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Medullary (thyroid) carcinoma-like carcinoids of the larynx

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Abstract
The histopathological spectrum of neuroendocrine neoplasms of the larynx includes a subset that may be indistinguishable from a medullary carcinoma of the thyroid gland. For a patient who presents with a medullary carcinoma-like metastasis in a cervical lymph node and in whom there is no clinically demonstrable thyroid lesion, a laryngeal atypical carcinoid must be excluded. The literature's third example of a primary medullary carcinoma-like atypical carcinoid of the larynx is presented.

Introduction

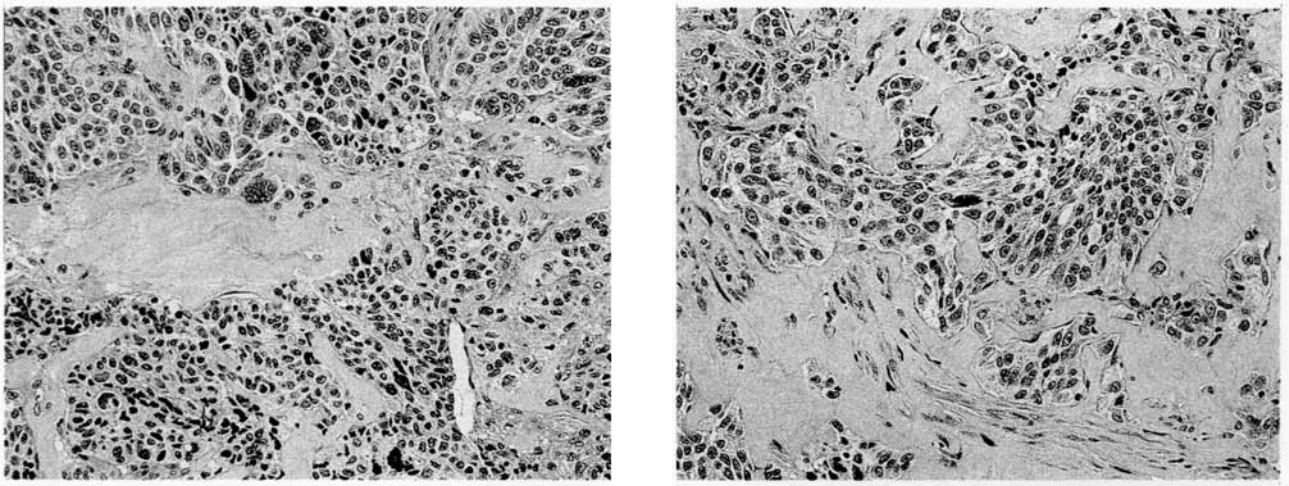
Neuroendocrine tumours are characterized by the production of marker hormones and electron-optically identified neurosecretory granules. It is now accepted that the histopathological spectrum of neuroendocrine tumours of the larynx is not unlike that of the lung (Woodruff *et al.*, 1985; Wenig *et al.*, 1988). Sub-classifications of these tumours at either site reflect this structural similarity and are currently interchangeable (Ferlito and Friedmann, 1989). There is also hormonal overlap but with differences. Bronchopulmonary neuroendocrine tumours most commonly express bombesin and serotonin; laryngeal neuroendocrine tumours often elaborate calcitonin (Woodruff *et al.*, 1985). On the basis of the latter, along with other histochemical, histological and immunohistological features, Woodruff *et al.* (1985) have concluded that the large cell neuroendocrine carcinomas (atypical carcinoids) of the larynx more closely resemble medullary carcinomas of the thyroid than their homologous pulmonary neuroendocrine carcinomas.

The differential diagnostic problems attendant to these similarities are not trivial given the clinical and biological differences between medullary carcinoma of the thyroid gland and some large cell (atypical carcinoid) neuroendocrine carcinomas of the larynx (Woodruff *et al.*, 1985; Wenig *et al.*, 1988).

In this report we present an atypical carcinoid of the larynx whose clinicopathological features were such as to be first mistaken as an 'adenocarcinoma' and then mistaken as a medullary carcinoma of the thyroid gland with metastasis to cervical lymph node. Electron-optic, immunocytochemical, and DNA flow cytometric characteristics of the neoplasm are discussed.

