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Adjuvant radiotherapy for primary mucosal malignant melanoma of the larynx

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Abstract
Primary mucosal malignant melanoma (PMML) of the larynx continues to be a rare entity. To date, there are few cases reported in the world literature consisting of mainly isolated case reports and literature reviews.

Traditionally believed to be radioresistant, we present a case of PMML of the right vocal fold managed with right cordectomy and adjuvant radiotherapy. The patient is well without any evidence of local recurrence or metastasis three years and four months from presentation.

Key words: Melanoma; Larynx; Surgery, operative; Radiotherapy, adjuvant

Case report

A 72-year-old Caucasian man presented with an increasing history of hoarseness over the past six months. There was no fluctuation of the voice quality and no period of complete normality or aphonia. There was no dysphagia, otalgia or weight loss.

He had given up smoking 40 years ago. He was an asthmatic, suffered from chronic pancreatitis and had had bilateral total hip replacements and left inguinal herniorrhaphy. He was of the view that his previous repeated intubations were responsible for his hoarseness.

Indirect laryngoscopy revealed a bulky, polypoidal right vocal fold. The rest of the ENT and systemic examination was unremarkable with no cervical lymphadenopathy.

His chest X-ray, full blood count, urea and electrolytes were within normal limits. A prompt microlaryngoscopy and biopsy arranged showed a one cm swelling of the mobile right vocal fold with a friable base and ulceration on the surface. The anterior commissure was free and there was no subglottic extension.

Histology showed a focally necrotic subepithelial spindle cell tumour composed of fascicles of cells with moderately pleomorphic hyperchromatic nuclei and elongated eosinophilic cytoplasm (Figures 1 and 2). Scattered atypical mitoses were present with occasional cells containing melanin pigment. The squamous epithelium was focally ulcerated and in one area, there was infiltration of the basal layer by atypical cells. This is suggestive of a junctional component. No vascular or lymphatic invasion was seen. The lesion was at least seven mm thick with incomplete excision. Immunohistochemistry was positive for S100 protein and HMB45 (Figures 3 and 4). No staining was seen for epithelial markers MNF116 (anti-cytokeratin) and EMA (epithelial membrane antigen) or muscle markers SMA (smooth muscle actin) and desmin.

The morphological and immunohistochemical features were those of a primary malignant melanoma of the larynx.

Following this, staging computed tomography (CT) scan of neck, chest and abdomen showed no extension beyond the right vocal fold or metastasis. A meticulous cutaneous examination was also carried out that failed to identify a cutaneous malignant melanoma. A right endoscopic cordectomy was then undertaken to excise the residual tumour mass. Histological examination confirmed complete excision.

The cordectomy was followed by adjuvant radical radiotherapy to the larynx (55 Gray in 20 fractions – 2.75 Gray per fraction over four weeks).

He has been closely followed up for the past three years and four months. There is no evidence of local recurrence or metastasis.

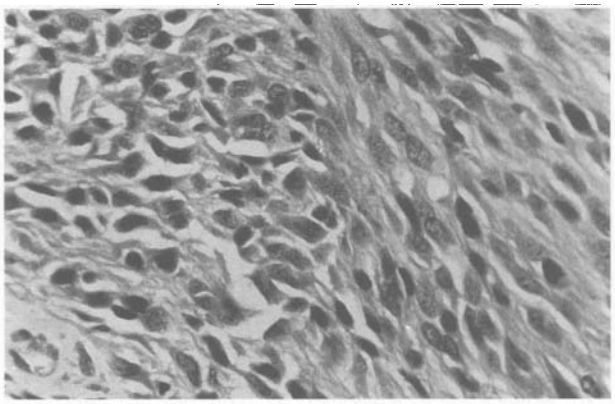

Fig. 1
Sheets and fascicles of spindle and epithelioid cells with hyperchromatic nuclei and moderate nuclear pleomorphism (H & E; × 250).

