# Primary Amelanotic Malignant Melanoma of the Esophagus: A Case Report

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**Abstract:** Primary malignant melanoma of the esophagus is an extremely rare disease with non-specific clinical presentations and radiological findings. We are presenting a case of 40 years old female admitted to the hospital complaining of dysphasia and weight loss. Esophagoscopy revealed an irregular fungating mass at the lower one third of the esophagus. The tumor was diagnosed provisionally as poorly differentiated carcinoma and was radically removed. The positive imumnohistochemical reactivity of tumor cells to melanoma markers and the detection of melanosomes and premelanosomes on ultrastructural level confirmed the diagnosis of amelanotic melanoma of esophagus. The identification of melanocytosis, foci of melanoma *in situ* and junctional activity in squamous epithelium along with absence of any cutaneous or ocular pigmented lesions proved the primary nature of the tumor . The **aim** of the current work is to report this rare tumor entity and to analyze the clinicopathological, immunohistological, and ultrastructural characteristics this rare tumor entity and compare our results with those in the literature to contribute to a better understanding of the disease. **In conclusion**, we contribute to the cumulative data in the literature with a case report of primary amelanotic melanoma of esophagus, a rare and aggressive tumor entity with controversial histogenesis that should be considered in the differential diagnosis of primary squamous and glandular carcinoma of the esophagus. Primary mucosal melanoma should be distinguished from metastatic malignant melanoma since it has a better prognosis.
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## 1. Introduction

Primary malignant melanoma of the esophagus is a very rare disease with an extremely poor prognosis. Few cases, approximately 300, have been reported in the literature worldwide (1). It constitutes less than 0.1% to 0.2% of esophageal malignancies and accounts for only 0.5% of non-cutaneous melanomas (2).

However, metastatic melanoma is the most common metastatic tumor of the gastrointestinal tract especially to the small intestine and can present with fairly common constitutional symptoms (3).

It was believed that primary malignant melanoma cannot arise from the esophagus since esophageal mucosa lack melanocytes. In 1963 De La Pava *et al.* (4) identified the presence of melanocytes in the submucosa of 4% of normal esophagus at autopsy examination. The origin of the esophageal mucosal melanocytes still remains unclear. The most accepted suggestion is that melanocytes are derived from migrating melanoblasts from the neural crest or from migrating pluripotent cells to the esophagus with subsequent differentiation into melanocytes (3,5). Primary melanoma of the esophagus is more common in males than females with an average age from 60 to 70 years. The disease has a higher incidence in Japan (2). Patients usually present with dysphagia for solid foods. The typical endoscopic feature is a polyploid pigmented lesion located at the lower two thirds of the esophagus (6,7). Primary melanoma of the esophagus has poor prognosis due to its aggressive biological behavior and advanced stage at the time of diagnosis . The preferred treatment method is surgical removal (6,7).

The **aim** of the current work is to report this rare tumor entity and to analyze the clinicopathological, immunohistological, and ultrastructural characteristics of this rare tumor entity and compare our results with those in the literature to contribute to a better understanding of the disease.

## 2. Case Report:

A 40-year-old female presented to King Abdulaziz University Hospital complaining of progressive difficulty in swallowing for the last five months that started with dysphasia for solid foods. She also complained of losing 20 kg of her weight during the last three months with late development of

attacks of vomiting and hematemesis. No serious illnesses in the past history of the patient.

Upon physical examination the patient was unremarkable with no evidence of enlarged cervical lymph nodes. Her routine blood work, laboratory investigations, chest x-ray film, and electrocardiogram did not show any significant abnormalities.

Esophagoscopy revealed an irregular fungating mass 25 cm from the incisor teeth. CT scan revealed a localized mass in the esophageal lumen with no invasion of the mediastinal structures. Endoscopic biopsy was obtained from the mass and sent for histopathological diagnosis. Histologically the mass was provisionally diagnosed as infiltrative poorly differentiated carcinoma.

