CASE REPORT

Primary glottic malignant melanoma of the larynx (PGMML): a very rare entity

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SUMMARY

Primary glottic malignant melanoma of the larynx (PGMML) is a very rare clinical entity with less than 20 cases reported in the literature so far. The most frequently reported subsite in primary malignant melanomas of the larynx is the supraglottic larynx. The vocal cord as a subsite for primary malignant melanoma is very rare. The present case is a primary glottic malignant melanoma involving both vocal cords. PGMML may present early due to associated hoarseness of voice, unlike other non-cutaneous melanomas in the head and neck. Non-cutaneous malignant melanomas in the head and neck are historically very aggressive in nature and known for poor outcomes and survival. Most non-cutaneous melanomas described in the literature have been superficial spreading or ulcerative in nature, unlike the present case, in which proliferative, polypoidal growth was seen. No associated risk factor was present in this case. Every reported case of this rare entity further adds to the better understanding of tumour biology and expression.

BACKGROUND

Primary non-cutaneous melanomas in the head and neck are uncommon lesions; these account for 6–20% of head and neck malignant melanomas and about 1% of all melanoma cases.^{1–3} The most frequent sites for malignant non-cutaneous melanomas of the head and neck are the sinonasal (55%) and oral (40%) cavity.⁴ Other rare sites, in order of frequency, are the pharynx, larynx and oesophagus.¹ About 98% of tumours of the larynx are of squamous cell histology, 1% are of glandular origin as adenocarcinomas, and about 0.5% are rare sarcomas, the malignant melanoma being the medical oddity in this latter group.⁵ Owing to rarity of the disease, treatment protocols and prognostic factors are not well established in the literature. So each case is important for understanding the natural course of the disease, tumour morphology and pattern of spread, and for establishing guidelines for further management of the tumour.

CASE PRESENTATION

A 70-year-old woman presented to the outpatient department, with a foreign body sensation in her throat for 7 months and hoarseness of voice for 5 months. The sensation of the foreign body in her throat gradually increased to difficulty in swallowing solids over the past 1 month. Her hoarseness had progressively increased over the last 5 months. The pain in her throat was associated with deglutition, for which she was taking analgesics routinely

for 1 month. There was no history of weight loss, fever, oral bleed or other complaint suggestive of an infective pathology. No other comorbidities such as diabetes or hypertension were noted. There was no relevant family history. The patient was a non-smoker and did not drink alcohol. On general physical examination, her ECOG status was one, and there was no positive clinical finding in general physical and skin examination. No palpable enlarged nodes were seen on clinical neck examination. On indirect laryngoscopy, there was polypoidal, proliferative growth with interspersed pigmented areas seen in the larynx, involving right and left vocal cords and extending to the plica vestibularis on both sides. Anteriorly, the growth just touched the anterior commissure and posteriorly invaded only the posterior commissure of the interarytenoid area. The epiglottis and piriform area were visibly free from tumour (figure 1).

INVESTIGATIONS

Chest X-ray, blood biochemistry and haemogram were normal. Meticulous skin examination was negative for any cutaneous lesion. Ultrasonography of the whole abdomen was performed to rule out any suspected visceral lesion; it was negative. Direct laryngoscopy was performed and biopsy taken. Microscopically, on H&E staining, marked atypia with multinucleated epithelioid polygonal cells admixed with spindle cells was seen (figure 2). Immunohistochemistry (IHC) suggested immunoreactivity with diffuse positivity for Melan-A, S-100 protein, HMB-45 and vimentin against a pleomorphic background (figure 3). IHC was negative

Figure 1 Direct laryngoscopy findings: pigmented, polypoidal growth involving both vocal cords and extending to the vestibular folds.

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Figure 2 Photomicrograph showing H&E staining (x200): pleomorphic picture of polygonal cells interspersed with spindle cells.

for synaptophysin and cytokeratin. All the clinical and histopathological findings suggested primary malignant melanoma of the larynx.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes melanosis, oral nevi, lentiginos, Addison's disease, angiomas or vascular lesions, metastasis, primary squamous cell carcinoma, neuroendocrine carcinoma, non-Hodgkin's malignant lymphoma, extramedullary plasmacytoma, malignant fibrous histiocytoma, fibrosarcoma and malignant schwannoma.⁶⁻⁷ On the basis of location, laterality and symmetry, melanosis can be differentiated clinically from malignancy.⁸ Mucosal lentiginos can be a part of LAMB (lentiginos, atrial myxomas, mucocutaneous myxoma and blue nevi) syndrome, so its characteristic findings allow for an early diagnosis. Addison's disease patients have diffuse pigmentation of mucosal surfaces of the oral cavity. Angiomas/vascular tumours may look nodular or fleshy and lack melanin (amelanotic melanoma adds to the diagnostic dilemma). The most diagnostically challenging task is to differentiate between primary lesion and metastatic mucosal lesion. Negative clinical history, meticulous skin

