American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2023; 24: e938617
DOI: 10.12659/AJCR.938617

Received: 2022.10.11
Accepted: 2023.01.01
Available online: 2023.01.12
Published: 2023.02.04

# Malignant Melanoma Arising from Esophageal Melanosis and Synchronous with Esophageal Squamous Cell Carcinoma

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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**Financial support:** None declared
**Conflict of interest:** None declared

**Patient:** Male, 62-year-old
**Final Diagnosis:** Esophageal malignant melanoma
**Symptoms:** None
**Clinical Procedure:** Esophagectomy
**Specialty:** Surgery

**Objective:** Rare disease

**Background:** Primary malignant melanoma of the esophagus is a rare disease. However, its exact etiology and progression from melanosis to malignant melanoma have not been elucidated due to its rarity.

**Case Report:** We report a case of esophageal melanosis that progressed to malignant melanoma and was synchronous with esophageal squamous cell carcinoma. A male patient in his 60s was diagnosed with right hypopharyngeal cancer. Cervical dissection and chemoradiation therapy were performed. Esophageal melanosis was discovered using gastrointestinal endoscopy during a pre-treatment screening 2 years later and revealed a 0-Ia tumor in the middle thoracic esophagus, coinciding with the esophageal melanosis site. A biopsy revealed malignant melanoma. We performed thoracoscopic total thoracic esophagectomy. The resected specimen showed a 0-Ia lesion, and the invasion depth of the esophageal malignant melanoma was submucosal (pT1b-SM3), N0, Stage I. A 0-IIc lesion was found in the resected specimen [squamous cell carcinoma in situ, intraepithelial mucosal (pTis/T1a-EP), N0, Stage 0]. The patient has been recurrence-free for 18 months post-surgery without postoperative adjuvant chemotherapy and is still receiving outpatient followup.

**Conclusions:** The close relationship between esophageal melanosis and primary malignant melanoma of the esophagus has implicated the melanosis as the origin of the malignant melanoma. The coexistence of esophageal melanosis and esophageal cancer warrants improved patient followup, including biopsy and multiple endoscopic examinations after esophageal melanosis diagnosis.

**Keywords:** Esophagus • Melanoma, Cutaneous Malignant • Esophageal Squamous Cell Carcinoma

**Full-text PDF:** https://www.amjcaserep.com/abstract/index/idArt/938617





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## Background

Primary malignant melanoma of the esophagus (PMME) is a rare disease. Various treatments, such as surgical and adjuvant therapies, have been suggested, but there is no established treatment method, and the prognosis is poor [1-3]. In many cases, the cause, underlying disease, and transition from melanosis to malignant melanoma have not been clarified. Such cases are extremely rare, and the reported cases are few [4,5]. We report a case of malignant melanoma diagnosed using pathological examination. The melanoma was discovered during a 2-year followup after treatment for hypopharyngeal cancer and esophageal melanosis, leading to surgery.

Limited evidence exists showing that esophageal melanosis is a precursor to PMME, because it is difficult to make a reliable distinction based on endoscopic findings. A biopsy should be performed when endoscopic diagnosis reveals findings regarding esophageal melanosis. Considering that some of the PMME may have been biopsied and the possibility of transitioning to PMME is considered, short-term endoscopy is appropriate approximately every 6 months when esophageal melanosis is diagnosed pathologically. Surgery should also be considered when a biopsy detects a melanoma component in a portion of the tumor. Therefore, when an esophageal melanosis-like lesion is detected, multiple endoscopic examinations should be performed every 6 months in the first year, or every 3 months if possible. If the lesion has not changed after the second year, it is appropriate to follow up with an endoscopy every other year, as this indicates a high probability of esophageal melanosis.

## Case Report

A male patient in his 60s who smoked 20 cigarettes a day underwent cervical dissection and cisplatin-combined radiation therapy with a diagnosis of right hypopharyngeal cancer T2N3bM0 at the Otolaryngology Department of our hospital. At that time, esophageal melanosis was found during the upper gastrointestinal endoscopy, which was performed as a pretreatment screening. Two years later, the upper gastrointestinal endoscopy revealed an elevated lesion in the middle thoracic esophagus, consistent with the site of esophageal melanosis. A biopsy led to a diagnosis of PMME. Pigmentation was observed on the entire body, including the skin, lips, and pubic area.