Case report

Five years before admission to the University of Texas M.D. Anderson Cancer Center for the evaluation of a left neck mass, a 42-year-old woman had surgical excision of a polypoid laryngeal 'adenocarcinoma' said to be glottic in origin. The excisional biopsy specimen of the neck mass was histologically consistent with metastatic medullary thyroid carcinoma in a



(a) (b)

FIG. 1
Metastatic carcinoma in cervical lymph node; A. Cellular and nuclear pleomorphism in neoplastic cells; B. Amyloid-like hyaline separates neoplastic islands.

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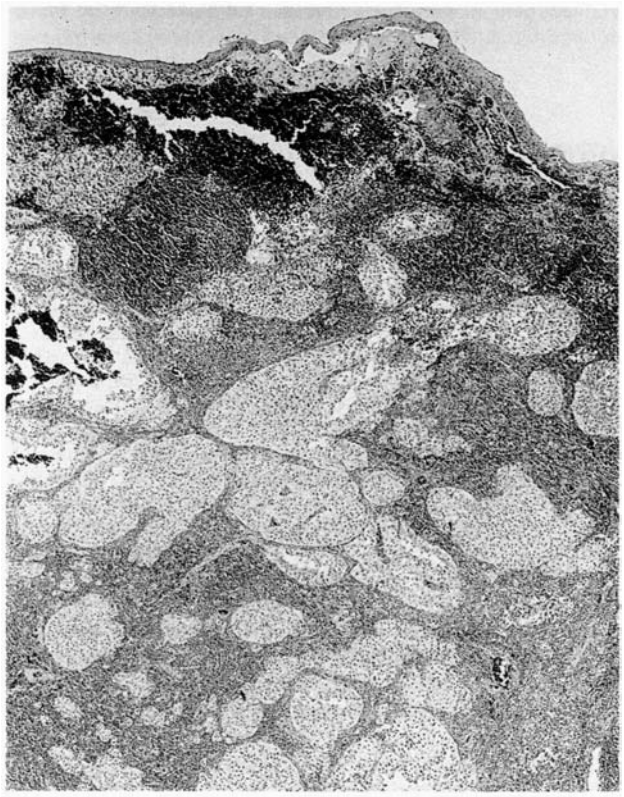
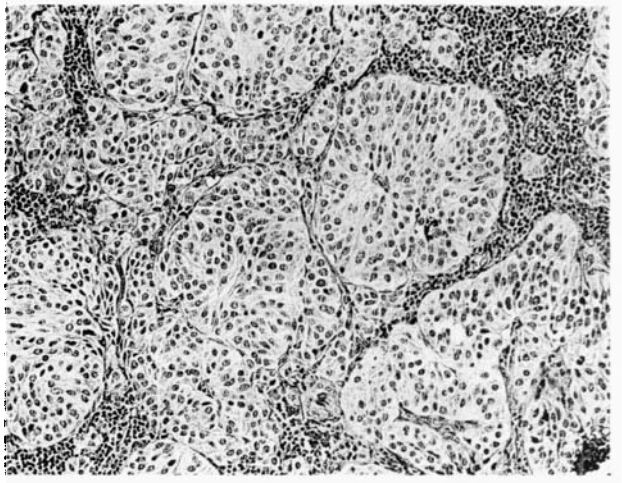


(a)



(b)

FIG. 2

Atypical carcinoid of the larynx; A. The neoplasm invades beneath an intact mucosal surface, hematoxylin and eosin ×45; B. Note the similarity to the metastasis in Figure 1.

lymph node. The patient had no personal or family history of thyroid disease or of multiple endocrine neoplasia. There were no signs nor symptoms suggestive of a carcinoid syndrome or other functioning neuroendocrine tumours. She was clinically euthyroid and there were no palpable abnormalities of the thyroid gland. CT and MRI examinations of the neck and upper chest did not demonstrate thyroid lesions. Serum calcitonin concentrations, in the basal and post-gastrin stimulation states, were not abnormal. Serum CEA concentration was also within normal limits.