The patient underwent subtotal esophagectomy and proximal gastrectomy via a right thoracotomy and laparotomy. Frozen sections for paraesophageal lymph nodes and both surgical safety margins were requested. Safety margins were adequate, whereas one paraesophageal lymph node was positive to tumor metastasis.

**Gross examination:**

The surgically resected specimen was received in our pathology lab revealed a subtotal esophagectomy with proximal gastrectomy specimen. The specimen measures 13.5 cm in length and 4.5 cm in diameter. On cut sectioning the esophagus , there was a fungating ulcerating mass measuring 9 x 4 x 3 cm invading the esophageal wall and was 1 mm away from the deep margin, 2 cm from the proximal margin and 2.5 cm from the distal margin. The cut sections of the tumor mass was grayish white in color, firm in consistency with multiple necrotic areas. No pigmentation was identified in the mass (Fig 1). Three lymph nodes were found attached to the outer surface of the esophageal segment measuring 2 x 1.5 x 1 cm and 0.7x 0.5x 0.5 cm respectively, 0.8x 0.5x 0.5 The bronchial and mediastinal groups of lymph nodes were received separately. There were 2 bronchial and 14 mediastinal lymph nodes.

**Microscopic examination:**

Tumor sections revealed partially circumscribed nodular neoplastic growth invading the esophageal wall, covered but not attached to partially ulcerated squamous epithelium (Fig 2 A). The tumor is composed of diffuse sheets of round, spindle and polygonal epithelioid cells, showing marked cytological atypia, high nuclear/cytoplasmic ratio with hyperchromatic vesicular nuclei , prominent cherry red nucleoli, and infrequent mitotic figures (Fig 2 B). The overlying stratified squamous epithelium was focally ulcerated and showed evidence of melanocytosis in the form of increased number of normal melanocytes within the squamous epithelium confirmed by immunohistochemical staining for HMB-45 was identified (Fig 2 C). Melanoma *in situ* component in the form of infiltration of upper mucosal layer by similar individual malignant cells was also noted (Fig 2 D). Evidence of junctional activity in the form of nested melanocytes limited to the lower part of the mucosa was seen (Fig **3** A). There was no intracellular or extracellular melanin pigment deposition. Malignant cells were invading full thickness of esophageal wall and were 1 mm close to the deep margin. Vascular invasion was identified. Three paraesophageal lymph nodes showed tumor metastasis with extra nodal extension. The bronchial and meditational lymph nodes showed no tumor metastasis. The differential diagnosis of these microscopic findings at this stage of the investigation included undifferentiated epithelial malignancy and malignant melanoma either primary or secondary. The tumor was negative to PAS-, PAS-D stain for mucin. Immunohistochemical studies demonstrated strong positive reaction in the tumor cells for HMB-45, Melan A, S-100 protein and vimentin antibodies( Fig 3 A-D), whereas these cells were negative for the epithelial markers (pan cytokeratin (AE1/AE3), neuroendocrinal markers (synaptophysin and chromogranin A), and the sarcoma markers (smooth muscle actin and desmin).

**Electron microscopy studies:** Ultrastructural analysis of the tumor cells revealed the rounded neoplastic cells which contain large ovoid or irregular nuclei with large prominent nucleoli. The cell cytoplasm is moderate and contains mitochondria, rough endoplasmic reticulum with small vesicles and few lysosomes (Fig 4 A). There is moderate number of membrane bound melanosomes which show a wide range of shape size and electron density, some of the aberrant melanosomes have clear zones (Fig 4 A, B). Few melanosomes demonstrate the characteristic feature of cross striation seen in the premelanosome stage of formation (Fig 4 C), other stages are noted with dark contents of higher electron dense melanin (Fig 4 D).

The case was diagnosed as ”primary intramucosal amelanotic melanoma of esophagus with Berslow stage IV” based on positive immunohistochemical staining for melanoma markers as well as the demonstration of melanosomes and premelanosomes in the tumor cells by electron microscopy.

