Eur J Cancer, Vol. 28A, No. 10, pp. 1755–1758, 1992.
Printed in Great Britain

0964-1947/92 $5.00 + 0.00

Clinical Oncology: Case Presentations from Oncology Centres—2. Carcinoid of the Larynx

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INTRODUCTION

MALIGNANT TUMOURS of the larynx are usually squamous cell carcinomas although other malignant tumours occur. In recent years it has become apparent that neuroendocrine tumours of the larynx are not so uncommon and that the finding of an undifferentiated carcinoma should raise suspicion of a neuroendocrine tumour.

CASE PRESENTATION

The patient, a 61-year-old female, consulted a pulmonologist and an otolaryngologist in May 1990 for a cough of six months' duration which was getting progressively worse. She complained of an irritant in the throat and had lost 7 kg in weight. She was a heavy smoker. Chest examination revealed no abnormalities and a chest X-ray showed hyperinflated lungs. Bronchoscopy revealed signs of a chronic bronchitis. The otolaryngologist found oedema of both vocal cords and a polypoid lesion on the left arytenoid, with a raspberry appearance, resembling an haemangioma. In September 1990 a microlaryngoscopy with stripping of the oedema of the vocal cords and partial excision of the lesion was performed. Histopathological examination unexpectedly revealed a poorly differentiated 'non- small cell' malign neoplasm, probably a squamous carcinoma. Consequently, tomography and computed tomography (CT) of the larynx were performed, localising a swelling in the left dorsal supraglottic region, expanding to the retro- and parapharyngeal space into the floor of the mouth. The patient was transferred to the University Hospital for staging and further treatment. Revision of the histological sections raised suspicion of a neuroendocrine tumour and this was confirmed by immunohistochemical staining, which was positive for S-100 and calcitonin and negative for carcinoembryonic antigen (CEA) (Figs 1–3). A diagnosis of atypical carcinoid was made. The tumour was totally excised by microlaryngoscopy and the wound bed was treated

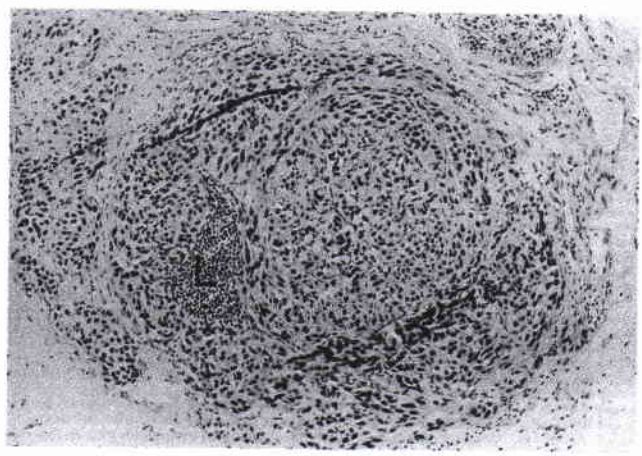

Fig. 1. The tumour consists of multiple nests of infiltrating intermediate sized cells. Note lymphocytic infiltrate (L).

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Received 28 Feb. 1992; accepted 4 Mar. 1992.

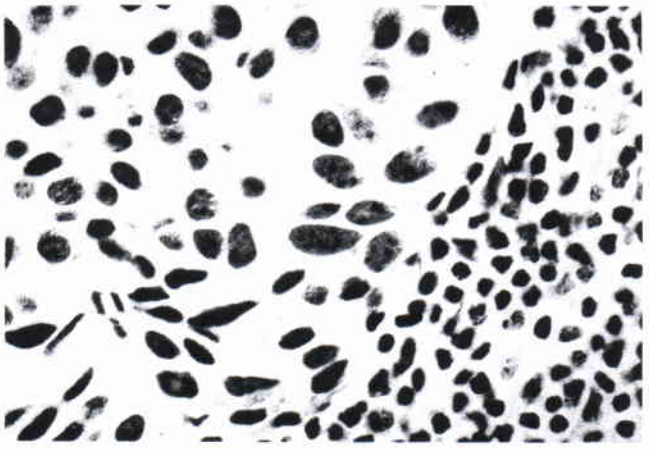

Fig. 2. The nuclei show marked pleiomorphism. Sometimes multiple nucleoli can be seen. Lymphocytic infiltrate on right side.