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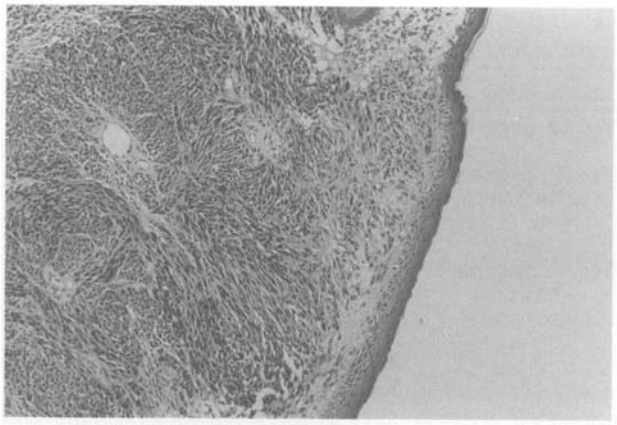

FIG. 2

Low power view showing undermining of the squamous epithelium by a spindle cell tumour. Note tumour cells replacing the basal squamous layer, possibly representing a junctional component (H & E; × 50).

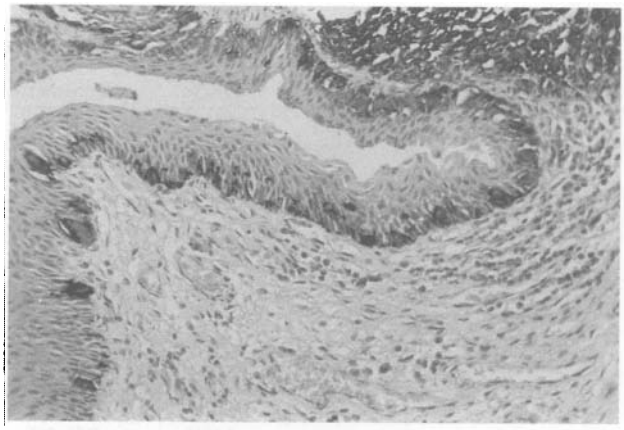

FIG. 3

Immunostaining for HMB45 confirming atypical basal melanocytic proliferation extending away from the main tumour (HMB45; × 200).

Discussion

Mucosal-derived malignant melanoma is encountered throughout the upper aerodigestive tract, where it is most frequently seen within the sinonasal tract and oral cavity (Berthelsen *et al.*, 1984; Conley, 1989).

Mucosal malignant melanoma of the upper aerodigestive tract represents from 0.5 to three per cent of melanomas from all anatomical sites (Shah *et al.*, 1977; Panje and Moran, 1986) whilst the very rare primary mucosal malignant melanoma (PMML) accounts for 0.4 to 10 per cent in the head and neck area (Mattavelli *et al.*, 1995). PMML, like other mucosal melanomas of the head and neck, are usually more lethal than their cutaneous counterparts and there is also lack of correlation between depth of invasion and prognosis (Blatchford *et al.*, 1986; Panje and Moran, 1986).

The clinicopathological features of our case report closely parallel those documented in previous reports, most of which feature Caucasian males presenting in the sixth or seventh decade (Kim and Park, 1982).

The symptoms associated with PMML are varied and include; hoarseness, dysphagia, sore throat, and sensation of a lump in the throat and a neck mass. The symptoms generally occur over relatively short periods of time, from three to six months. Although more than 60 per cent of adequately documented cases occur in the supraglottic larynx (Wenig, 1995), our case clearly arose in the glottic region.

Much is known about the aetiology of cutaneous melanoma, including relationship to sun exposure and genetic predisposition. However, the aetiology of PMML is uncertain. Reuter and Woodruff (1986) speculated that tobacco smoking plays an important role in its development. Our patient is an ex-smoker who gave up smoking 40 years ago.

The diagnosis of PMML generally is not clinically determined but is dependent on histopathological evaluation. The presence of an *in situ* or junctional component in some cases has been cited as evidence to confirm origin of these melanomas from the laryngeal mucosa (Reuter and Woodruff, 1986). The presence of S-100 protein and HMB-45 reactivity in a pleomorphic epithelioid or spindle cell neoplasm is virtually diagnostic of a melanoma. In the absence of a previous or concurrent malignant melanoma elsewhere, the laryngeal melanoma can be considered as a primary lesion (Wenig, 1995).

Traditionally, the treatment of choice for mucosal malignant melanoma, including PMML, is complete surgical excision. These tumours are generally regarded to be radioresistant. However, *in vitro* studies on cutaneous melanoma cell lines show that they may not be intrinsically radioresistant, and high dose per fraction therapy is necessary to avoid the cell lines resisting sublethal radiation doses (Wenig, 1995). The relevance of fraction size in the radiotherapy of melanoma is still somewhat unclear. Most retrospective series for metastatic cutaneous melanoma indicate a higher response rate and better long-term control when fraction sizes of >400 cGy have been used (Trotti and Peters, 1993). However, due to the potential toxicity of large doses per fraction, each case must be individualized with respect to the choice of fraction size and total dose.