Pathological examinations

Cervical metastasis: The neoplasm in the left posterior triangle lymph node (4 × 3.5 × 1.5 cm) was arranged in solid nests of polygonal and spindled cells or gland-like cords. The neoplastic cells manifested a moderate degree of pleomorphism with focal necrosis and readily identifiable mitoses (Fig. 1A). Occasional multinucleated, neoplastic giant cells were also seen. A hyaline, amyloid-like, extracellular material separated the neoplastic cells and in some areas dominated the microscopic fields of examination (Fig. 1B). The overall haematoxylin and eosin appearance was that of a metastatic medullary carcinoma of the thyroid.

Laryngeal neoplasm: Sections of the 'adenocarcinoma' of the larynx were obtained and reviewed. This neoplasm was described as a polypoid 1.2 × 0.7 cm lesion arising from the left glottic area. A 0.3 × 0.2 cm stalk supported the nodular tumour.

The neoplasm was entirely submucosal and covered with an intact squamous epithelium (Fig. 2A). It was composed of solid and glandular organoid structures formed by uniform small cells with centrally placed nuclei and a clear to amphophilic cytoplasm (Fig. 2B). Mitotic figures were sparse and necrosis and pleomorphism were absent.

TABLE I

SOURCE AND DILUTION OF ANTISERA

Antisera	Solution	Source
NSE	1:1,000	DAKO Corporation Carpinteria, Ca
Chromogranin	1:270	Boehringer Mannheim Indianapolis, IN
Serotonin	1:1,200	Bioproducts for Science, Inc. Indianapolis, IN
ACTH	1:1,200	Incstar Corporation Stillwater, MN
Calcitonin	1:2,000	Incstar Corporation Stillwater, MN
CEA	1:2	Incstar Corporation Stillwater, MN
Somatostatin	1:5,000	Incstar Corporation Stillwater, MN

Histochemistry and immunocytochemistry

The cells of the endolaryngeal neoplasm and the intranodal neoplasm were strongly argyrophilic but were argentaffin negative by the Fontana-Masson technique.

Table I lists the antisera used for the immunocytochemical characterization (method of Hsu *et al.*, 1981) of the endo-

TABLE II

LARYNGEAL NEOPLASM LYMPH NODE METASTASIS

Antigen	Immunoreactivity	
Somatostatin	−	−
Serotonin	++	+
ACTH	−	−
Neuron specific enolase	++	++
Chromogranin	+++	+++
CEA	++	+
Calcitonin	++	++

(−) Negative, (+) >10 to 25 per cent of cells positive, (++) 25 to 50 per cent positive, (+++) >50 per cent positive.

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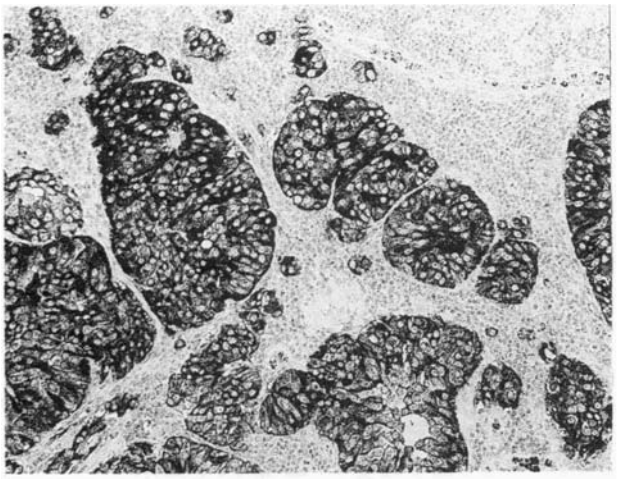


FIG. 3

Atypical carcinoid of the larynx manifesting strong immunoreactivity with antibodies against calcitonin.

laryngeal and nodal neoplasms. Table II presents the immunocytochemical findings. The neoplasm at each site reacted strongly with antibodies directed against chromogranin, neuron-specific enolase, and calcitonin (Fig. 3). Neither neoplasm manifested immunoreactivity with antibodies against somatostatin or ACTH.

Electron microscopy

The principal ultrastructual findings in the neoplastic cells at both sites of involvement were dense-core neurosecretory granules in the cytoplasm (Fig. 4A). The amyloid-like material was shown to be condensed collagen (Fig. 4B).