Thorough postoperative systemic evaluations including a detailed history, clinical examination, endoscopic assessment, and radiologic imaging were done to rule out the presence of a primary melanoma in cutaneous, anal, or ocular locations, or in any other site; however, no primary site was found. Absence of primary melanocytic lesion elsewhere and the

presence of epithelial junctional activity confirmed the primary nature of the tumor. Close follow-up showed that the patient is doing well with no evidence of regional recurrence or distant metastasis for 3 months after surgery.

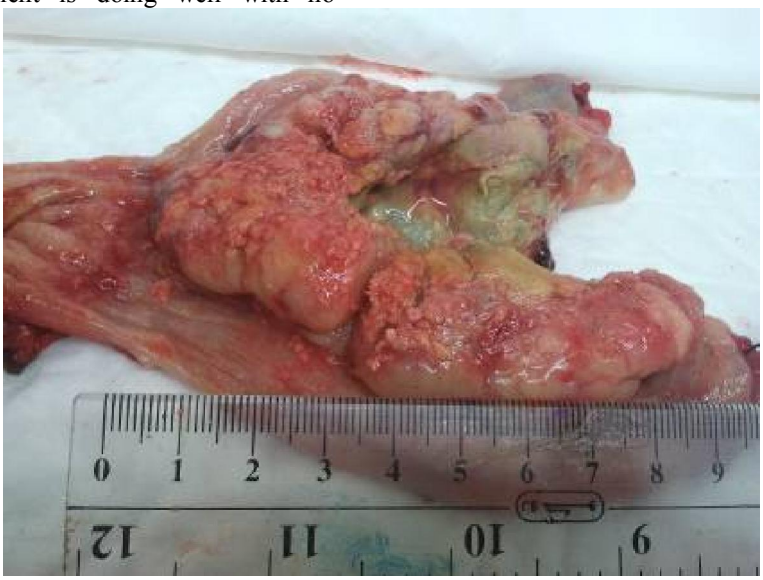

**Figure 1: Opened esophageal segment showing a fungating ulcerating mass measuring 9 x 4 x 3 cm invading the esophageal wall. Note the absence of brown pigmentation.**

