with the immunotherapy.

Follow-up PET/CT scan after two sessions of immunotherapy showed further gross and metabolic progression of the esophageal mass (SUVmax 22.6) now measuring 10.9 x 5.3 x 3.8 cm; interval decrease in FDG activity (SUVmax 16.2) of the grossly stable confluent/ matted upper paratracheal lymphadenopathies; stable FDG-avid (SUVmax 7.0) left supraclavicular lymph node; and interval appearance of an FDG-avid (SUVmax up to 3.8) bilateral level I, right level III and left level V cervical lymph node (Figure 2).

The patient was then shifted to Carboplatin plus Paclitaxel chemotherapy as a second line of treatment for advanced metastatic esophageal cancer. Subsequent follow-up study after 2 cycles of chemotherapy revealed significant gross and metabolic regression of the esophageal mass (SUVmax 11.0) and upper paratracheal lymphadenopathies (SUVmax 9.2) now measuring 7.8 x 3.2 x 2.6 cm and 4.8 x 3.0 x 3.8 cm, respectively; and complete metabolic resolution of the bilateral unenlarged cervical lymph nodes. At this point, it came to the consensus that the patient would complete another 2 cycles of chemotherapy to further decrease the size of the lesions before performing surgical resection. However, on follow-up FDG PET/CT scan, there is a significant increase in the size and FDG-activity of the esophageal mass (SUVmax 17.6) now measuring 9.3 x 4.6 x 4.0 cm; and metabolic progression of the grossly stable right upper paratracheal lymphadenopathy (SUVmax 11.6) (see figure 3 for comparison). After a thorough examination and review of the case, the oncologist and surgeon decided to perform surgical resection of the mass and paratracheal lymph node.

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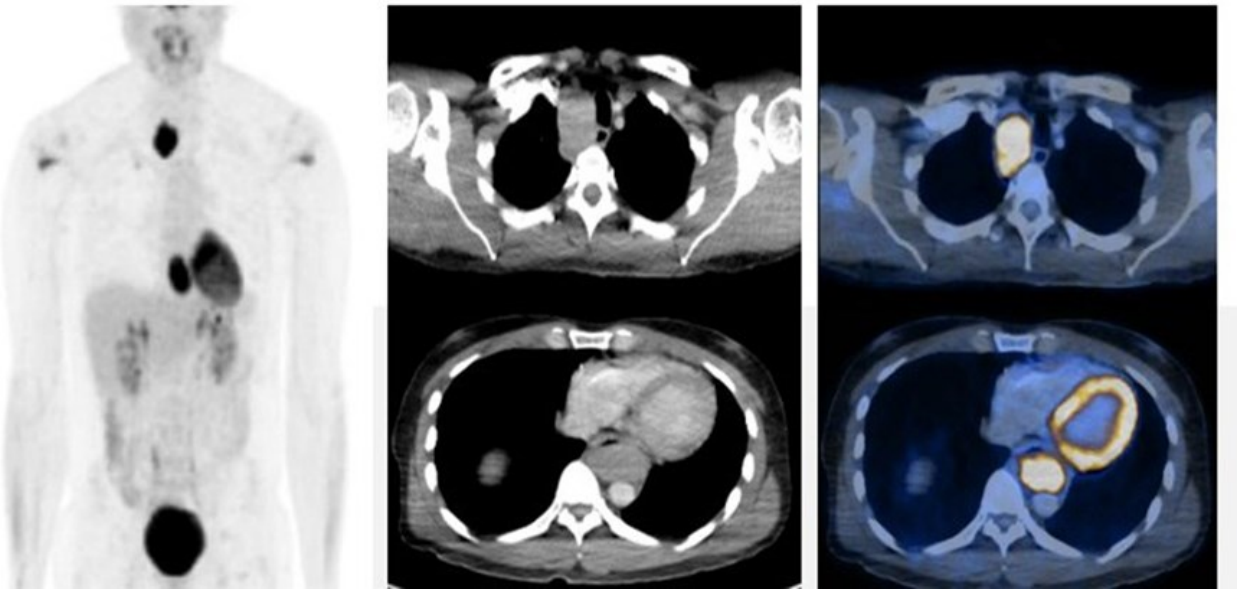