DNA flow cytometry

Single-cell nuclear suspensions were prepared from formalin-fixed paraffin-embedded tissue by a modification of the method of Hedley *et al.* (1983). Samples were stained with propidium iodide and analysed on a Coulter Profile Flow Cytometer. Lymphocytes in the suspensions served as internal diploid standards. A diploid DNA stem line was defined as the first G0/1 peak. An aneuploid DNA stem line was defined as the presence of a second distinct peak to the right of the first G0/1 peak on the DNA content histogram. Coefficients of variation for the diploid peaks were 1.7 and 2.1 respectively.

The DNA content in the largngeal neoplasm was diploid and with low S-phase percentage (Fig. 5A). The cervical node neoplasm manifested an aneuploid DNA content in approximately 70 per cent of the cells (Fig. 5B).

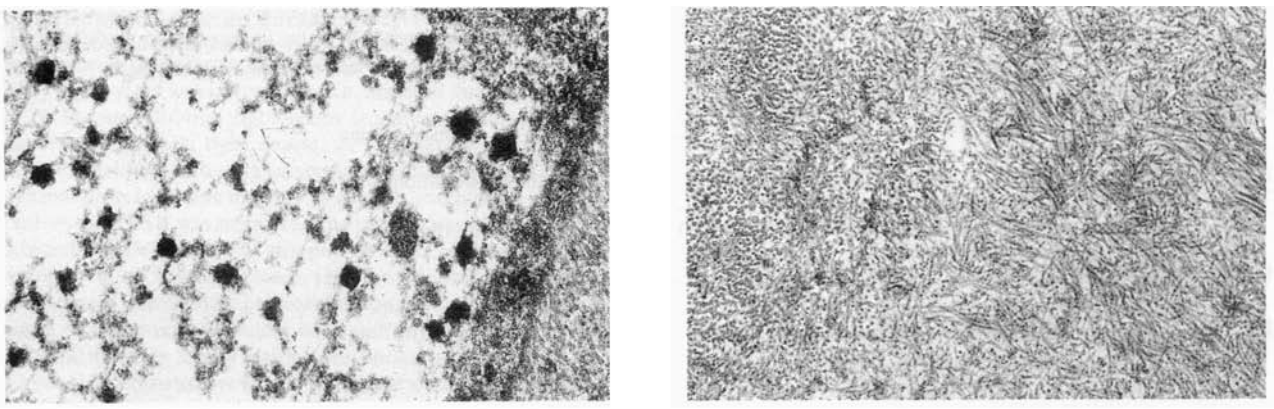
Discussion

Two published cases of medullary (thyroid) carcinoma-like carcinoids of the larynx precede ours (Smets *et al.*, 1990; Sweeney *et al.*, 1981). Sweeney *et al.* (1981) reported a neuroendocrine neoplasm of the larynx with synchronous metastasis to a cervical lymph node and an elevated serum calcitonin concentration as an 'ectopic medullary carcinoma of the larynx.' Smets *et al.* (1990) followed with their report of a laryngeal neuroendocrine neoplasm that also manifested concurrent metastasis to lymph nodes and high serum calcitonin concentrations. Thyroidectomy in each of the patients failed to disclose a primary thyroid neoplasm.

Each of the two previously reported laryngeal neoplasms and their metastases manifested the same cytopathological features as the atypical carcinoid in our patient. These features are: an organoid atypical carcinoid architecture, argyrophilism, immunoreactivity to calcitonin and CEA antibodies, and ultrastructural evidence of neurosecretory granules. Sites of involvement have been supra-glottic or glottic (laryngeal surfaces of epiglottis, pyriform sinus, vocal cord). Hypercalcitoninaemia was never in evidence in our patient.

The DNA flow cytometric findings in the neoplasm of our patient are of particular interest. An aneuploid DNA stem line in the metastasis as opposed to the diploid DNA content in the laryngeal primary suggests the evolution of an abnormal clone during neoplastic progression (James *et al.*, 1988; Clarke *et al.*, 1990). While correlating with the aggressiveness of the neoplasm in its metastasis, the absence of aneuploidy in the primary serves to caution against an unmodified acceptance of DNA analysis to the predict biological course. The abnormal DNA content in the metastasis did, however, mirror the mitotic activity, cellular pleomorphism and necrosis; findings not seen in the laryngeal primary.

