ABSTRACT

The review considers management strategies for malignant melanoma metastatic to the larynx. This rare clinical entity lacks clear treatment recommendations because extirpative surgery can often result in severe functional debilitation in patients with limited life expectancy. Here, we report a case of melanoma metastatic to the larynx in a patient with a prior history of Hodgkin lymphoma. The patient was treated with partial laryngectomy and local radiation therapy. The rationale for treatment decisions and for surgical and radiotherapeutic techniques and the associated literature are discussed.

KEY WORDS

Laryngeal melanoma, mucosal melanoma

1. INTRODUCTION

Malignant melanoma metastatic to the mucosa is extremely rare. Review of the literature shows that 0.6%–9.3% of patients with cutaneous melanoma will have metastases to the mucosa of the upper aerodigestive tract, and of those metastatic sites, 12% will be laryngeal. Given the rarity of the problem, optimal management is unclear, and clinicians are faced with a therapeutic dilemma, given that treatment options can result in great differences in quality of life. This article discusses a patient with laryngeal metastatic malignant melanoma and the therapeutic strategies used in the case.

2. CASE DESCRIPTION

A 61-year-old man presented to NYU Medical Center with midline neck discomfort, but without difficulty breathing or swallowing, voice changes, hemoptysis, or weight loss. He had a history of a T3N0M0 cutaneous malignant melanoma involving the left supraclavicular skin that had been treated with wide local excision and immunotherapy 7 years earlier in Russia. The details of his prior therapy were not available.

The patient’s past medical history also revealed prostate adenoma, benign gastrointestinal polyps, thoracotomy, and Hodgkin lymphoma treated with splenectomy, chemotherapy, and radiation therapy (rt). Those therapies had been performed in Russia at a facility that had since been closed, per the patient’s history. Details on the therapies were therefore unavailable, but the patient recalled having chemotherapy for 3 months and rt for 4 weeks.

Biopsy determined that the laryngeal lesion was metastatic malignant melanoma, and the patient came to the United States for treatment. A fibre-optic endoscopic exam revealed a pigmented, exophytic mass lesion in the supraglottic posterior commissure region. No abnormalities of vocal cord motion were noted, and there was adequate secretion clearance and swallowing, and a clear airway. Imaging by positron-emission tomography/computed tomography (pet/ct) revealed intense 18F-deoxyglucose uptake to the larynx, consistent with malignancy. There was no evidence for local recurrence at the left shoulder or for any other site of metastatic disease.

After direct laryngoscopy and esophagoscopy, partial laryngopharyngectomy (Figure 1) and radial forearm microvascular free flap were performed. Although a formal neck dissection was not performed, lymph nodes at level III were removed as part of the primary resection. The tumour was removed and the pyriform sinus wall and aryepiglottic fold were reconstructed with the intention of functional restoration.

Pathology assessment (Figure 2) revealed pleomorphic epithelioid cells with areas of pigmentation. Immunostains were diffusely positive for S-100 protein, HMB-45, melan-A, and PNL2. Those findings are consistent with melanoma. All margins were clear of disease, and level III lymph nodes were found to be negative for metastatic melanoma.
The patient’s postoperative course was complicated by bronchopneumonia; however, he was decannulated 32 days after surgery. He was able to tolerate a regular diet and to speak without difficulty. Postoperative endoscopic exam revealed bilateral true vocal cord mobility and an adequate airway (Figure 3).

The patient underwent postoperative adjuvant RT 31 days after the surgery. The clinical target volume was the laryngeal remnant, with a margin of surrounding soft tissues. This volume was adequately encompassed with 10×10-cm right and left lateral opposed portals with custom blocking. Although level II and III lymph nodes were included in the treatment volume by virtue of the technique, lymph node basins were not electively treated given the metastatic nature of the lesion and the patient’s prior history of neck irradiation. Generous flash occurred anteriorly, and the spinal cord was blocked throughout treatment. To provide a sufficient superficial