FIGURE 1. Initial FDG PET/CT shows intensely FDG-avid (a) right upper paratracheal lymph node and (b) distal esophageal mass

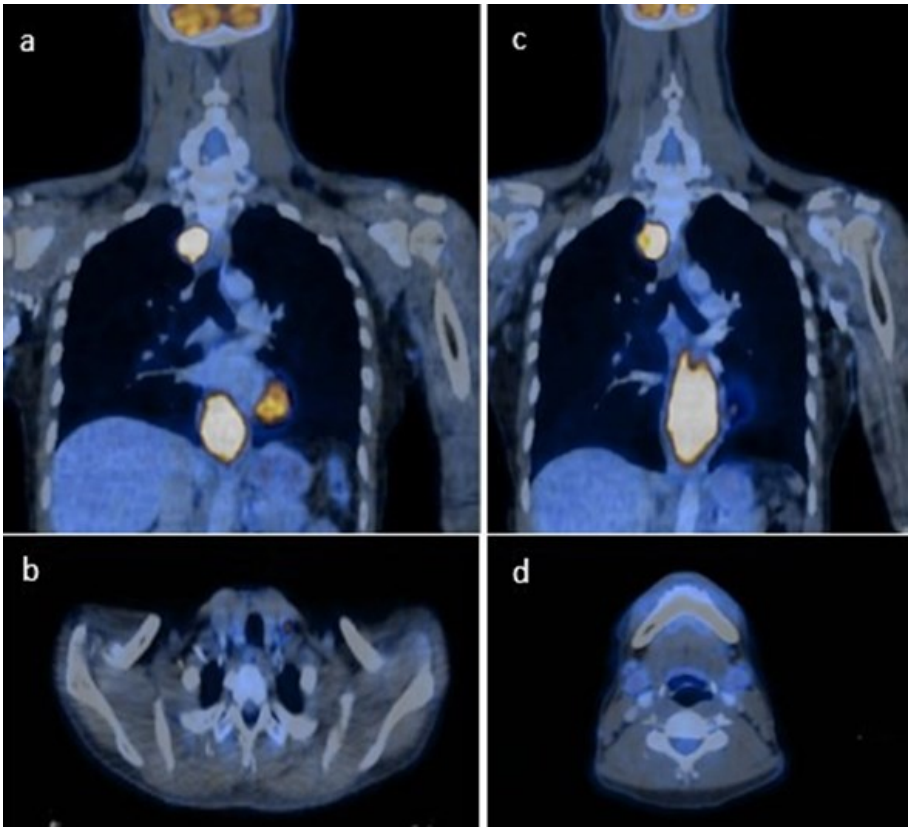

FIGURE 2. After 2 sessions of immunotherapy, follow-up FDG PET/CT revealed [a] Metabolic progression of the esophageal mass and metabolic regression of the paratracheal lymphadenopathy and; [b] FDG-avid left supraclavicular lymph node. Follow-up FDG PET/CT scan after additional immunotherapy revealed [c] gross and metabolic progression of the esophageal mass and paratracheal lymph node and [d] new FDG-avid cervical lymph nodes.