Since our case was a glottic tumour, complete surgical excision but with very narrow margins was possible by way of a right cordectomy. The decision to follow this with adjuvant radiotherapy was supported by the fact that the vocal folds have few lymphatic vessels, hence malignant tumours limited to them might not be expected to spread readily by lymphatic permeation (Gray and Hawthorne, 1992).

Reviewing the literature, only eight cases of glottic PMML were found, the rest being supraglottic. The treatment and outcome of these glottic tumours are presented in (Table I). It can be seen that various treatment options led

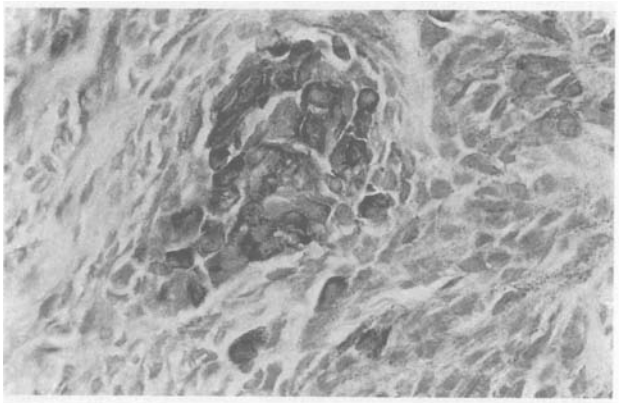

FIG. 4

Immunohistochemistry showing focal staining of tumour cell cytoplasm (centre of field) with melanin specific antibody (HMB45; × 250).

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TABLE I
THE TREATMENT AND OUTCOME OF GLOTTIC PMML REPORTED IN THE LITERATURE

Author(s)	Age/Sex	Treatment	Cervical metastases	Local recurrence	Follow-up
Loughead and Bushnell (1954)	M/68	LE	Yes (at diagnosis)	No	AWD 3.5 mths
Cremonesi (1956)	M/39	RT, ND	Yes (at diagnosis)	NF	Lost to f/u
El-Barbary *et al.* (1968)	M/40	LE, RT	Yes (at 3 mths)	No	DWD 9.5 mths
El-Barbary *et al.* (1968)	M/60	LE	No	Yes	Lost to f/u
Lorentz (1979)	F/38	None	Yes (at diagnosis)	NF	Lost to f/u
Hussein and Whitehead (1989)	M/69	RT, LA, ND	Yes	Yes	A-NED 24 mths
Wenig (1995)	M/84	LA, TL, RT	Yes	NF	DWD 36 mths
Duwel and Michielssen (1996)	F/67	TL	No	No	A-NED 39 mths
Present case	M/72	EC, RT	No	No	A-NED 40 mths

AWD, alive with disease; A-NED, alive no evidence of disease; DWD, dead with disease; EC, endoscopic cordectomy; LA, laser ablation; LE, local excision; ND, neck dissection; NF, never free of disease, RT, radiotherapy; TL, total laryngectomy.

to varying outcomes. Therefore, although not advocating adjuvant radiotherapy as the treatment of choice, our case achieved a comparably favourable outcome.

Several reports have reviewed the role of radiotherapy alone with curative or palliative intent for mucosal malignant melanoma, the largest of which reported on the outcome of 28 cases with nasal cavity and paranasal sinus tumours. The control rate was 49 per cent at three years using a treatment schedule of 50–55 Gy in 15–16 fractions (Schmidt-Ullrich and Johnson, 1996). Overall survival is poor in this disease with five year survival less than 20 per cent (Reuter and Woodruff, 1986). PMML has a low incidence of local recurrence, but the final outcome is still poor due to the 80 per cent of metastatic disease to regional lymph nodes or to distant sites (Karagiannidis *et al.*, 1998). Our patient continues to remain disease free three years and four months from presentation. Combination therapy may have been helpful in achieving this favourable outcome, but clearly, continued follow-up is essential.

Conclusion

PMML is a rare tumour with generally very poor survival. Despite the traditional view that even localized cases presenting early ought to be treated with radical surgery, this case illustrates that extended remission can be obtained with adequate excision biopsy and radical radiotherapy.

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