

## CASE REPORT

# Laryngeal primary malignant melanoma: a case report

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## Abstract

Malignant melanoma of the larynx is a rare cancer that can appear as a primary tumor or as a metastasis from a cutaneous head and neck primary lesion. We present a new case of primary laryngeal malignant melanoma diagnosed by histological examination of an excisional biopsy specimen. The patient was a 53-year-old man with a history of smoking and hoarseness but without any clinical evidence of other cutaneous malignant melanocytic lesions. Microscopically, the tumor consisted of polygonal-epithelioid cells admixed with more elongated, spindle-shaped cells. Some of the tumoral cells demonstrated dark brown cytoplasmic and nuclear melanin. Despite significant ulceration and disruption of the epithelium, *in situ* malignant melanocytes were recognized within the remaining epithelium. Immunohistochemical stains were strongly positive for S-100 protein, HMB-45 and Melan-A. On the other hand, cytokeratin stains were negative. Based on the clinical and histological findings, a diagnosis of primary malignant melanoma of the larynx was established.

**Keywords:** primary melanoma, larynx, S-100 protein, HMB-45.

## Introduction

Compared with cutaneous melanomas of the head and neck, primary mucosal melanoma of the upper airways and digestive tract is associated with a very poor prognosis. Such a lesion is known to be insidious and remains dormant for most of its course. In general, mucosal melanoma of the head and neck is an uncommon lesion and comprises only 0.5% to 3% of all cases of malignant melanomas [1]. Laryngeal malignant melanoma constitutes only 3.8% to 7.4% of these cases [2, 3]. To date, only 60 cases of primary malignant melanoma of the larynx have been reported in the medical literature. Therefore, clinicopathological features, treatment protocols, and prognostic factors are not clearly established in primary malignant melanoma of the larynx. Furthermore, pathological and histological criteria to discriminate primary from secondary lesions are not well defined.

The aim of this paper is to report a very rare case of primary laryngeal melanoma in a middle age male patient with an aggressive outcome, especially when he refused additional therapeutic methods and died two months later.

## Case report

We present the case of a male patient (RA), 53-year-old, who presented with midline neck discomfort, hoarseness and very difficult breathing, but not hemoptysis or weight loss. The patient admitted smoking 20 to 40 cigarettes a day for more than 30 years. He was also an occasional drinker. All vital signs and laboratory tests were within normal range. There was no evidence of cutaneous malignant lesion. A biopsy was performed by fibro-optic endoscopic exam (laryngoscopy) in the Department of Otorhinolaryngology of "St. Apostle Andrew" Emergency County Hospital of Constanța, Romania. The excised material was performed in the Clinical Service of Pathology of the same Hospital. The specimen was fixed in 10%

formalin and paraffin-embedded. The sections were first stained with Hematoxylin–Eosin (HE) and then microscopic images were taken with a Nikon camera using a Nikon Eclipse E600 microscope. Macroscopic examination revealed the presence of multiple fragments with variable diameters, which measured overall 4.5/2.5/0.7 cm, gray-colored, with hard consistency. On the routine HE staining, histopathological examination revealed a laryngeal mucosa with wide ulcerated areas, overlying a well-defined lesion composed of sheets of malignant atypical cells, with eosinophilic cytoplasm (Figure 1), big, round and vesicular nuclei with one or many nucleoli. The tumor cells demonstrate pleomorphic nuclei (Figure 2). Some of these tumor cells contain cytoplasmic and nuclear brown pigment (Figures 2 and 3). Some areas of the tumor consisted of elongated, spindle-shaped cells, while others showed polygonal to epithelioid cells. There were present areas of necrosis and a high mitotic rate (10 mitoses/HPF – high-power field). Despite of extensive ulceration of the mucosa, there were identified neoplastic malignant melanocytes within the epithelium (Figure 4). We considered that evaluation by immunohistochemical techniques was mandatory.

Immunohistochemical stains for cytokeratin 5/6, cytokeratin 20, cytokeratin 7, and human melanoma black 45 revealed the following aspects: strong positivity for HMB-45 (Figure 5); negativity for CK5/6, CK7, and CK20.