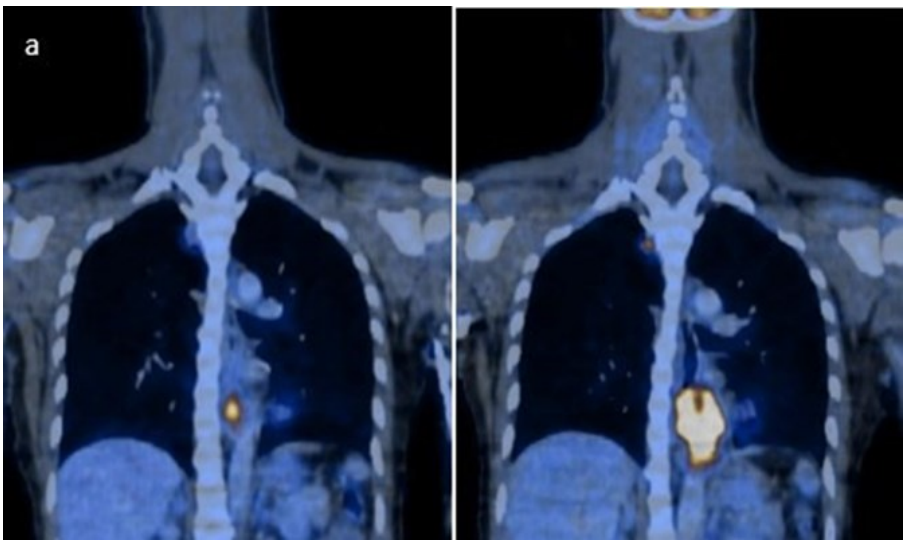

FIGURE 3. a. After 2 cycles of chemotherapy, FDG PET/CT reveals good response to therapy as evidenced by gross and metabolic regression of the esophageal mass and upper paratracheal lymph node. b. Follow-up PET/CT scan after additional cycle of chemotherapy shows interval gross and metabolic progression of the esophageal and upper paratracheal lymph node.

DISCUSSION

Background and epidemiology

Primary malignant melanoma of the esophagus (PMME) is exceedingly rare and accounts for only 0.1% to 0.5 % of all esophageal malignancies. As of 2016, only 339 cases have been reported in the literature. It is an aggressive disease with an average overall survival of only 10-13 months and a 5-year survival rate of 0% to 4%. The average age of patients with PMME is 60.5 years, and the ratio of males to females is 2:1 [5]. PMME usually occurs in the lower and middle third of the esophagus, which is reported in approximately 90% of cases, possibly because of large numbers of melanocytes gathered in these locations, which was consistent with our observation in this case [16,17].

Symptoms and Staging

The clinical manifestation of PMME is not significantly different from other esophageal tumors, and dysphagia is the most common symptom. Other associated symptoms include heartburn, retrosternal pain, hematemesis, black stool, and weight loss, whereas a few patients are asymptomatic at diagnosis like in this case [18].

Approximately 40% of patients are reported to have metastases at the time of diagnosis and the most common sites are the paraoesophageal lymph nodes (10.8%), supraclavicular lymph nodes (7%), liver (7%), lungs (6%), celiac lymph nodes (4%), and bones (2.9%) [16]. PMME spreads through a hematogenous and lymphatic pathway. The American Joint Commission on Cancer in 2009 introduced a new classification for staging melanoma of the aerodigestive tract. In this classification, T1, T2, and stages 1 and 2 were removed due to the aggressive nature of mucosal melanomas (Tables 1 and 2) [19]. Based on this classification, our case was identified with a stage IVA (T3N1M0).

Diagnostic Procedures

At present, endoscopy with biopsy and CT scan is part of the diagnostic evaluation for PMME. The diagnostic criterion for primary malignant melanoma requires the presence of melanin granules within the tumor cells, but 20 to 50% of cases do not present with melanin granules [2,17]. In this case, immunohistochemistry for melanocyte markers is needed, such as a positive study for S-100 protein, HMB-25, neuron-specific enolase, and negative for cytokeratin and CEA, which confirms the diagnosis of PMME [2,5,17]. In our case, the patient presented with positive HMB-45 and negative for CK and CD20. Ruling out metastatic lesions is important if melanoma is found in the esophagus. In addition, the diagnosis of PMME can be accepted only in patients with no history of melanoma and no evidence of physical examination of melanoma involving the cutaneous surface such as the skin, eye, anus, or vagina [20].