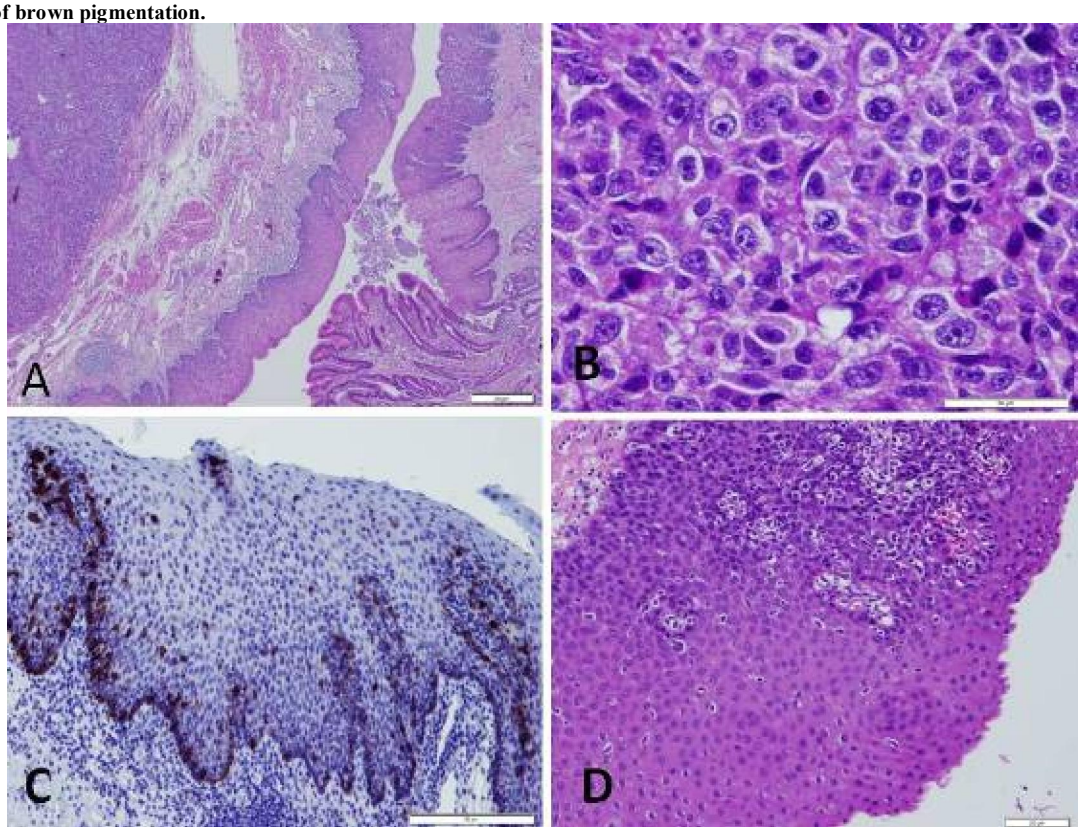


**Figure 2: A: A nodular tumor growth infiltrating esophageal wall showing intact overlying esophageal squamous and gastric mucosa. (H&E , X40)**
**B: High power view of malignant cells showing epithelioid cells with high grade cytological atypia and prominent esinophilic nucleoli. (H&E , X400)**
**C: Increased number of benign melanocytes in the epidermis confirmed by HMB-45 immunostain.**
**( IHC, X100)**
**D: Intraepithelial infiltration by individual malignant melanocytes. (H&E , X200)**

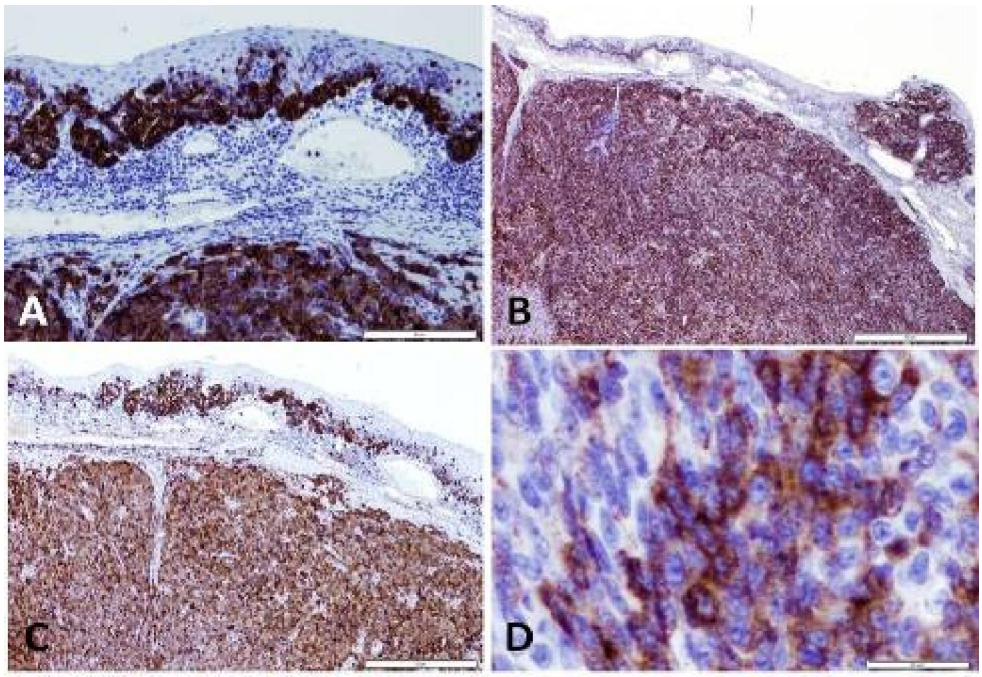


**Figure 3: A: Positive cytoplasmic reactivity to HMB-45 in nodular tumor growth . Note positive staining in overlying nests of malignant melanocytes in basal squamous epithelium (junctional activity). ( IHC, X200)**
**B: Positive cytoplasmic reactivity to MELAN-A in nodular tumor growth and in tumor component invading the epithelium .( IHC, X40)**
**C: Positive cytoplasmic reactivity to S100 in nodular tumor growth and in overlying nests of malignant melanocytes in basal squamous epithelium, ( IHC, X100)**
**D: High power view of positive melanoma cells to HMB-45 . ( IHC , X400)**