Table 1. *Epidemiology of neuroendocrine tumours of the larynx (review of literature)*

	Nr	M:F	Age			Smokers	Ref.
			Range	Mean	Peak		
TC	13	11:1	45–80	58		80%	[6]
ATC	200	3:1	36–83	61	50–70	78%	[9]
SCNC	125	3:1			50–70	+++	[7]
OCT			23–91	58		+++	
ICT							
CCT			37–83			68%	
PG	81	1:3	14–80	47			[8]

Nr: Number of reported cases; M:F: male to female ratio; TC: typical carcinoid; ATC: atypical carcinoid; SCNC: small cell neuroendocrine carcinoma; OCT: oat cell type; ICT: intermediate cell type; CCT: combined cell type; PG: paraganglioma.

by laser vaporisation. Screening of the patient for other tumours, including abdominal echography, X-ray of the thorax, meta-iodobenzylguanidine (MIBG) scan and biochemical determination of 5-hydroxyindoleacetic acid (5-HIAA) in urine were negative. At her last visit in February 1992, which was 20 months after her initial presentation, the patient was still clinically tumour-free.

NEUROENDOCRINE TUMOURS

Since the description of the APUD (amino precursor uptake and decarboxylation) system in 1968 by Pearse and the increasing availability of immunocytochemical techniques, neuroendocrine cells have been localised throughout the human body [1]. The exact origin of these cells is still a matter of some debate, since it seems that some may have an entodermal rather than a neuroectodermal origin [2]. The cells of this system produce biogenic amines such as ACTH, MSH, parathormone, calcitonin, insulin, histamine, catecholamines and prostaglandins. They are identified as Kulchitsky cells in the gastrointestinal tract, and very similar cells are present in the epithelium and submucosal glands of the respiratory tract [3]. Neoplastic changes give rise to neuroendocrine tumours, histologically divided into small or large cell tumours. The best known small cell neuroendocrine tumour is the oat cell carcinoma of the lung. Large cell neuroendocrine tumours are called carcinoids. They were first described in 1969 by Goldman and can be found in the gastrointestinal tract, lungs, thymus, ovaries, urinary bladder and middle ear [4]. Both small and large cell neuroendocrine tumours have been described in the larynx [5–8]. To rationalise the many different names and classifications used for this type of tumour, the WHO recently made recommendations for the universal classification of the neuroendocrine neoplasms of the upper respiratory tract [5]. According to these recommendations, they can be divided into tumours of epithelial or neural origin. The latter consist of the paragangliomas. The group of epithelial origin can be subdivided into the typical carcinoid tumour (well differentiated), the atypical carcinoid (moderately differentiated) and the small cell neuroendocrine carcinoma (poorly differentiated), the latter consist of the oat cell type, the intermediate cell type and the combined cell type, respectively. This classification, which is based on histological features, is clinically meaningful in view of prognosis and therapy. The neuroendocrine nature of these tumours is based on the presence of argyrophilic cytoplasmic granules, on a positive staining for neuroendocrine markers (e.g. neuron-specific enolase, chromogranin, synaptophysin, Leu-7, protein gene product 9.5, neurofilament protein) and on the ultrastructural presence of membrane-bound dense-core neurosecretory granules [5].

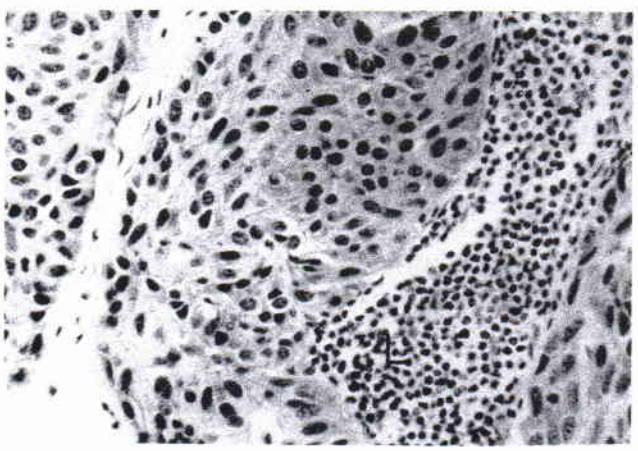

Fig. 3. Immunohistochemical staining for chromogranin shows diffuse positivity of the cytoplasm of the tumour cells. Note lymphocytic infiltrate (L).

CARCINOID OF THE LARYNX

In recent review papers, 13 'typical' and 200 'atypical' carcinoids of the larynx have been identified from the literature [6, 9]. As shown in Tables 1 and 2, the typical patient is a heavy-smoking male in the sixth or seventh decade of life, presenting with hoarseness, dysphagia, a sore throat or a lump in the throat. A mass in the neck is not typical and a carcinoid syndrome, resulting possibly from the action of secreted hormones, has not been described for laryngeal carcinoids.