Blood tests at admission revealed no abnormal findings, such as tumor markers. However, upper gastrointestinal endoscopy showed previously identified esophageal melanosis 26-28 cm from the upper incisor and a 0-IIa lesion at the same site (**Figure 1**). Computed tomography (CT) showed a slight contrast effect on the esophageal wall and no obvious metastasis

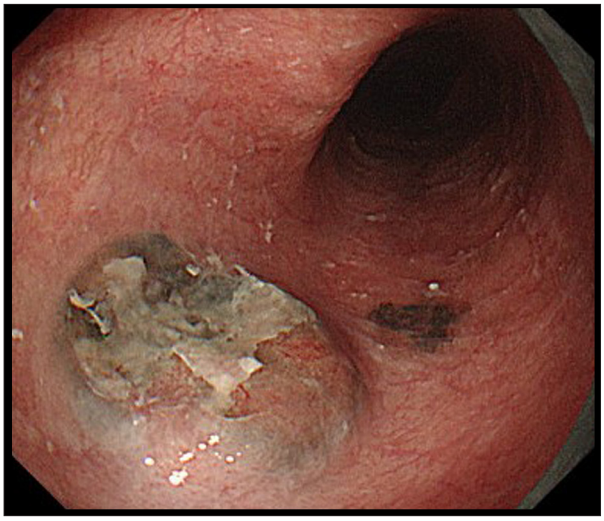

**Figure 1.** Known esophageal melanosis observed 26-28 cm from the upper incisor, and a 0-IIa lesion observed at the same site.

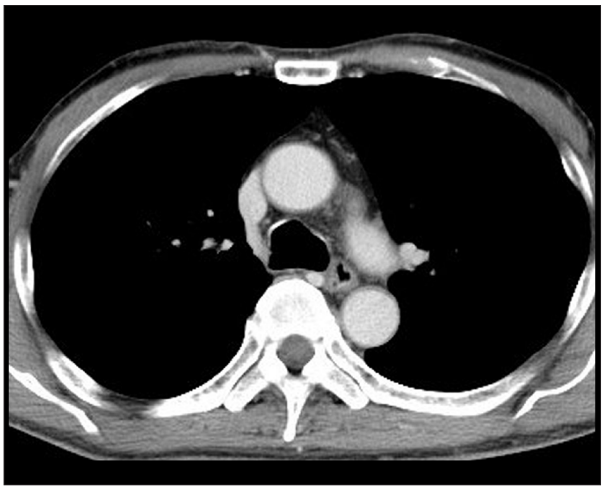

**Figure 2.** Computed tomography (CT) showing a slight contrast effect on the esophageal wall and no obvious metastasis to lymph nodes or other organs.

to the lymph node or other organs (**Figure 2**). Positron emission tomography/CT showed an accumulation of maximum standardized uptake value (SUV max) of 4.33 at the tracheal bifurcation level of the thoracic esophagus, and no abnormal accumulation suggestive of lymph node metastasis or distant metastasis (blood glucose 99 mg/dL, **Figure 3**).

With a diagnosis of malignant esophageal melanoma (Mt, type 1, c-T1bN0M0: stage I: UICC TNM 8$^{th}$), thoracoscopic esophagectomy, laparoscopic gastric tube preparation, and post sternal route cervical esophagogastric anastomosis were performed. The operative time was 7 hours and 15 minutes, and the bleeding volume was 211 mL. The resected specimen showed a type 1 lesion with a size of 21×18×9 mm. The





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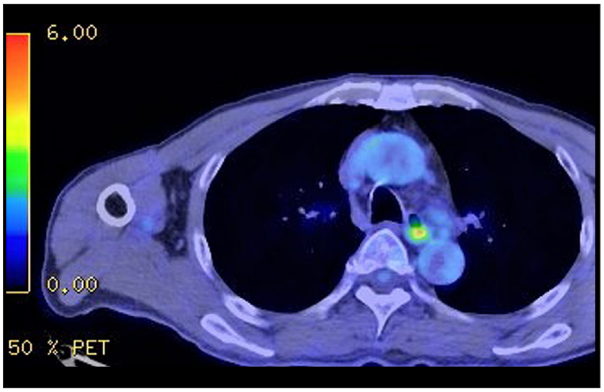


