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Well-differentiated (oncocytoid) neuroendocrine carcinoma of the larynx with multiple skin metastases: a brief report

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Abstract

A 63-year-old woman presented with a history of increasing dysphagia of about two weeks duration. Laryngoscopy revealed a nonulcerated supraglottic epitheliomatous lesion that morphologically appeared well-differentiated and distinctly oncocytoid. Although the tumour lacked any criteria for malignancy such as cellular atypia, pleomorphism or necroses, it recurred twice after primary surgery and later gave rise to multiple painful skin metastases. The diagnosis of an oncocytoid differentiated neuroendocrine carcinoma of the larynx (laryngeal carcinoid) was made. Misinterpretation of laryngeal carcinoids is common, but can be avoided if one is familiar with this rare variant of laryngeal neoplasms.

Key words: Laryngeal neoplasms; Carcinoid tumour

Introduction

It has become more and more common to classify neuroendocrine carcinomas of the larynx into three distinct subtypes: well-differentiated neuroendocrine carcinoma (typical carcinoid); moderately differentiated neuroendocrine carcinoma (atypical carcinoid); and undifferentiated (small cell) neuroendocrine carcinoma (Ferlito and Rosai, 1991).

These laryngeal neoplasms are rare tumours with atypical carcinoid the most frequent variant. Atypical carcinoids of the larynx follow a more aggressive clinical course than do cases of typical carcinoids, usually giving rise to multiple distant metastases (Ferlito and Friedmann, 1989).

Morphologically, this subtype differs from a typical carcinoid in presenting with cellular atypia and pleomorphism, higher mitosis counts, and tumour necroses (Woodruff and Senie, 1991). Thus, tumour histology and prognosis seem to be closely correlated in laryngeal carcinoids. However, there are cases of laryngeal carcinoids that, although well-differentiated and lacking any criteria for malignancy, may yet follow a malignant course. An oncocytoid morphology was reported in some of these neoplasms (Blok *et al.*, 1985; Stanley *et al.*, 1986).

In this paper we report on an oncocytoid laryngeal carcinoid since misdiagnoses of such cases can be easily avoided, if one is familiar with the morphological spectrum of these tumours. Furthermore, knowledge of these neoplasms enables one to predict exactly their biological behaviour which is necessary as a basis for adequate therapeutical decisions.

Case report

A 63-year-old woman presented with a history of dysphagia of about two weeks duration. Direct laryngoscopy revealed a left-sided tumorous lesion arising from the aryepiglottic region. A biopsy was performed and initially interpreted as salivary gland adenoma. After complete tumour resection the tumour recurred twice, 12 and 14 months later, and was reclassified as salivary gland carcinoma of low malignancy potential. In the following 15 months, multiple skin metastases occurred and were resected. Once more, the tumour was reclassified and the diagnosis of an atypical laryngeal carcinoid was made. No clinical evidence of a carcinoid syndrome was observed. The patient died from extensive formation of metastases 33 months after the primary diagnosis. An autopsy was not performed.

Pathology

Light microscopy

Haematoxylin–Eosin-stained sections of the primary tumour and of multiple skin metastases revealed remarkably constant morphological features (Figure 1). The tumour was characterized by medium-sized polyhedral and rounded cells growing in compact sheets, nests, and occasionally in trabeculae. The cytoplasm of the tumour cells stained slightly eosinophilic and generally had a fine granular appearance. The tumour cells contained rounded nuclei with one to three minute nucleoli and a stippled chromatin pattern. In the periodic-acid-Schiff-reaction, occasional cells displayed intracytoplasmic mucin droplets. Cellular pleomorphism was totally absent. Mitoses could be identified, but were exceedingly rare. Tumour necroses were not observed. The tumour tissue stained positively on immunostaining for cytokeratin, chromogranin, and neuron specific enolase.

Ultrastructure

Ultrastructurally, the neoplastic cells were closely apposed with clearly identifiable junctional complexes. Microvillous surface projections were numerous. Membrane-bound neurosecretory granules were scattered throughout the cytoplasm and ranged in diameter from 150 to 400 nm (Figure 2). An abortive glandular differentiation in scattered tumour cells with intracytoplasmic lumina containing finely granular substances was also evident. True oncocytic features with mitochondrial hyperplasia were not observed. Tumour cells positive for neuron specific enolase are shown in Figure 3.