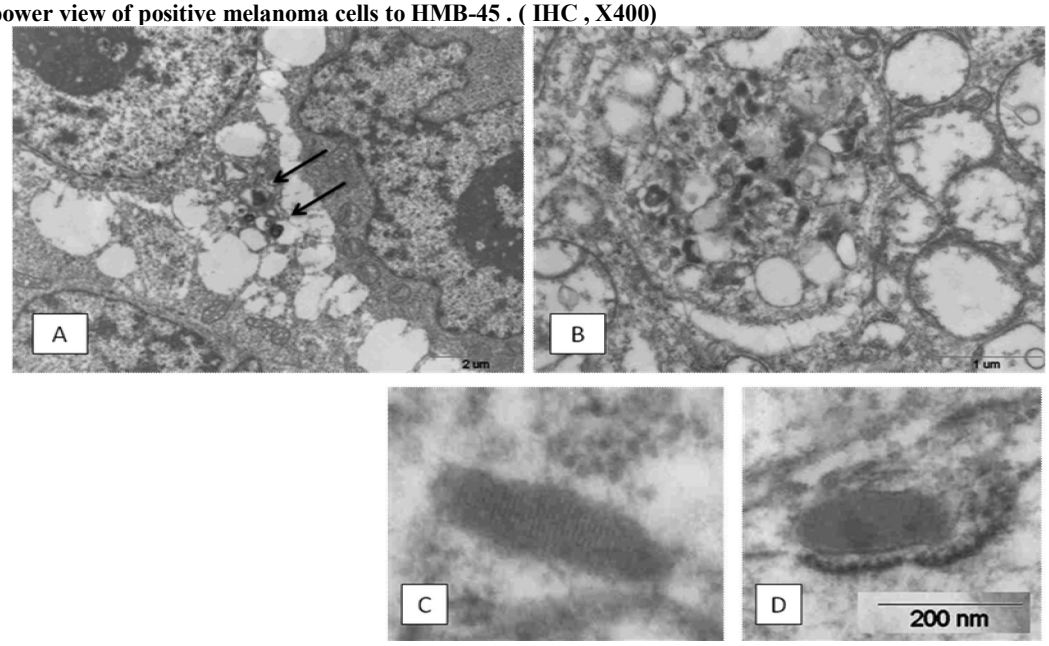


**Figure 4: Transmission electron micrographs demonstrate neoplastic melanocytes; (stained with lead citrate and uranyl acetate). Magnification indicated by Micron bar.**
**A) Portion of tumor cells showing irregular nuclei and conspicuous nucleoli, the cytoplasm contain few organelles such as mitochondria and rough endoplasmic reticulum and few aberrant melanosomes (arrows).**
**B) Multiple melanosomes variable in size, shape and densities.**
**C & D) Higher magnification of two melanosomes demonstrating the characteristic cross-striated lattice in (C) and the other is showing a dense melanin content (D).**

**3. Discussion**

The current study is concerned with the clinicopathological characterization of a case of mucosal melanoma of the esophagus in comparison to those reported in the literature.

Mucosal melanoma is a rare cancer; the number of such cases reported worldwide is very limited (1). It is clearly a distinct from which is different from its cutaneous counterpart in biology, clinical course and prognosis. Unfortunately, the survival rate for mucosal melanoma is quite low because of the advanced stage at presentation (7).