examination, no systemic finding and positive histology suggests a diagnosis of primary melanoma. A gross nodular/proliferative and pigmented appearance, no accessory mucosal lesion, lack of bilaterality and lack of systemic or syndromal features assist in solving this diagnostic challenge. Gross appearance, histology and, most importantly, immunohistochemistry, contribute towards the final diagnosis. IHC is generally positive for S-100, Melan A, HMB-45 and vimentin. The S-100 protein and HMB-45 positivity in a pleomorphic spindle cell or epithelioid background in a neoplasm is almost diagnostic of a melanoma. Some authors suggested a BRAF mutation for malignant melanoma, but later it was found to be more common in cutaneous melanomas than their mucosal counterpart lesions, suggesting a different mechanism and differential response to treatment protocols.⁹

TREATMENT

Melanomas are less radiosensitive than tumours of other lineage and most recent studies refute the advantage of locoregional control in the postoperative setting, so no upfront radiation therapy was planned.¹⁰ The patient was referred for surgical oncology for radical laryngectomy in view of the localised and surgically favourable site lesion. In spite of her advanced age, the patient's general condition was good at the time of presentation and there was no clinical nodal spread. However, she was non-compliant and had never taken surgical advice. She was subsequently lost to follow-up but returned after 4 months in poor general condition and with acute breathlessness. Chest X-ray and ultrasonography of the whole abdomen was carried out, and suggested multiple lung and liver metastasis. The prognosis was explained to the relatives of the patient. As the patient preferred to go home and spend her last days at home, she was discharged with symptomatic treatment and palliative care advice.

OUTCOME AND FOLLOW-UP

Despite the palliative intervention, the patient succumbed a week after her second visit. The duration from first visit to death was about four and half months. Although no surgery, chemotherapy or radiotherapy was administered to this patient at any point of time, this case gives insight into the natural

Figure 3 Immunohistochemistry showing diffuse positivity for Melan A, HMB-45, S100 and vimentin.

history, tumour biology and expression of this condition. It also shows how a rare, but apparently resectable tumour, can become aggressive and rapidly fatal, if not treated early.

DISCUSSION

The first case of non-cutaneous or mucosal melanoma was described in 1856 by Weber, but its distinct entity was given by Lucke in 1869.^{11 12} Cutaneous melanoma comprises 91.2% of all melanomas, whereas ocular, mucosal and unknown primaries account for 5.2%, 1.3% and 2.2% of cases, respectively.¹³ In another study, by McLaughlin *et al*,¹⁴ head and neck mucosal melanomas represented 0.4% of all melanomas and 8.4% of non-cutaneous melanomas. Until 2006, only about 60 cases of melanoma of the larynx and 13 cases of the glottic larynx had been reported in literature (table 1).

In the past, no clear distinction regarding the origin as primary or metastatic was made in the literature. So, it was not known how many cases of mucosal melanomas were metastatic and how many were primary. Primary mucosal melanomas are very rare neoplasms and are diagnoses of exclusion against a background of positive histopathology. Despite the dramatic increase in the incidence of cutaneous melanoma in recent years, the incidence of mucosal melanoma has been relatively stable.^{13 15} Median age of presentation in primary non-cutaneous melanomas is in the seventh decade, which is a decade later than for their cutaneous counterparts.⁴ The aetio-pathogenesis of mucosal melanomas has not yet been fully elucidated. Melanocytes are neuroectodermal in origin and usually migrate to the endodermal mucosal structures such as the skin, uveal tract, retina and other ectodermal structures. Very rarely, they migrate to the nasopharynx, larynx or tracheo-oesophageal mucosa, and this explains the rarity of this disease in these locations.¹⁶ Many cases have described primary junctional melanocytic activity solely within the mucosa, but this is not a cardinal sign in establishing a diagnosis of primary malignant mucosal melanoma.¹⁷ Every attempt should be made to rule out any possible cutaneous lesion. Chest X-ray, ultrasound of the thorax, abdomen and pelvis, and positron emission tomography/CT evaluate metastatic spread from the primary and locate possible primary lesions. The growth pattern of the mucosal melanoma of the larynx in our case resembles a nodular/polypoidal pattern. Classification according to depth (Breslow) is not suitable for these kinds of tumours, because of locally advanced

disease at presentation and poor prognostic value. The Ballantyne staging system was used in the past by most authors, but presently the TNM system is advocated for most head and neck cancers, including melanomas.¹⁸ No T1–2 or stage I and II was included in AJCC as mucosal/non-cutaneous melanomas are aggressive tumours in the head and neck, irrespective of subsite involvement (table 2).