Discussion

Neuroendocrine carcinomas of the larynx may not be as rare

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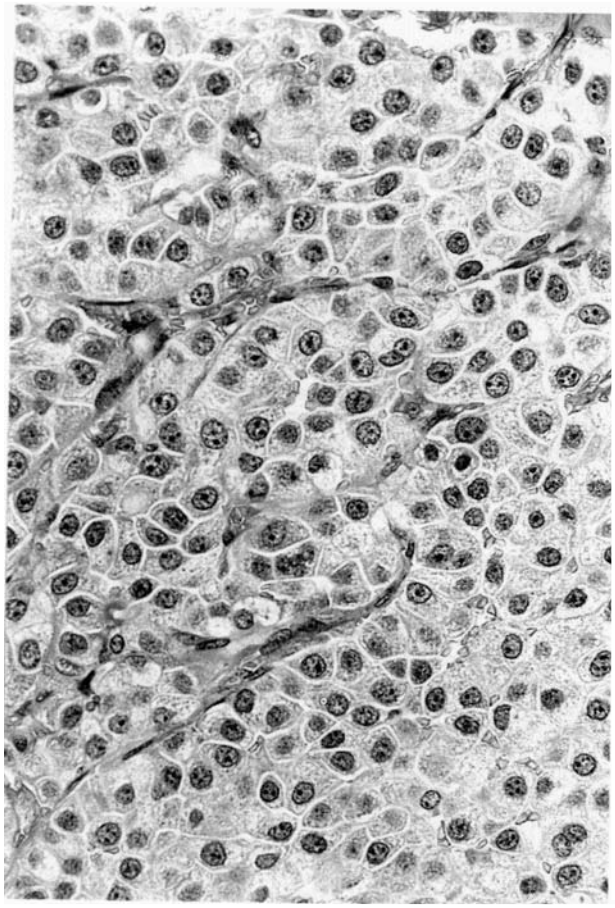

FIG. 1

Oncocytoid laryngeal carcinoid. Note uniformity of tumour cells which lack nuclear atypia and pleomorphism. (H&E; ×360).

as was formerly thought. The total number of case reports in the world literature now amounts to several hundreds (Ferlito and Rosai, 1991). However, although surgical pathologists are more and more aware of this entity, laryngeal carcinoids may still present diagnostic problems, and their misinterpretation is common.

The clinical features of laryngeal carcinoids are non-specific. These tumours present with hoarseness, dysphagia or otalgia which might have been longstanding from weeks up to several years (Wenig *et al.*, 1988). The primary site of most tumours is the supraglottis (Wenig *et al.*, 1988; Woodruff and Senie, 1991). In contrast to the much more common squamous carcinomas the overlaying mucosa typically remains intact (Wenig *et al.*, 1988).

Morphologically, neuroendocrine carcinomas of the larynx exhibit a broad spectrum of differentiation patterns including well-differentiated neuroendocrine carcinoma (typical carcinoid), moderately differentiated neuroendocrine carcinoma (atypical carcinoid), and undifferentiated (small cell) neuroendocrine carcinoma of the larynx (Ferlito and Friedmann, 1989; Ferlito and Rosai, 1991).

Most of the cases are subclassified as atypical carcinoids. Concerning the histological differentiation as well as the clinical behaviour, atypical carcinoid is thought to be intermediate between typical carcinoid and small cell carcinoma of the larynx (Ferlito and Friedmann, 1989). Thus, atypical carcinoid differs from typical carcinoid by cellular atypicalities and pleomorphisms, higher mitosis rates and the occurrence of tumour necroses (Ferlito *et al.*, 1988; Woodruff and Senie, 1991). Clinically, atypical carcinoids are likely to form distant metastases (Ferlito *et al.*, 1988; Woodruff and Senie, 1991), whereas typical cases are not.

In view of these facts it is tempting to assume that histopathological subclassification and clinical outcome are well correlated with one another in laryngeal carcinoids. However, variants occur that although characterized by high tissue differentiation and bland cytomorphology, yet follow an aggressive course. There is some evidence from the literature indicating that some of these tumours are oncocytoid in appearance. Thus, Blok *et al.* (1985) reported on three cases of laryngeal carcinoids composed of uniform cells with eosinophilic granular cytoplasms. Two out of the three cases metastasized. Similarly four out of five cases of well-differentiated laryngeal carcinoids reported by Stanley *et al.* (1986) gave rise to metastases; the morphological phenotypes of these neoplasms were also reported to be oncocytoid.

The case presented here belongs to this small group of well-differentiated oncocytoid laryngeal neoplasms. Although tumour morphology appeared to be quite inconspicuous without atypias and more than an occasional mitosis, the tumour recurred twice after primary resection and later gave rise to a great number of cutaneous metastases. An oncocytoid appearance with finely granular-structured cytoplasm was an outstanding feature of all tumour biopsies. One has to keep in mind, therefore, that – as far as laryngeal carcinoids with an oncocytoid morphology are concerned – the absence of cellular atypias, pleomophisms, tumour necroses, and high mitosis counts does not exclude malignancy.