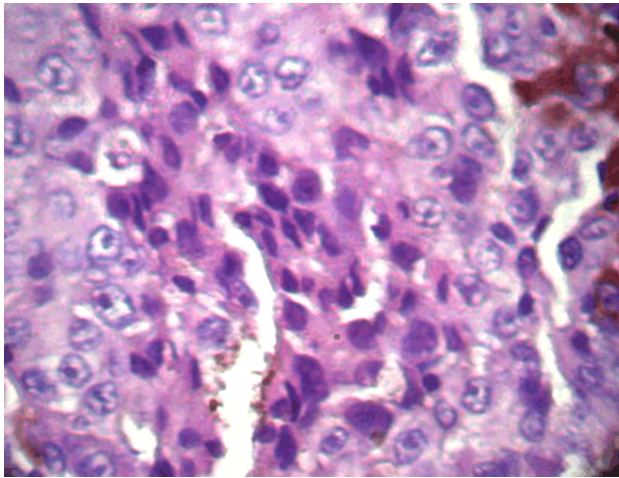
Diffuse, strong positivity for HMB-45 limited the diagnostic at two malignant tumors: malignant melanoma and perivascular epithelioid cell tumor (PEC-oma). The immunohistochemical stain for S-100 protein and Melan-A revealed the following aspects: strong positivity for S-100 protein (Figure 6); strong positivity for Melan-A (Figure 7).

The characteristic features of immunohistochemical reactions oriented for the final diagnosis of malignant melanoma of larynx. Extensive physical exam by a

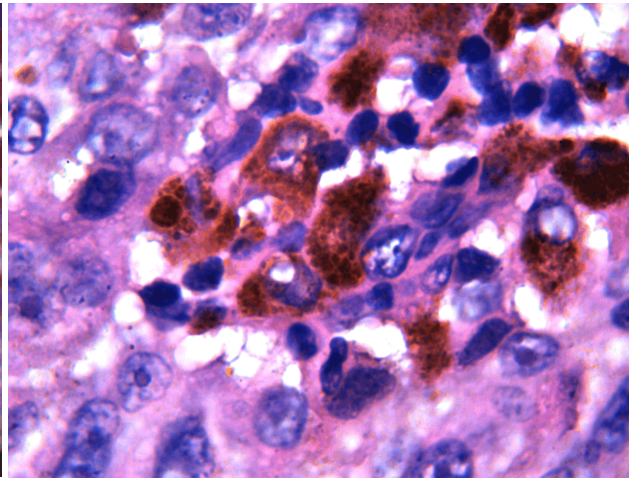


dermatologist failed to reveal a primary cutaneous lesion. The patient underwent a computed tomography (CT)-scan evaluating the presence of a possible primary malignant melanoma, which was negative. Finally, the patient was diagnosed with primary malignant melanoma of the larynx.

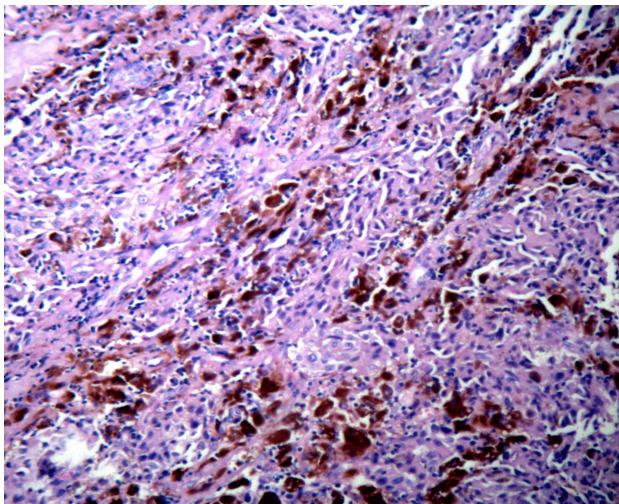
Following the surgical excision, he refused all additional therapeutic modalities. After one month, the patient presented to the hospital with multiple subcutaneous nodules and died two months later.



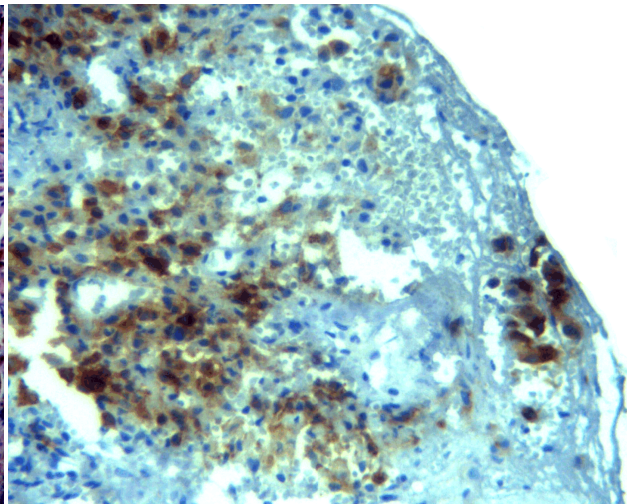
**Figure 1** – Sheets of malignant atypical cells with eosinophilic cytoplasm (HE staining, 400×).