TABLE 1 Tumor-node-classification by the American Joint Commission on Cancer staging for melanoma of the upper aerodigestive tract

T3	Epithelium (mucosal disease)
T4a	Deep soft tissue, cartilage, bone or overlying skin
T4b	Brain, dura, skull base, lower cranial nerves, masticator space, carotid artery, prevertebral space, mediastinal structures, cartilage, skeletal muscle or bone.

TABLE 2 American Joint Commission on Cancer staging for melanoma of the upper aerodigestive tract

Stage III	T3	N0	M0
Stage IVA	T4a	N0	M0
	T3, T4	N1	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

While CT and endoscopy yield anatomic visualization, positron emission tomography (PET) is a nuclear medicine imaging modality that allows the measurement of physiological and biochemical processes and, hence, provides functional imaging of esophageal cancer. A positron-emitting radiotracer, 2-[^{18}F]-fluoro-2-deoxyglucose (FDG) is a glucose analog and is transported intracellularly and phosphorylated to 2-[^{18}F] fluoro-2-deoxyglucose-6-phosphate (FDG-6-phosphate) via the same pathways as glucose. Due to insufficient amounts of intracellular glucose phosphatase, F-18-FDG cannot be metabolized further and remains effectively trapped within cancer cells [5-15]. The role of FDG PET has been established in staging and follow-up of malignant melanoma. Studies have demonstrated that radiolabeled glucose analogs were preferentially taken up in murine melanomas and human melanoma xenografts, setting forth the rationale for the potential use of FDG PET in patients with melanoma [21].

Recently, FDG-PET scans have been combined with CT in a single diagnostic study. This technology is able to provide both functional and anatomical information and has been shown to improve diagnosing and staging esophageal cancer. It has a role in re-staging disease and evaluation of treatment response [5-15]. Lesion activity in PET is usually reported in the terms of standard uptake value (SUV) which shows the quantitative value for lesion metabolism. In general, an SUV greater than 2.5 has been considered suspicious for malignancy. When evaluating response to therapy, a change in the SUV, at least 20% is considered to be significant [22].

Another potential radiotracer used in assessing melanoma is radiolabeled benzamide and its analogs which specifically target melanin [23]. In a recent phase III clinical study involving multiple centers, it was observed that 123I-BZA2, a benzamide derivative with an affinity for melanin in melanoma cells, demonstrated higher specificity in diagnosing melanoma metastases compared to 18F-FDG, as indicated by a lesion-based analysis [23,24]. Furthermore, recently formulated radiotracers like 18F-FBZA, 18F-5-FPN, 18F-MEL050, 18F-FITM, and 18F-ICF01006 exhibit potential for enhanced precision in identifying small lymph node and lung metastases in melanoma when compared to the capabilities of 18F-FDG PET/CT [23].

As recently discussed, 40% of PMMEs are usually diagnosed in advanced stages. Metastasis to regional lymph nodes is an important prognostic factor in esophageal cancer. In a study by Kim et al., forty-seven patients were pre-operatively evaluated with FDG-PET and CT scan for metastatic lymph node detection. The sensitivity, specificity, and accuracy of FDG-PET for metastatic lymph node detection in their study were 53%, 94%, and 84%, respectively, compared to 15%, 97%, and 77%, respectively, for CT. The authors concluded that FDG-PET had similar specificity, but significantly greater sensitivity and accuracy when compared with CT in detecting nodal metastasis [25].

In this specific case, FDG PET/CT played a pivotal role in identifying probable nodal metastasis in the paratracheal and cervical regions. Additionally, it successfully ruled out malignancy in the cutaneous region, a crucial criterion for definitively diagnosing PMME. This highlights the significance of FDG PET/CT providing comprehensive information for accurate diagnosis and staging of PMME. Furthermore, the case emphasizes the crucial role of this modality in assessing the extent of the disease and guiding treatment decisions in PMME.

