Proceedings of Anticancer Research, 2024, Volume 8, Issue 5
http://ojs.bbwpublisher.com/index.php/PAR
ISSN Online: 2208-3553
ISSN Print: 2208-3545

Primary Malignant Melanoma of the Larynx: Case Report and Literature Review

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Abstract: Primary malignant melanoma of the larynx is extremely rare. This paper reports a case of a patient with primary malignant melanoma of the larynx. Preoperative laryngoscopy revealed a cauliflower-like mass in the supraglottic region, and a CT scan of the pharynx suggested laryngeal cancer with cervical lymph node metastasis. The patient underwent a total laryngectomy with lymph node dissection, and postoperative pathology confirmed a malignant melanoma in the supraglottic region of the larynx.

Keywords: Larynx; Primary; Malignant melanoma

Online publication: September 25, 2024

1. Basic information

In February 2023, the patient, male, 70 years old, was admitted to the hospital due to a sore throat accompanied by hoarseness for half a month. Laryngoscopy showed a grayish-white mass on the right edge of the epiglottis, extending to the laryngeal surface, with a cauliflower-like growth on the right side of the laryngeal surface. A CT scan of the pharynx suggested laryngeal cancer with cervical lymph node metastasis (**Figure 1A**). The preoperative diagnosis was a laryngeal tumor. Under general anesthesia, the patient underwent a total laryngectomy with lymph node dissection. Postoperative pathology revealed a cauliflower-like mass measuring 4.0 × 3.0 × 2.5 cm at the base of the supraglottic epiglottis. The cut surface was gray-white and reddish-brown, with a soft texture (**Figure 1B**).

Microscopic examination showed invasive tumor growth with necrosis and an unclear boundary with surrounding tissues. Under high magnification, the tumor cells exhibited marked atypia, with slightly basophilic cytoplasm, prominent nucleoli, and frequent mitotic figures (**Figures 1C–E**).

Immunohistochemical staining results: S-100, Melan-A, HMB-45 (positive); CK, P40, CK5/6, CgA, Syn (negative); Ki-67 (70% positive) (**Figures 1F–I**). After excluding other possible primary lesions in other parts of the body, the final diagnosis was primary malignant melanoma of the larynx with lymph node metastasis.