The rich lymphatic and vascular network in the submucosa contributes to early spread to locoregional nodes and distant sites but may vary according to the subsite involved. Because of lack of early presenting signs and symptoms, unlike this case, and unusual anatomic sites, such tumours are only diagnosed at advanced stages.¹⁹ Because of their aggressive biology, even localised lesions may require wide radical surgery for optimal results. Prognosis still remains grave despite adjuvant treatment. Early detection allows the best hope for cure. Irrespective of nodal spread in regional nodes, surgical resection is the primary treatment for localised melanomas. Complete resection with melanoma-free margins is often achieved in the early stage of primary laryngeal melanoma, unlike in the other sites in the head and neck. However, most patients present in a state of advanced disease with extensive supraglottic, subglottic, transglottic, nodal and distant spread that preclude surgical intervention. Older mean age at presentation and associated age-related comorbidities are other concerns for radical dissection. The literature on prophylactic lymph node dissection and elective nodal dissection does not correlate with survival advantage.²⁰ In the past, melanomas were thought to be radioresistant, but a few recent studies show a locoregional benefit (lymph node field control) in a postoperative setting restricted to cases with high risk of nodal relapse.¹⁰ Long-term follow-up studies confirm no additional survival benefit.²¹ To overcome this relative radioresistance, the use of high-linear energy transfer radiation such as using neutrons is under investigation. Local recurrence after treatment in most of the reported literature of malignant melanoma of larynx was around 19% as compared to other sites of

Table 1 Primary glottic malignant melanoma of the larynx (PGMML) cases reported in the literature

Primary glottic malignant melanoma of the larynx (PGMML)			
1.	Cremonesi*	1956	No follow-up
2.	Welsh and Welsh ⁵	1960	No follow-up
3.	El Barbary <i>et al</i> *	1968	Died of disease (9 m)
4.	El Barbary <i>et al</i> *	1968	No follow-up
5.	Lorentz*	1979	No follow-up
6.	Maki*	1984	Died of disease (14 m)
7.	Hussain and White head*	1989	No evidence of disease (24 m)
8.	Wenig ¹⁷	1995	Died of disease (36 m)
9.	Duwel and Michielssen*	1996	No follow-up
10.	Nakanishi <i>et al</i> *	1996	Alive with disease (10 m)
11.	Asare-Owusu <i>et al</i> ¹⁹	1999	No evidence of disease (40 m)
12.	Szmeja <i>et al</i> *	2000	?? No details
13.	Amin <i>et al</i> ³	2001	No follow-up
14.	Present case	2015	Died of disease (4.5 m)

*cases mentioned/compiled in article by Terada *et al*.

Table 2 AJCC (TNM) classification of mucosal melanoma of the head and neck*

Primary tumour			
T3	Mucosal disease		
T4a	Moderately advanced disease. Tumour involving deep soft tissue, cartilage, bone, or overlying skin		
T4b	Very advanced disease. Tumour involving the brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space or mediastinal structures		
Regional lymph nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastases		
N1	Regional lymph node metastases present		
Distant metastasis			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis present		
Clinical stage			
Stage III	T3	N0	M0
Stage IVA	T4a	N0	M0
	T3-4a	N1	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

*AJCC Cancer Staging Manual, 7th ed.

the head and neck, where it ranges from 42% to 64%. The reason is not known but it is probably due to the easy resectability of laryngeal tumours.^{22 23} Most of the patients who have poor locoregional control or local recurrence, have been found with metastatic disease on work up. It has been reported that 88.8% of those who succumb due to distant metastasis also had local site or regional nodal failure.²⁴ Because of the rarity of primary laryngeal melanomas, no trials on aetiology, treatment and outcome seem possible. So every reported case of this rare disease is an important source for collecting vital information regarding epidemiology, presentation, treatment and prognosis and for understanding the tumour biology and behaviour.

Learning points

- ▶ Primary malignant melanoma is a very rare tumour in the larynx, and a glottic primary is a medical oddity.
- ▶ The aetiopathogenesis is still not known and a critical pathological review of postoperative and autopsy specimen findings can solve the dilemma in future.
- ▶ Tumour expression, pattern of spread, mutation profile and prognostic indicators are different from those of cutaneous melanoma sites.
- ▶ Early operable lesions can be rapidly fatal if not treated urgently, due to the exceptionally aggressive nature of this rare entity.

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