**Figure 3.** Positron emission tomography/CT showing the accumulation of SUV max of 4.33 at the tracheal bifurcation level of the thoracic esophagus. CT, computed tomography; SUV max, maximum standardized uptake value.

pathological diagnosis was PMME (pT1b-SM3, INFa, ly0, v2, pIM0, pPM0, pDM0, N0, stage I) according to the "The Japan Esophageal Society Esophageal Cancer Handling Regulations (11th Edition)." An irregular black spot, 30×28 mm in size, was spread around the tumor, and individual cell proliferation of melanocytes with poor atypia was observed on the basal side of the epithelium; however, no development of malignant melanoma was observed. There was an iodine-unstained zone on the anal side of the tumor, and a 16×14 mm-sized 0-IIc lesion was found on the resected specimen. The pathological diagnosis was squamous cell carcinoma in situ, pTis/T1a-EP, ly0, v0, pIM0, pPM0, pDM0, N0, Stage 0. Immunohistochemical staining was positive for HMB45, MelanA, and S-100 protein, and the other primary lesions were negative, leading to the diagnosis of PMME (**Figure 4A-4D**).

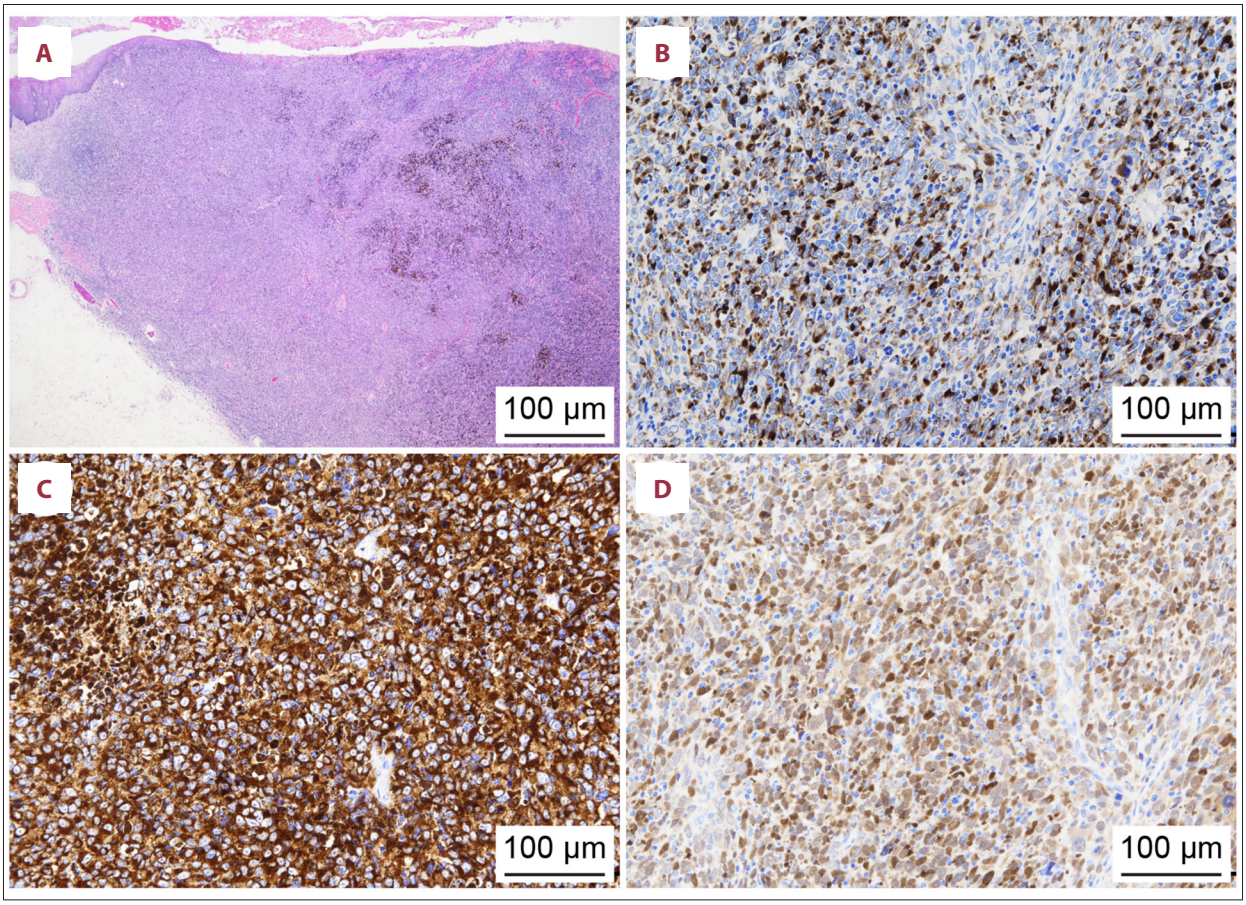


**Figure 4.** (**A**) Tumor cells with nucleoli and swelling anisocytosis of different sizes densely proliferating in sheet-like and large-sized follicle-like forms. The lesion was accompanied by the deposition of melanin pigment. Cellular proliferation of melanocytes was observed on the intraepithelial basal side of the melanoma around the tumor, but no development of malignant melanoma was observed (hematoxylin and eosin, ×20). (**B**) Immunohistochemical staining for MelanA was positive (×200). (**C**) Immunohistochemical staining for HMB45 was positive (×200). (**D**) Immunohistochemical staining for S100 was positive (×200).





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The patient was discharged on postoperative day 16 and did not undergo postoperative adjuvant chemotherapy. There was no recurrence for 18 months after surgery, and outpatient followup is currently ongoing.

## Discussion

We report a case of esophageal melanosis that progressed to malignant melanoma and had a co-occurrence of squamous cell carcinoma of the esophagus. The case was reported following informed consent and the approval of the Institutional Review Board, Tokyo Medical University.

PMME is a rare disease, accounting for 0.1-0.8% of all malignant tumors of the esophagus [1-3]. Malignant melanoma is most frequently and primarily seen in the skin and mucous membranes, and skin, nasal, and eye locations account for 80% of the total cases (32.7%, 27.1%, and 21.4% in the epidermis, nasal/oral cavity, and eye, respectively) [4]. Esophageal primary lesions account for only 0.5% [5]. The most common esophageal lesions are in the middle and lower esophagus; these