Histologically, the tumour cells are organised in nests, cords, sheets, glandular or rosette-like structures, diffusely infiltrating a hyalinised and well-vascularised connective tissue stroma which sometimes contains amyloid [1, 10]. The cells contain a centrally placed nucleus, sometimes eccentrically in the atypical carcinoid. The chromatin is finely stippled or vesicular in the carcinoid, while the cells of the atypical carcinoid often display some hyperchromasia or chromatin clumping. In the atypical carcinoid the nucleolus may be prominent. Mitotic figures are

Table 2. Symptoms of neuroendocrine tumours of the larynx (review of literature)

	Hoarse	Dysphagia	Sore throat	Neck mass	Haemoptysis	Lump	Dyspnoea	Carcinoid syndrome	No symptoms
TC	25%	33%	17%		8%	17%		0%	17%
ATC	71%	71%	19%	8%				0%	
SCNC	+++			++				Rare	
OCT	69%	18%		22%			13%		
ICT									
CCT	37%	20%	17%	4%	11%				
PG	67%	29%	11%	9%		6%	23%	Rare	6%

For abbreviations and references see Table 1.

commonly reported only in the atypical carcinoid. They are rare in the carcinoid. The cytoplasm is clear or slightly eosinophilic and granular in the carcinoid, whereas it is eosinophilic and granular in the atypical form [10]. Cellular pleiomorphism, invasion into the overlying surface squamous epithelium, prominent perineural cuffing and invasion, and focal necrosis are only described in the atypical carcinoid, thus explaining the easy confusion with poorly differentiated squamous cell carcinomas [1, 11, 12]. Histochemical staining is positive for argyrophily (Grimelius, Churukian-Schenk, Sevier-Munger, Bodian, Wilder or Pascual staining) and negative for argentaffiny (Fontana-Masson, Masson-Hamperl, Diazo or Schmorl staining). Ultrastructural examination demonstrates the typical membrane-limited dense core neurosecretory granules, ranging in diameter from 70 to 420 nm [11, 12]. Mitochondrial hyperplasia has been described [1]. Table 3 summarises the results of immunohistochemical staining.

Diagnosis is based on clinical findings completed with histological, histochemical, immunocytochemical and ultrastructural examinations. It is essential to include these techniques in the diagnostic protocol of undifferentiated laryngeal neoplasms. A pathognomonic finding is the elevated level of 5-HIAA in urine, a consequence of an impaired tryptophan metabolism [1]. In addition to a complete history and physical examination, diagnostic investigations include chest X-ray, upper aerodigestive tract endoscopy and biochemical analysis of the urine. Isotope scintigraphy of liver and bones is only indicated in cases of biochemical anomalies. Investigation of the gastrointestinal tract does not seem to be indicated since metastasis to the larynx of primary gastrointestinal carcinoma has never been reported [13]. Over the last decade, research in nuclear medicine has developed two radiolabelled compounds useful for scintigraphical detection and delineation of carcinoids: iodinated MIBG and radiolabelled somatostatin. Like norepinephrine, MIBG is concentrated and stored in the neurosecretory granules of chromaffin cells derived from the neural crest. In 1984 the first patient study showing visualisation of a carcinoid with [^{131}I] MIBG was reported [14]. Several large patient series reported in the literature indicate a sensitivity for carcinoids of approximately 70% [15]. Most of these patients had a primary tumour in the lung with metastases in lymph nodes, liver, lung, bone and ovary. To our knowledge no patient with a primary carcinoid tumour of the larynx was included. The establishment of the concentration of [^{131}I] MIBG can be of diagnostic value to localise lesions not shown by other techniques. Moreover, it can provide a therapeutic modality as a source of internal radiation for at least palliative treatment [15]. Radiolabelled somatostatin analogues provide another approach to image carcinoid tumours scintigraphically. High densities of somatostatin receptors have been found on several neuroendocrine tumours including carcinoids. Somatostatin analogues are currently used therapeutically to suppress hormonal hypersecretion from these tumours [16]. Recently, a radiolabelled variant of somatostatin was developed, enabling *in vivo* visualisation of somatostatin-receptor-positive tumours [17]. A wide variety of these tumours, including pituitary and endocrine pancreatic tumours, neuroblastomas, brain tumours, breast cancer, carcinoids, etc. have been studied. Using ^{123}I-labelled somatostaatin analogue Tyr^3-octreotide, primary and metastic carcinoids could be visualised in 12 of 13 patients. Liver metastases were discovered in 11 of these 13 patients. Extrahepatic metastases were found in the neck lymph nodes in 7 patients. Somatostatin analogue scintigraphy revealed more tumour localisations than CT in 50% of patients [17]. One of the patients studied had a primary carcinoid of the middle ear,