Tumour entities thought to be important in the differential diagnosis of neuroendocrine carcinoma of the larynx are undifferentiated carcinoma, poorly-differentiated squamous cell carcinoma, medullary carcinoma of the thyroid, malignant melanoma, paraganglioma, and acinar cell carcinoma (Ferlito *et al.*, 1988; Wenig *et al.*, 1988). In our view, most of these tumours may readily be distinguished from laryngeal carcinoids, and

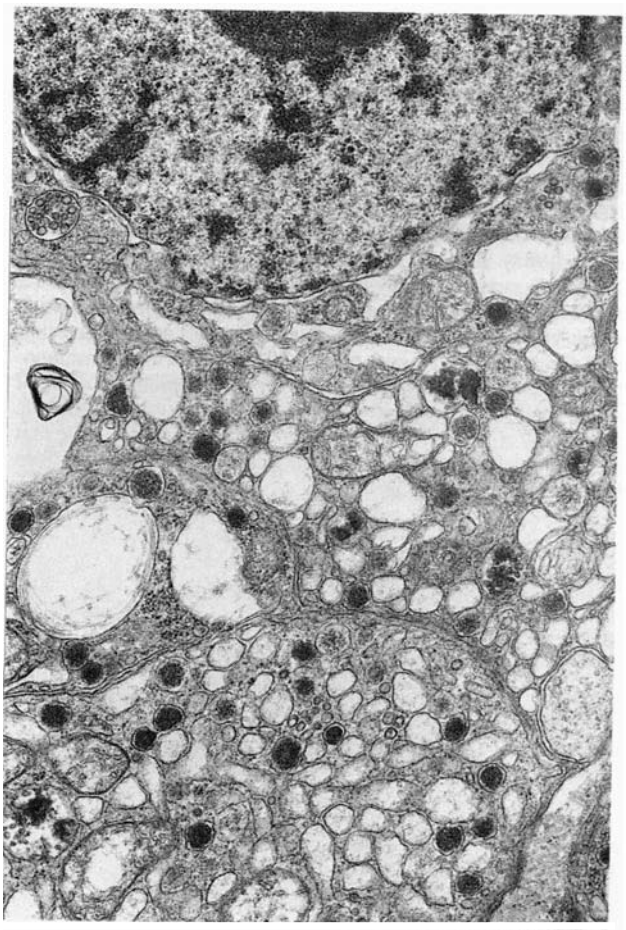

FIG. 2

Electron micrograph of a tumour cell with neurosecretory-type, dense core granules. (Lead citrate and uranyl acetate; ×15 000).

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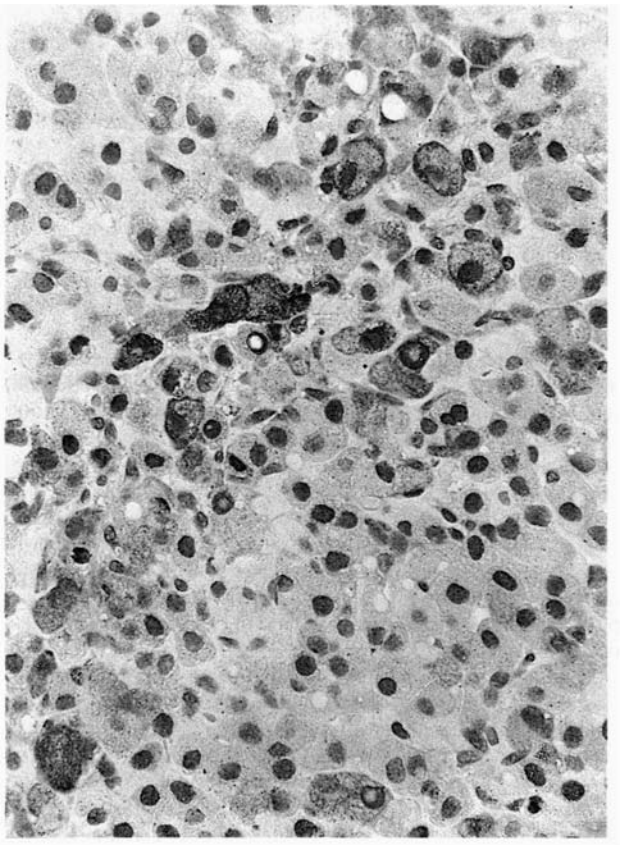

FIG. 3

Laryngeal carcinoid with some tumour cells (dark cells) positive for neuron specific enolase. (NSE; ×360).

often a simple routinely stained haematoxylin–eosin-section suffices to make the correct diagnosis. Besides, paraganglioma and malignant melanoma can be excluded, if intracytoplasmic mucin droplets are identified in PAS-stained sections, as is the case with more than 90 per cent of laryngeal carcinoids (Wenig *et al.*, 1988). It has to be stressed, however, that rare cases of laryngeal carcinoids may occur which histopathologically are indistinguishable from medullary thyroid carcinoma. A high serum calcitonin level favours the diagnosis of a medullary thyroid carcinoma (El Naggar *et al.*, 1991). Furthermore, immunohistochemistry may be helpful in the differential diagnosis of acinar cell carcinoma as well as undifferentiated carcinoma, poorly-differentiated squamous cell carcinoma, and malignant melanoma, since all of them differ from laryngeal carcinoids in lacking chromogranin-positivity.

Conclusions

The prognosis for neuroendocrine carcinoma of the larynx is poor and distant metastases may develop early in its course involving bones, skin, lung and liver, independently from an innocent appearing histology and differentiation. Therapeutic concepts differ, but this is not surprising in view of the rarity of laryngeal carcinoids. Wide surgical excision is recommended by most authors, because chemotherapy and radiation have, so far, not been shown to be effective in controlling this disease.

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