**FIGURE 1** Intraoperative exposure of the malignant melanoma metastatic to larynx.

**FIGURE 2** (A) Gross laryngeal excision specimen showing a polypoid mass. (B) Whole-mount picture of the laryngeal polyp. (C) A magnified view shows dense cellularity of the submucosal space of the polyp. (D) Higher magnification reveals pleomorphic cells with scattered pigmented cells (arrows). The insert shows melanocytes stained positive for S-100 protein.
dose, 6 MV photons were selected, and to optimize homogeneity, 15-degree wedges were used. The patient received a dose of 50 Gy in 25 fractions over 5 weeks. The treatment was well tolerated, with minor dysphagia and hoarseness as the only side effects.

The patient subsequently developed metastases in lung and bone 6 months after surgery. He was placed on palliative care medications and returned to Russia at that time, with a prognosis of several weeks of life.

3. DISCUSSION

Melanoma is a neoplasm that arises from the neural crest, the melanocytes being of neuroectodermal origin. Primary malignant melanoma of the mucosa is more common than metastatic disease and has a different site predilection, occurring more often in the nasal cavity and the maxilla. However, melanoma metastatic to the mucosa of the head and neck has been encountered most often in larynx, tongue, and tonsil. The supraglottis
appears to be the most affected location for laryngeal metastatic deposits.

Hematogenous and lymphogenous spread of malignant cells to the larynx have both been postulated. Vascular spread may be of the “vena cava” type—that is, vena cava to right heart to pulmonary circulation to left heart to aorta to external carotid artery to upper thyroid artery to laryngeal artery, or retrograde through the vertebral venous plexus. Lymphatic spread may follow a similar orderly cascade or be retrograde via anastomoses.

Histopathologically, primary melanoma tumours show junctional activity in the overlying or adjacent lateral mucosa (or both), but metastatic melanoma is typically covered by an intact mucosal layer. A metastatic tumour has both intact overlying mucosa and adjacent mucosa devoid of junctional changes. The diagnosis depends on histopathologic evaluation and appearance and also immunoreactivity with S-100 protein and melanocytic markers including HMB-45, melan-A, or PNL2. The presence of S-100 protein and reactivity for any one of the foregoing melanocytic markers in a pleomorphic epithelioid or spindle cell neoplasm is almost diagnostic of melanoma.

In our current case, the polypoid tumour was lined by intact squamous mucosa. The submucosal space was replaced by pleomorphic epithelioid cells with areas of pigmentation. Immunostains demonstrated tumour cells diffusely positive for S-100 protein, HMB-45, melan-A, and PNL2. At the ultrastructural level, the melanocytes contained pre-melanosomes and melanosomes.

The differential diagnosis with a laryngeal lesion includes primary tumours (squamous cell carcinoma, sarcoma, neuroendocrine carcinoma, lymphoma, and other more rare entities) or metastatic tumours, of which melanoma and renal cell carcinoma most commonly affect the larynx.

The treatment of choice for primary malignant melanoma of the larynx has been complete surgical excision. An incomplete surgical excision results in prompt local recurrence. In our case, the lesion was excised with uninvolved margins, and a radial forearm microvascular free flap was used for reconstruction to restore function. Because the incidence of regional lymph node metastasis is considered low, elective neck dissection is not typically performed.

To date, 39 cases of laryngeal metastatic malignant melanoma, including the current one, have been reported. Early experience involved comprehensive surgery, including reports of total laryngectomy (Juan in 1956 and Franzoni in 1964). More recently, investigators have used organ-sparing techniques: Morgan et al. reported using CO2 laser excision and RT, and Ikeda et al. reported a case of excision with a tonsillectomy snare and KTP laser vaporization of residual disease. However, given the small number cases, heterogeneity in presentation, and variations in treatment (Table 1), firm practice guidelines are difficult to establish.