Table 3. Immunohistochemical staining of neuroendocrine tumours of the larynx (review of literature)

	Argyro	Argenta	CG	NSE	KER	CAL	CEA	5-HT	SS	S-100	ACTH
TC	+++	−	+++	++	+	−	−	+	++	−	
ATC	+++	−	+++	++	+++	+	++	+	++	+	+
SCNC	+	−	+++		+++	+	++	+			+
PG			+++	++	−	−	−	+	−	++	

TC: typical carcinoid; ATC: atypical carcinoid; SCNC: small cell neuroendocrine carcinoma; PG: paraganglioma; CG: chromogranin; NSE: neuron-specific enolase; KER: keratin; CAL: calcitonin; CEA: carcinoembryonic antigen; SS: somatostatin; +++: > 90%; ++: 50–90%; +: 10–50%; −: < 10% positive staining. For references see Table 1.

Table 4. Therapy of neuroendocrine tumours of the larynx (review of literature)

	Conservative surgery	Radical surgery	Neck dissection	Radio-therapy	Chemo-therapy	Lymph nodes and metastasis
TC	+	Rare	−	−	−	Surgery
ATC	+	+	+	−	−	Surgery
SCNC	−	−	−	+	+	
PG	+	Rare				

For abbreviations see Table 1.

showing intense uptake of the radiopharmaceutical and excellent delineation of the tumour (Lamberts 1992, personal communication).

The therapy of neuroendocrine tumours depends on the nature of the tumour and is summarised in Table 4. The treatment of choice for carcinoids is surgery wherever possible [1, 4, 6, 9, 10]. Conservative resection is often possible for typical carcinoids, unless they are too extensive, in which case total laryngectomy is indicated. On the other hand, atypical carcinoids require wide resection beyond clinically detectable margins [18] and, therefore, conservative therapy may be inadequate. In view of the malignant character of the atypical carcinoid, elective neck dissection is advised in the case of negative local lymph nodes, and radical neck dissection in the case of positive nodes [9, 18]. Metastases should be palliatively treated with surgical excision [1, 13]. The effectiveness of radiotherapy (pre-, per- or postoperatively) or chemotherapy has not been demonstrated and hence is not considered to have a place in the routine management of these tumours [4, 6, 17, 19].

The prognosis of the typical carcinoid is generally good. Of the 13 reported cases in the literature, only one died of disease. The others died from unrelated causes or were considered to be tumour-free [6]. The atypical carcinoid in contrast is an aggressive malignant tumour, potentially widely metastasising [1]. More than 40% are reported to have positive cervical lymph nodes and about 66% have distant metastases at diagnosis [1]. The 5-year survival is about 50%.

In conclusion, the present report adds another case of atypical carcinoid to the list of 200 reported cases in the literature. In an earlier report we described three cases of carcinoid of the larynx, without specifying them as typical or atypical [4]. After revision they should all be classified as atypical. Case 2, which was interpreted as typical carcinoid in the review paper by El Naggar and Batsakis [6] has developed local recurrence and distant metastases after 6 years. Revision of the initial biopsy with immunostaining was positive for keratin and focally for calcitonin. Biopsies of the metastases were positive for keratin, calcitonin and CEA, therefore, it has to be considered an atypical carcinoid. This reduces the number of reported typical carcinoids to 12, of which 10 cases have not shown recurrences to date [6]. When comparing with the 200 reported cases of atypical carcinoid, the relevance of this classification is questionable. Differential diagnosis with squamous cell carcinoma is difficult and is based on histological features together with a panel of immunohistochemical staining. Routine diagnostic screening procedures are completed by biochemical assays (such as determination of urine levels of 6-HIAA) and by new isotope-imaging techniques. The therapy consists of surgical removal of the primary tumour and its metastases. The prognosis depends on the type of carcinoid, but is generally rather poor. In the present case, a conservative attitude towards the tumour was chosen in view of its very small size. After 20 months the patient is free from any signs of the disease.

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Acknowledgements—We thank Professor D. J. Ruiter (Department of Pathology) for expert advice with the interpretation of the pathological slides.