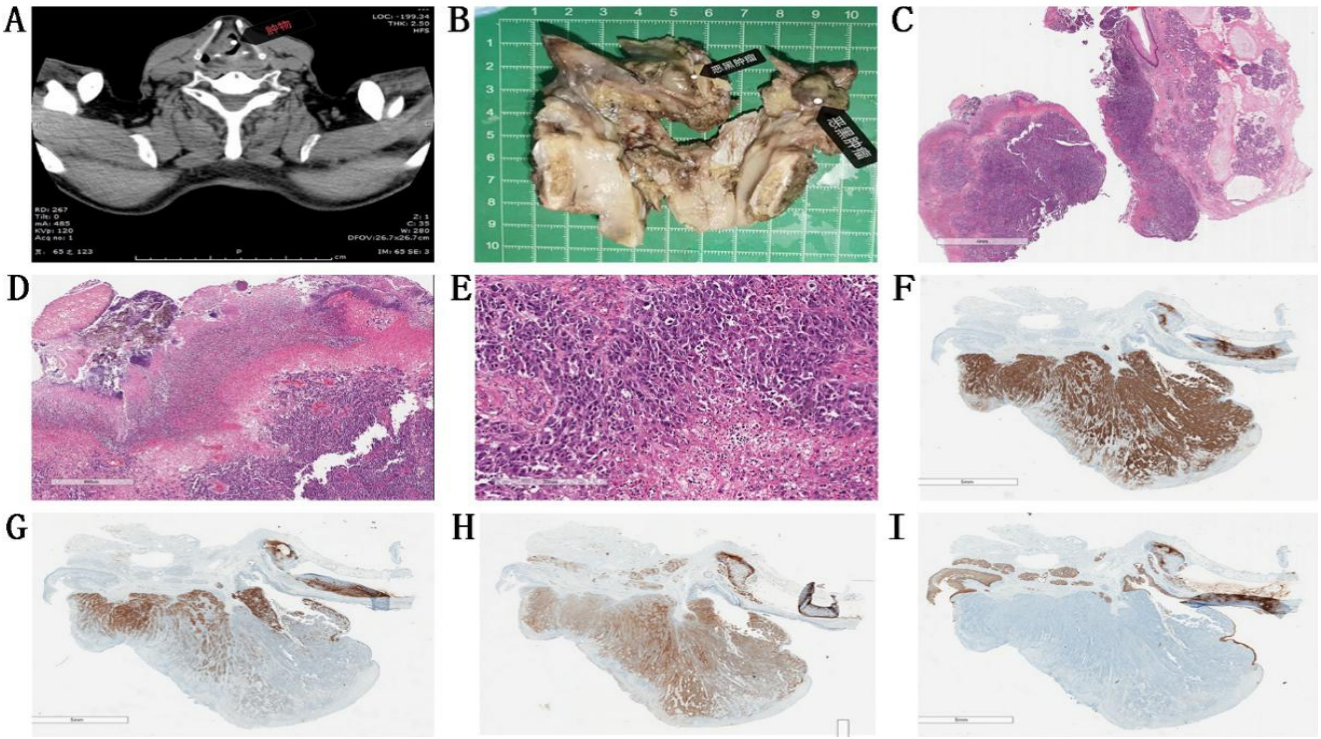

Figure 1. CT and pathological examination images of primary laryngeal melanoma. **(A)** CT scan shows a mass on the right edge of the epiglottis; **(B)** Gross examination reveals a cauliflower-like mass, 4.0 × 3.0 × 2.5 cm in size, at the base of the supraglottic epiglottis, with a gray-white and reddish-brown cut surface and soft texture; **(C)** Low-power microscopic view shows invasive tumor growth (HE ×40); **(D)** Medium-power microscopic view shows abundant sinusoids in tumor cells, with some pigmentation and extensive necrosis (HE ×200); **(E)** High-power microscopic view reveals marked tumor cell atypia, frequent mitotic figures, and prominent nucleoli (HE ×400); **(F–H)** Immunohistochemical staining shows tumor cells positive for HMB-45, Melan-A, and S-100 (×40); **(I)** Tumor cells negative for CK (×40).

2. Discussion

Malignant melanoma is a type of cancer that originates from melanocytes derived from the neural crest and accounts for 1% to 3% of all malignant tumors. It can occur in various tissues or areas, such as the skin and mucous membranes [1]. Mucosal melanoma refers to melanoma occurring in mucous membrane sites such as the nasal cavity, sinuses, oral cavity, esophagus, gastrointestinal tract, anal canal, and genitourinary system. Compared to cutaneous melanoma and other subtypes, mucosal melanoma has a poorer prognosis, with more patients presenting with distant metastases at initial diagnosis and a significantly lower 5-year survival rate. Terada *et al.* [2] indicated that primary mucosal malignant melanoma of the head and neck might originate from dispersed melanocytes in the mucosa. These cells may be present in the epithelial basal layer of the nasal cavity, oral cavity, oropharynx, and esophagus, while melanocytes are rarely detected in the larynx, which could explain why primary laryngeal melanoma is so rare. This article presents a case of primary malignant melanoma originating from the larynx.

The histology of primary laryngeal malignant melanoma is consistent with that of malignant melanomas at other sites: the tumor grows invasively, melanin is visible, cells exhibit significant atypia, nuclear membranes are clear, nuclear grooves and intranuclear inclusions are observed, prominent nucleoli are visible, and abundant mitotic figures are present. Immunohistochemical staining is positive for S-100, HMB-45, and Melan-A. It is necessary to distinguish it from metastatic malignant melanoma and other laryngeal tumors.

(1) Metastatic malignant melanoma is often multifocal, with lymphatic or vascular invasion, and patients

usually have evidence of tumors outside the larynx.

(2) Poorly differentiated squamous cell carcinoma, the most common laryngeal tumor, often presents as a well-defined sheet-like structure, with positive immunohistochemical markers for CK, P40, and P63.

(3) Neuroendocrine tumors, the second most common tumors in the larynx, are composed of uniform round or small polygonal cells, arranged in nests, rosettes, or glandular patterns, with abundant sinusoids in between. Neuroendocrine markers (CgA, Syn, CD56) are positive. These tumors include typical carcinoids, atypical carcinoids, neuroendocrine-type small cell carcinoma, and mixed neuroendocrine-type small cell carcinoma.