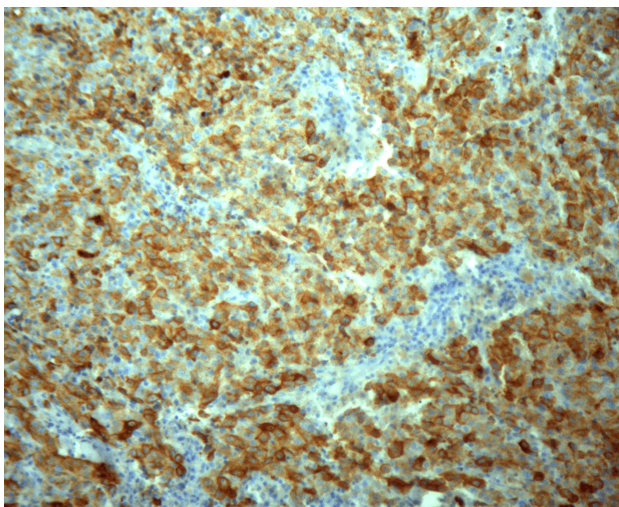
**Figure 2** – Malignant cells with big, round, vesicular nuclei with nucleoli and cytoplasmic melanic pigment (HE staining, 900×).



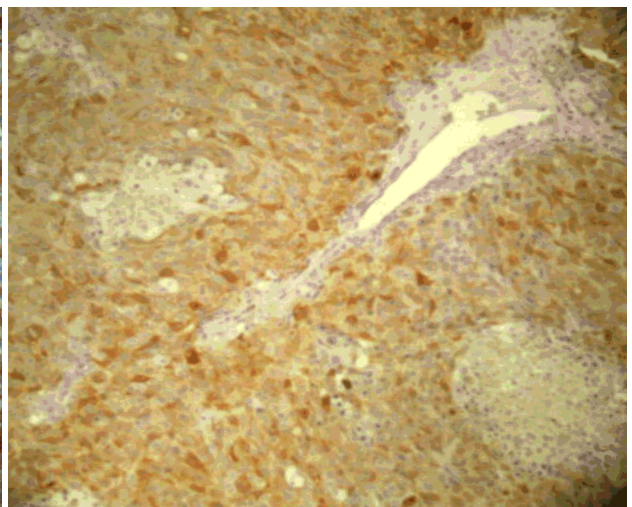
**Figure 3** – Malignant spindle-shaped cells mixed with pigmented cells (HE staining, 100×).