Treatment

Surgery

The rarity of PMME prevents randomized studies to support therapeutic decisions from being carried out. Some studies have suggested that total, almost total, or partial esophagectomy, with or without gastrectomy is the preferred surgical treatment in resectable disease [16, 21-26]. Esophagectomy with three-field lymph node dissection (periesophageal, mediastinal and celiac trunk) is the treatment of choice when possible [29]. However, surgical resection is associated with high postoperative morbidity and mortality. Survival after radical resection is 14.18 months and after limited local excision is only 9 months [3,16].

Immunotherapy

According to the current treatment strategy outlined in the National Comprehensive Cancer Network Guidelines for patients with unresectable malignant melanoma, first -line therapy for patients involves immune-checkpoint inhibitors, such as an anti-PD-1 antibody (nivolumab/ pembrolizumab) and anti-CTLA- 4 antibody (ipilimumab) [30]. These drugs have been reported to demonstrate a substantial clinical benefit for patients with metastatic melanoma, with objective response rates of 31.0–40.0% [17,31,32].

However, not all patients will respond to this treatment. For this case, Nivolumab and Ipilimumab were used as the first line treatment, unfortunately the patient did not respond to the regimen as evidenced by metabolic progression of esophageal mass and paratracheal lymph node as well as interval appearance of a hypermetabolic cervical lymph nodes. This underscores the variability in individual responses to immunotherapy and emphasizes the complexity of managing unresectable esophageal malignant melanoma.

Chemotherapy

Chemotherapy usually includes dacarbazine, nimustine, vincristine, cisplatin, and carboplatin for malignant melanoma [5]. The Dutch Esophagus Cancer Guideline dictates that chemotherapy can be considered in metastatic esophageal cancer but does not recommend one specific treatment regimen. A study made by Polle et al., a phase II study of paclitaxel and carboplatin as palliative treatment for patients with metastatic esophageal cancer, showed that the weekly regimen appeared to be tolerable and effective with an overall response rate of 54% [27,28,29,33]. Another study made by Hodi et al., a phase II study of a combination therapy of carboplatin and paclitaxel in 15 patients with malignant melanoma showed that 20% had a partial response; 47% had stable disease and 33% presented with progressive disease. They concluded that a combination of paclitaxel and carboplatin had moderate activity against malignant melanoma [32].

In this particular case, the patient, following an unresponsive phase to immunotherapy, underwent a treatment shift to a combination of carboplatin and paclitaxel chemotherapy. Initial observations indicated a positive treatment response marked by noticeable regression of the esophageal mass and upper paratracheal lymph node, accompanied by metabolic resolution of the cervical lymph nodes. However, with subsequent cycles of chemotherapy, a follow-up study revealed an overall progression of the lesions. This occurrence demonstrates the aggressive characteristics of PMME.

CONCLUSION

Primary malignant melanoma of the esophagus is an extremely rare and aggressive disease with a poor prognosis. Its clinical presentation mirrors that of other esophageal cancers, often being identified at an advanced stage. There is currently no established standard treatment protocol for PMME, though surgical resection is considered the preferred option when feasible. Chemotherapy and immunotherapy may be used in advanced diseases but show variable effects. The utilization of FDG PET/CT scans has emerged as a valuable tool in both the initial staging and assessment of treatment response for individuals diagnosed with PMME. This imaging technique aids physicians in evaluating the extent of the disease and monitoring the effectiveness of the chosen treatment strategies. Given the scarcity of cases, the establishment of a standard diagnosis and treatment for PMME remains a challenge, emphasizing the need for further research and clinical exploration in managing this rare malignancy.

Informed Consent

Informed consent was obtained from the patient. This case report follows the protection and confidentiality of the patient in accordance with the Data Privacy Act of 2012 and in the rules and principles of the 1964 Declaration of Helsinki.

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