The origin of the laryngeal neoplasm presented in this report and the two others in the literature is unlikely to be from ectopic thryoid tissue. Laryngotracheal rests of thyroid tissue are the rarest of all thyroid ectopias. Rotenberg *et al.* (1979) found ectopic thyroid tissue in only two of 250 serially sectioned larynges. We also hold untenable the likelihood of direct invasion of the laryngotrachea by an *occult* medullary carcinoma. Even in patients with known carcinomas of the thyroid gland, an invasion extensive enough to produce *intraluminal* masses is unusual (Djalilian *et al.*, 1974; Batsakis, 1987). In a 60 year period at the Mayo Clinic, only 18 patients of 2,000 with thyroid cancer had neoplastic intraluminal involvement of the larynx or trachea (Djalilian *et al.*, 1974). Medullary carcinoma (one case) was the least common type. Important from a differ-



(a) (b)

FIG. 4

Electron-optic examination of the laryngeal and intra-nodal neoplasm demonstrated; A. neurosecretory granules and B. non-amyloid condensed collagen.

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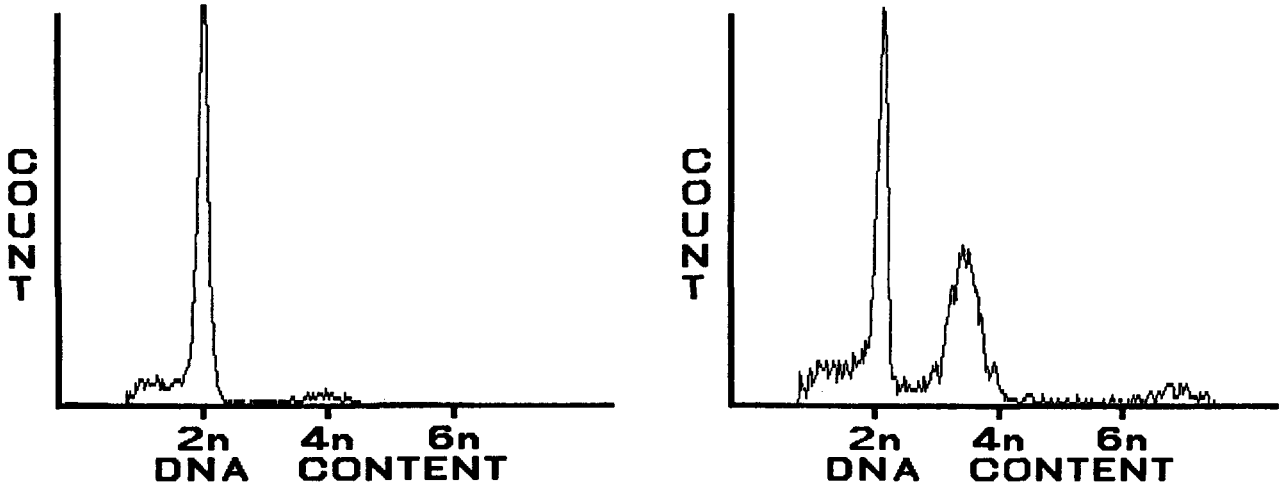

FIG. 5

DNA histograms prepared from flow cytometric analysis of the endolaryngeal primary (A) and the metastasis in the cervical lymph node (B). The former is diploid; the latter is aneuploid.

ential diagnostic standpoint is the observation that the preponderance of either ectopic thyroid rests or intraluminal invasion by thyroid carcinomas is sub-glottic or tracheal (Djalilian *et al.*, 1974; Friedman *et al.*, 1982; Batsakis, 1987), not supra-glottic-glottic as in the instances of the medullary carcinoma-like carcinoids of the larynx (Woodruff *et al.*, 1985; Wenig *et al.*, 1988; Ferlito and Friedmann, 1989).

Our case underscores the problems in the clinical and pathological differential diagnosis posed by a patient with a medullary (thyroid) carcinoma-like metastasis in a cervical lymph node. The fact that the cellular and, at times, systemic manifestations of calcitonin manufacture mark moderately to well differentiated neuroendocrine (carcinoids) neoplasms of the larynx as well as medullary thyroid carcinomas serve to give notice that the former be always considered as a source for the metastasis.

Acknowledgement

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