Malignant melanoma may arise from any mucosa which contain melanocytes such as epithelium lining the respiratory, alimentary, and genitourinary tracts as well as from the skin. However the etiology and predisposing factors of primary mucosal melanoma of the esophagus are not clear. It has been reported that melanocytosis; a condition associated with increased number of melanocytes in the basal layer of the esophageal mucosa, may play a role as a premalignant factor (3).

The most common clinical presentation of primary mucosal melanoma of esophagus is dysphagia mainly for solid foods, with 33% of the patients complaining of epigastric pain; whereas hematemesis and melena had been reported in occasional cases (7-10). The patient in our study presented clinically with dysphagia for solid food, vomiting and hematemesis. It is known that these clinical presentations are common symptoms for any esophageal carcinoma and are not specific for primary esophageal melanoma, so distinction could not be made on the clinical presentation.

Primary malignant melanoma of esophagus has been reported mostly in the distal two thirds of the esophagus in 90% of the cases. Most of the reported cases present grossly as fungating, polypoid intraluminal mass with irregular ulcerating surface (7-12). Similarly the case in our study presented with a fungating ulcerated mass located in the lower osophagus.

Histopathological diagnosis of the present case was challenging particularly due to the absence of melanin pigments on the initial routine histological studies, furthermore it was not even suspected during the endoscopic examination. Microscopically the lesion in the present case demonstrated neoplastic growth characterized by nests of malignant epithelioid cells invading into mucosa, submucosa and muscle layer, with frequent angioinvasion, and a relative lack of lymphoplasmacytic reaction to the tumor. Negativity of tumor cells to mucin stains, strong immunoreactivity to HMB45, Melan A and S100 , and identification of free melanosome granules and the characteristic premelanosomes in the tumor cell cytoplasm differentiated between poorly differentiated squamous cell carcinoma; adenocarcinoma and melanoma.

The diagnosis of a primary esophageal melanoma remains challenging, and it is very difficult to definitively rule out a metastasis based solely on histologic studies. Malignant melanoma is known to have metastasis to the gastrointestinal tract, most frequently to the small intestine, followed by the colon (5). Hence before considering the diagnosis of primary malignant melanoma, it was essential to rule the possibility of metastasis from other sites such skin, retina, anal canal, or under the nail, and less frequently at other locations like penis, or vagina. For this reason thorough systemic investigations were performed and the no primary tumor in other sites could be found. In addition, there was no history of previous removal of any atypical melanocytic skin tumor from this patient.

Collectively the findings in this patient support the diagnosis of primary malignant melanoma of esophagus; which are summarized as the presence of junctional activity detected on routine H&E histopathology sections, the positive immune stain for melanoma markers and there is no evidence of other primary tumor in the patient.

Tumor staging in general is essential for the management plan; however the staging system for mucosal melanoma has not been well established, this is owed to the advanced presentation of most of these cases. The use of Breslow depth alone seems to be of little value in staging of the majority of primary mucosal melanomas (13). Most clinicians use the American Joint Committee on Cancer (AJCC) staging system, referring to distant metastatic disease as stage IV (14). It is apparent that establishment of an effective staging system based on prognostic factors unique to mucosal melanoma would be of great benefits.

The treatment of mucosal melanoma is not unified for all cases. It varies regarding the tumor size, tumor location and the presence of metastasis. Because of the lack of efficient systemic treatment options, surgical resection with wide surgical margins remains the treatment of choice and can result in cure (6-11). Follow-up for at least 5 years is recommended since these tumors have very poor prognosis with less than 5% 5-year survival rate with mean survival rate less than 8 months and recurrence can occur many years after the original diagnosis (1).

**In conclusion,** we contribute to the cumulative data in the literature with a case report of primary amelanotic melanoma of esophagus, a rare and aggressive tumor entity with controversial histogenesis that should be considered in the differential diagnosis of primary squamous and

glandular carcinoma of the esophagus. Primary mucosal melanoma should be distinguished from metastatic malignant melanoma since it has a better prognosis.

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