make up approximately 75% of the total [6]. They are mainly broad-based elevated lesions with smooth surfaces, and ulcer formation is frequently observed. The color tone is usually white or greyish-white and difficult to distinguish from submucosal tumors macroscopically [7]. There are also cases in which no pigmentation is observed (amelanotic melanoma) [8]. The average patient age for esophageal melanoma is 60.5 years, and it is relatively rare. There are fewer occurrences of this type of esophageal cancer than any other type of malignant esophageal tumor, and it is twice as common in men as in women [2,3]. Hyperplastic epithelium and chronic esophagitis can be precursor lesions of PMME [2]. The definitive diagnosis is performed using immunohistological staining; definitive diagnosis for PMME includes positivity for S-100 protein, neuron-specific enolase, and HMB-45 antibody; and negativity for cytokeratin, carcinoembryonic antigen, p-53, estrogen receptor, and progesterone receptor [9]. Surgery is the first-line treatment; other treatments include chemotherapy (DAV therapy: dacarbazine, nimustine, vincristine), immunotherapy, and radiation therapy [10,11]. Currently, human-type anti-human PD-1 monoclonal antibody (nivolumab) is expected to have therapeutic effects. A comparison of the efficacy of dacarbazine and nivolumab for unresectable malignant melanoma has shown that nivolumab offers better overall survival and progression-free survival [12,13]. Previously, malignant melanoma had a poor prognosis; however, with the increasing number of cases detected relatively early due to the spread of endoscopy, the prognosis has improved in recent years (1-year postoperative survival rate: 74.1%, 5-year survival rate: 30.7%) [3,14]. Factors leading to poor prognosis include age (≥60 years), invasion depth (T2 or deeper), lymph node metastasis, and distant metastasis [8]. In addition, the prognosis naturally deteriorates as the stage progresses [3].

Organ-specific views differ on whether melanosis is a precursor to malignant melanoma. It has been reported that approximately 75% of the lesions develop from normal skin without prodromal lesions, and others are preceded by a melanocyte nevus [15]. Although a close relationship between malignant melanoma and melanosis is suspected in the esophagus and oral mucosa, a clear mechanism of formation from precursor lesions has not been established [16,17]. Since esophageal melanosis frequently merges with PMME [18,19], a close relationship between esophageal melanosis and PMME has been suspected as an origin of the disease [20]. However, there are only 2 reports of malignant transformation during the followup of esophageal melanosis [21,22]. Currently, it is unclear whether esophageal melanosis is a precursor lesion of PMME [23].