**Figure 4** – Malignant melanocytes in the epithelium (Melan-A staining, 100×).

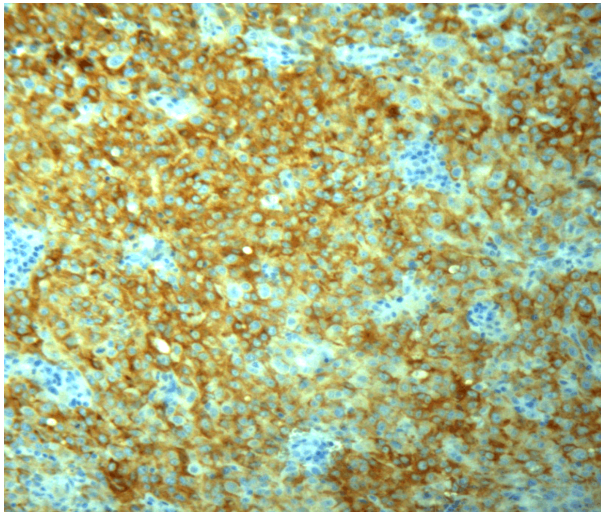


**Figure 5** – Immunoreaction for HMB-45 showing strong positivity staining of the tumor cell (100×).



**Figure 6** – Immunoreaction for S-100 protein showing strong positivity staining of the tumor cells (100×).





**Figure 7 – Immunoreaction for Melan-A showing strong positivity staining of the tumor cells (100×).**

## Discussion

Malignant melanomas are malignant tumors, most of them with cutaneous origin. A small number of melanomas do occasionally arise from non-cutaneous tissue that contains melanocytes, such as leptomeninges, uvea and gastrointestinal, respiratory and genitourinary tracts [4]. Mucosal melanomas account for approximately 10% of all malignant melanomas of the head and neck [5] and 1.3% of all malignant melanomas [6, 7]. The most common sites of involvement are the nasal cavity, paranasal sinuses and oral cavity [5]. Mucosal melanoma of the larynx is extremely rare tumor with about 60 cases reported in the medical literature [8], but is more frequent than metastatic disease [9]. Several authors classify malignant melanoma of the larynx into primary and secondary (metastatic) types [10, 11]. When diagnosing primary mucosal melanoma, especially in some sites on which it rarely arise, it is of crucial importance to exclude possibility of metastatic lesion from primary cutaneous or ocular melanoma. Differentiation of primary from the secondary lesion may be challenging, especially because of the fact that melanoma may disappear from primary site after metastasis [12–14]. Presence of melanocytes was observed in normal laryngeal mucosa [8], so although it is uncommon, origin of primary mucosal melanoma in larynx is possible. Most patients with laryngeal melanoma are white men in their sixth and seventh decade of life, with only two reports in Asian individuals [6, 9] and about 80% are males [8, 13]. It mostly occurs in supraglottic region and true vocal cords [8–13]. Smoking is a major risk factor [15], but exposure to sunlight, human papilloma virus, chronic irritants and carcinogenic compounds are also presumed to play a role [16]. Recently, several studies reported that malignant melanomas are related to an altered immune system and many genes have been speculated to be involved in its pathogenesis [6]. The most common presenting symptom is hoarseness, followed by throat irritation and shortness of breath [8]. Other presenting symptoms include sore throat, dysphagia, neck swelling, and pain. Our patient presented with hoarseness, neck discomfort and very difficult breathing.

On gross examination, malignant melanoma may have slate gray, brown or black pigmentation, which may be a clue to diagnosis [17]. Histopathologically, primary melanoma tumors have junctional activity (malignant melanocytes in the dermo–epidermal junction) in the adjacent lateral or overlying mucosa or both [18]. Also, may be identify *in situ* component (malignant melanocytes in the surface epithelium) [19]. On the other hand, the identification of melanocytes in the submucosal compartment and mucoserous glands of the larynx led to the assumption that primary malignant melanoma could arise in the larynx not only from mucosal melanocytes, but also from those present in the submucosa [20]. Thus, some authors consider that the presence of a dermo–epidermal junctional or *in situ* component is not a cardinal feature in the diagnosis of primary laryngeal lesion [9]. In the present case, malignant melanocytes were identified in the mucosa despite of its extensive ulceration. In case of metastatic laryngeal melanoma, the overlying mucosa is intact and the malignant sheets cells are dispersed in the submucosal layer [18]. The tumor histology also shows a variety of cells with spindled, polygonal, round and mixed shapes [1]. Cells often contain dark brown cytoplasmic and nuclear melanin however, some lesions are amelanotic and others demonstrate features similar to malignant neoplasm of different origins. Immunohistochemical staining must be performed in order to establish and confirm the diagnosis of malignant melanoma [13]. The diagnosis depends in immunoreactivity with S-100 protein and melanocytic markers including HMB-45 and Melan-A in a pleomorphic epithelioid or spindle cell neoplasm is almost diagnostic of malignant melanoma [2, 9]. Electron microscopy may identify the presence of melanosomes or premelanosomes. PET-scan and/or magnetic resonance imaging (MRI) can be used to stage primary melanoma [14].

Mucosal melanomas are more aggressive and have worse prognosis than cutaneous tumors with overall five-year survival of less than 10% [8]. In the literature review of Terada *et al.* [8], of 28 patients for whom data were available, only two survived more than five years. Poor prognosis is associated with early presentation of distant metastases despite adequate locoregional control [4, 21]. At the time of diagnosis, most of mucosal melanomas already have distant micrometastases [12]. The treatment for mucosal melanomas of the head and neck, including laryngeal lesions, is complete surgical excision. Postoperative radiation therapy to the affected area has been shown to improve local control in several retrospective series, but is not clear if this translates to an improvement in prognosis [4, 22]. Sirikanjanapong *et al.* [6] have shown an involvement of immune system dysregulation in pathophysiology of mucosal melanomas with identification of certain genes like IL-17A and CD70. This can be a major finding towards development of effective adjuvant immunotherapy for the treatment of melanomas [17].

Although several histopathological features, such as pleomorphism, anaplasia, mitotic activity and depth of invasion are known to affect the prognosis of cutaneous malignant melanoma, similar correlation has not been established in mucosal malignant melanoma of the head

and neck owing to the rarity and unpredictability of these lesions [13].

## ✉ Conclusions

Primary laryngeal mucosal melanomas are very rare but aggressive tumors. The diagnosis of melanoma is based on histopathological examination and immunohistochemical stains, but in order to diagnose a primary laryngeal melanoma any other primary lesion (cutaneous or mucosal) it has to be excluded.

## Conflict of interests

The authors declare that they have no conflict of interests.

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