Radiation therapy has been used for the adjuvant treatment of cutaneous melanoma of the head and neck in the setting of risk factors for local relapse, such as desmoplastic subtype, close surgical margins, and multiple positive lymph nodes or extracapsular nodal extension. Laryngeal melanoma—primary or metastatic—is exceedingly rare, but similar principles can be applied to its management. In this case of supraglottic metastasis, a wide excision would have required total laryngectomy, which is inappropriate in the setting of metastatic disease. Therefore, after partial laryngopharyngectomy, RT was applied to provide durable local control and maintenance of laryngeal function.

Many RT regimens for melanoma involve hypofractionation, in which large single doses of 4–6 Gy are given 2–3 days each week to total doses of 30–40 Gy. This practice is based on in vitro and in vivo studies that proposed that melanoma’s radioresistance results from an unusually large “shoulder” in the radiation cell survival curve, suggesting the ability of cells to repair large amounts of sublethal radiation damage. However, clinical studies of hypofractionation have shown mixed results, and the optimal RT fractionation for melanoma remains controversial.

The main reason for the selection of standard fractionation in the present case was the history of prior neck irradiation in the setting of recent supraglottic laryngectomy. The exact laryngeal dose from 1982 was not known, but it was likely in the 25- to 30-Gy range. After partial laryngectomy, RT with conventional doses (50–60 Gy) and standard fractionation can result in functional complications, particularly from late damage to normal tissues. This unusual set of circumstances led us to use standard fractionation. The total dose (50 Gy) was similarly chosen to provide durable local control without high risk of laryngeal edema and necrosis, which can result as the cumulative dose exceeds 80 Gy.

4. CONCLUSIONS

Mucosal melanomas are aggressive tumours and the prognosis in malignant melanoma metastatic to the larynx is poor. Given that these patients typically have limited survival, clinicians must use treatment strategies that provide functional benefit so as to maintain quality of life without excessive toxicity. In our view, a multidisciplinary approach of partial laryngectomy and moderate-dose RT can provide effective yet well-tolerated therapy in this challenging patient population.
### Table 1: Cases of laryngeal metastatic malignant melanoma in the literature

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Location of metastasis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Massie, 1900</td>
<td>5</td>
<td>Subglottis</td>
<td>Excision</td>
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<td></td>
<td></td>
<td>Epiglottis,</td>
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<td></td>
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<td>true and false vocal cords</td>
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<tr>
<td>Fisher and Odess, 1951</td>
<td>1</td>
<td>Right vocal cord</td>
<td>Excision</td>
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<td>Loughead, 1952</td>
<td>1</td>
<td>Left vocal cord</td>
<td>Excision</td>
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<td>Faaborg—Anderson, 1953</td>
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<td>Left arytenoid</td>
<td>Radiotherapy</td>
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<td>Juan, 1956</td>
<td>1</td>
<td>Epiglottis</td>
<td>Total laryngectomy</td>
</tr>
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<td>Auriol et al., 1959</td>
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<td>Epiglottis, aryepiglottic fold, hypopharynx</td>
<td>Radiotherapy</td>
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<td>Shaheen, 1960</td>
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<td>Left arytenoids and false vocal cord</td>
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<td>Bauer and Fuchs, 1961</td>
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<td>Total laryngectomy, radical neck dissection, radiotherapy</td>
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<td>Franzoni, 1964</td>
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<td>Right arytenoid, right true and false vocal cords</td>
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<td>Tolstov et al., 1977</td>
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<td>Left aryepiglottic fold</td>
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<td>Glanz and Kleinsasser, 1978</td>
<td>1</td>
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<td>Snow et al., 1978</td>
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<td>Sacre and Lejeune, 1982</td>
<td>2</td>
<td>Report of 2 cases</td>
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<td>Ferlito and Caruso 1984</td>
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<td>Epiglottis, pharyngeal wall, left false vocal cord</td>
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<td>Morgan et al., 1985</td>
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<td>42</td>
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<td>Pirodda et al., 2002</td>
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<td>Right pyriform sinus</td>
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<td>Current case</td>
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<td>Right supraglottis, posterior commissure</td>
<td>Excision, reconstruction, radiotherapy</td>
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M = male; F = female.

### 5. References


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