Melanosis is a pigmentation manifesting as blackish esophageal mucosa resulting from a marked increase in melanin granules in the basal layer. Melanosis is frequently used as a clinical diagnostic term in endoscopic findings. Melanosis, which is present as pigmentation in the esophagi of healthy people, is observed at a frequency of 0.11% [3]. Blackish brown esophageal mucosal pigmentation due to increased inflammation of melanin-bearing cells in the basal layer of the esophageal epithelium and the appearance of epithelialized melanophages need to be differentiated from melanoma in situ. Pathological diagnosis of melanoma in tiny biopsy tissue sites is frequently difficult; however, the main points of differentiation between the pigmentation of a pigmented nevus and malignant melanoma on the skin are helpful. These are: 1) increased cell atypia in the basal layer of esophageal epithelium, 2) the randomness of the arrays, and 3) discontinuity of the esophageal epithelial basement membrane. The presence of intraepithelial lesions (junctional activity) with these 3 characteristics is essential [24]. If a lesion suspected to be melanosis is found, such as a black area on the mucosa, a differential diagnosis using a biopsy should be performed.

In the present case, melanosis was diagnosed through endoscopic findings. A positive and careful pathological diagnosis should have been conducted to recognize junctional activity through biopsy, but this was a valuable case suggesting that melanosis may be a precursor lesion of PMME. Although pathological assessment is necessary to confirm the diagnosis, there is an argument that biopsy may cause disseminated lesions and should be avoided. However, the number of cases where dissemination has occurred is extremely limited [2], so a diagnosis should be performed using active biopsy, considering the above course. In our department, only 3 cases have been diagnosed with PMME and all 3 underwent surgery after 1990. Among these, there are 2 cases in Japan (including the





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present case) in which PMME was diagnosed endoscopically after a long-term observation period of 2 years [21]. Surgical indications at the stage when melanocyte markers (S-100 protein, MelanA, and HMB-4 antibody, among others) are present are controversial; there is no common view on the frequency of followup and test items for patients diagnosed with esophageal melanosis and those who are positive for melanocyte markers. The onset of PMME has been associated with melanocytosis for some time, but this association has not yet been confirmed [15].

There are few reports on the relationship between esophageal melanosis and esophageal squamous cell carcinoma; particularly, there was only 1 report of early-stage esophageal cancer in Japan, a case similar to ours [25]. In a study of esophageal melanosis in 93 cases of squamous cell carcinoma, Nishi et al [26] reported that esophageal melanosis was associated with 19.3% of esophageal cancers and was predominantly associated with middle thoracic esophageal cancer. In addition, Yokoyama et al [27] investigated the relationship between orophagoesophageal melanosis and esophageal iodine-unstained zone, esophageal cancer, and oropharyngeal cancer in alcohol-dependent men. Esophageal melanosis is more common in alcoholics, particularly those heterozygous for aldehyde dehydrogenase 2 (ALDH-2) deficiency. Esophageal melanosis and esophageal cancer may coexist because of the high exposure to acetaldehyde due to ALDH-2 deficiency in these patients. Therefore, it is necessary to follow up with the patients, considering the possibility of the coexistence of esophageal melanosis and esophageal cancer.

## Conclusions

The close relationship between esophageal melanosis and PMME has been suspected as a root of the PMME disease condition. However, our results also show that esophageal melanosis and esophageal cancer may coexist. Therefore, when endoscopic diagnosis reveals findings of esophageal melanosis, a biopsy should be performed. Moreover, it is important to note that when an esophageal melanosis-like lesion is found, it may transform into PMME and esophageal squamous cell carcinoma may develop. Specifically, patients with risk factors for esophageal squamous cell carcinoma, such as ALDH-2 deficiency, require close endoscopic followup.

### Acknowledgements

The authors thank Dr. Takafumi Watanabe, Dr. Toru Sakurai, and Dr. Moe Matsumoto (Department of Gastrointestinal and Pediatric Surgery, Tokyo Medical University) for their aid in patient management, and Dr. Aoi Sukeda (Department of Pathology, Tokyo Medical University) for his help in visualization.

We would like to thank Editage (www.editage.com) for English language editing.

### Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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