(4) Undifferentiated carcinoma is highly aggressive, with a nested, lobular, or sheet-like distribution under the microscope. It lacks squamous or glandular differentiation, has a high nuclear-to-cytoplasmic ratio, and necrosis and mitotic figures are common. Ki-67 is highly positive on immunohistochemical staining.

This case exhibited typical histomorphological features, and after thoroughly excluding metastasis and other tumors, the diagnosis was confirmed as primary malignant melanoma of the larynx.

The pathogenesis of mucosal melanoma has not been fully elucidated. Some scholars believe that melanocytes originate from the neuroectoderm and can migrate to mucous membranes of the endoderm (such as skin, uvea, and retina) and other ectodermal tissues, but they rarely migrate to the mucosa of the nasopharynx, larynx, or trachea-esophageal tract [3]. Melanoma is usually associated with alterations in signaling pathways such as Ras/MAPK, INK4A/ARF, and PTEN/AKT [4], with abnormal activation of the Ras/MAPK pathway playing a critical role in melanoma development. Approximately 50% of melanomas are associated with activating mutations of the *BRAF* gene in this pathway [5]. A retrospective study in China found that the mutation rate of the *BRAF* gene in Chinese melanoma patients is about 23.7% [6]. The molecular characteristics of mucosal melanoma differ significantly from those of cutaneous melanoma, primarily showing a low mutation burden, fewer point mutations, and higher genomic instability [7]. The mutation frequency of *BRAF* and *NRAS* is much lower than that of cutaneous melanoma, and most of the mutations are of low activity. In contrast, mutations in *KIT*, *SF3B1*, and *SPRED1* are more frequent than in cutaneous melanoma [8], indicating that primary laryngeal malignant melanoma may have a different pathogenesis, leading to differences in treatment strategies.

The treatment for mucosal melanoma primarily involves surgical resection combined with neoadjuvant therapy [1]. Research has shown that dual immunotherapy with PD-1 antibodies and CTLA-4 antibodies is superior to monotherapy. The combination of toripalimab and axitinib as a first-line treatment is promising. Toripalimab is an anti-PD-1 monoclonal antibody, and axitinib is a VEGFR1-3 inhibitor. VEGF exerts an immunosuppressive effect by inhibiting dendritic cell maturation. It also reduces the number of regulatory T cells and myeloid-derived suppressor cells, enhancing the efficacy of PD-1 therapy [9].

Prognostic factors for malignant melanoma include gender, age, location, tumor Breslow thickness, and tumor Clark invasion depth [10]. Although mucosal melanoma cannot be evaluated using Breslow thickness or Clark invasion depth, pathological examination, in this case, revealed that the tumor invaded the lamina propria and submucosa but did not invade the laryngeal cartilage or bone tissue. Local excision of the tumor in melanoma patients can clear the local lesion and reduce recurrence rates, but the prognosis for malignant melanoma of the larynx remains poor. Studies have shown that, following surgical excision, the recurrence rate of laryngeal malignant melanoma is lower than that of other head and neck melanomas [11], though the cause remains unclear. The cure rate for primary malignant melanoma of the larynx is still not ideal, with a 5-year survival rate below 20% [12], and most patients die from distant metastases. Due to the rarity of primary malignant melanoma of the larynx, there is a lack of data on prognostic indicators. In this case, the patient remained disease-free for 2 months postoperatively, with no recurrence or metastasis observed to date.

Primary malignant melanoma of the larynx is a rare disease with an extremely low incidence. Diagnosis relies mainly on clinical history, imaging studies, histopathology, and immunohistochemical staining. The main treatment for this disease is surgical excision combined with postoperative targeted therapy. The extent of surgical excision is determined by the size, location of the tumor, and the presence or absence of lymph node metastasis. Primary malignant melanoma of the larynx is highly invasive, has a poor prognosis, and is characterized by high postoperative recurrence and systemic metastasis rates. Clinicians should aim for early diagnosis, early surgery, and combined treatment with postoperative radiotherapy and chemotherapy.

Disclosure statement

The authors declare no conflict of interest.

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