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Chemodectoma of the Larynx

A Clinico-Pathological Study

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Summary. The present case report is concerned with a clinico-pathological study, including ultrastructural investigation, of a rare and uncommon laryngeal tumour, a chemodectoma, in a 62 year old patient. There have been 23 cases of laryngeal chemodectomas reported in the literature, and only three of them, including our own report, were investigated by electron microscopy. The tumours arise from the superior and inferior laryngeal non-chromaffin paraganglia or possibly from Kultschitzky-cells of the normal bronchial mucosa.

Ultrastructurally they have all the characteristics of apudomas whose parent cells (the APUD-cells), usually show endocrine function and probably have their origin in the neural crest.

The tumours show an aggressive type of behaviour, despite usually benign histological features when compared to chemodectomas at other sites in the head and neck region. Surgery is thus the therapy of choice.

Key words: Chemodectoma – Larynx – Ultrastructure.

Introduction

The non-chromaffin paraganglia, associated with the 9th and 10th cranial nerve, are believed to be chemoreceptors. Occasionally they give rise to tumours usually arising from the carotid body, the vagal body or glomus jugulare. They rarely present as a laryngeal tumour.

Material and Methods

Biopsies were taken during direct laryngoscopy. Blocks of 1:2 mm were fixed in cold 3% glutaraldehyde, 1 M. cacodylate buffer, pH 7.4 for two hours. Rinsing in three changes of cacodylate buffer

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pH 7.4 was followed by postfixation in 1% OsO_4 for one hour. Embedding in araldite was then carried out. Ultrathin sections were contrasted with uranyl acetate and lead citrate, semithin sections were stained with methylene blue and azur II (Richardson, 1960). The ultrathin sections were examined with an EM 9 S_2/Zeiss. Formaldehyde and glutaraldehyde fixed paraffin-embedded blocks were stained as follows: Haematoxylin and eosin, lead haematoxylin (Solcia et al., 1969), Fontana's silver reaction.

Case Report

The 62-year-old patient had suffered from hoarseness for several years, from pain on pressure on the right side of the larynx for six months and more recently from dysphagia with pain on swallowing radiating to the right ear.

Laryngoscopically there was a red and focally ulcerated tumour of 1.5 cm in diameter, involving the dorsum of the false cord and extending from the right aryepiglottic fold to the processus vocalis of the right arytenoid cartilage.

On the 13.11.75 a right pharyngotomy was done and the tumour was excised together with the right half of the hyoid bone and the apex of the right arytenoid cartilage. The tumour showed no fibrous capsule, so separation from the intact surrounding tissue was difficult. During the course of the operation considerable laryngeal edema developed, so tracheotomy was necessary.

There were no postoperative complications. Decannulation was carried out four days later. Up to the date of this report the patient is in good health.

Pathological Findings

Light Microscopy

Immediately beneath the laryngeal epithelium, which showed slight thickening, the tumour cells were arranged in nests of varying size. They were separated by a vascular stroma with moderate amounts of inflammatory cells. The tumour cells were partly polygonal and usually formed an alveolar pattern, but spindle-shaped cells also were arranged in columns and strands in close relation to the capillary vessels. In the semithin sections "dark" and "light" tumour cells were distinguished by the appearance of their cytoplasm. No mitotic activity was observed (Figs. 1 and 2). Silver impregnation was negative. Staining with lead haematoxylin (Solcia et al., 1969), which is known to stain endocrine cells including the chemoreceptive cells of the carotid body, was negative. This was probably due to different concentration of our fixatives compared with those used by Solcia.

Electron Microscopy

The tumour cell nests consisted of a mosaic arrangement of cells, which sometimes interdigitated with each other by cytoplasmic processes and which were surrounded by a delicate basement membrane (Fig. 2). The nuclei were round to oval, occasionally showing prominent nucleoli (Fig. 1b). Within dark or light cells the hyaloplasm showed a varying electron density and content of free ribosomes. In addition, bundles of microfibrillae were sometimes observed,

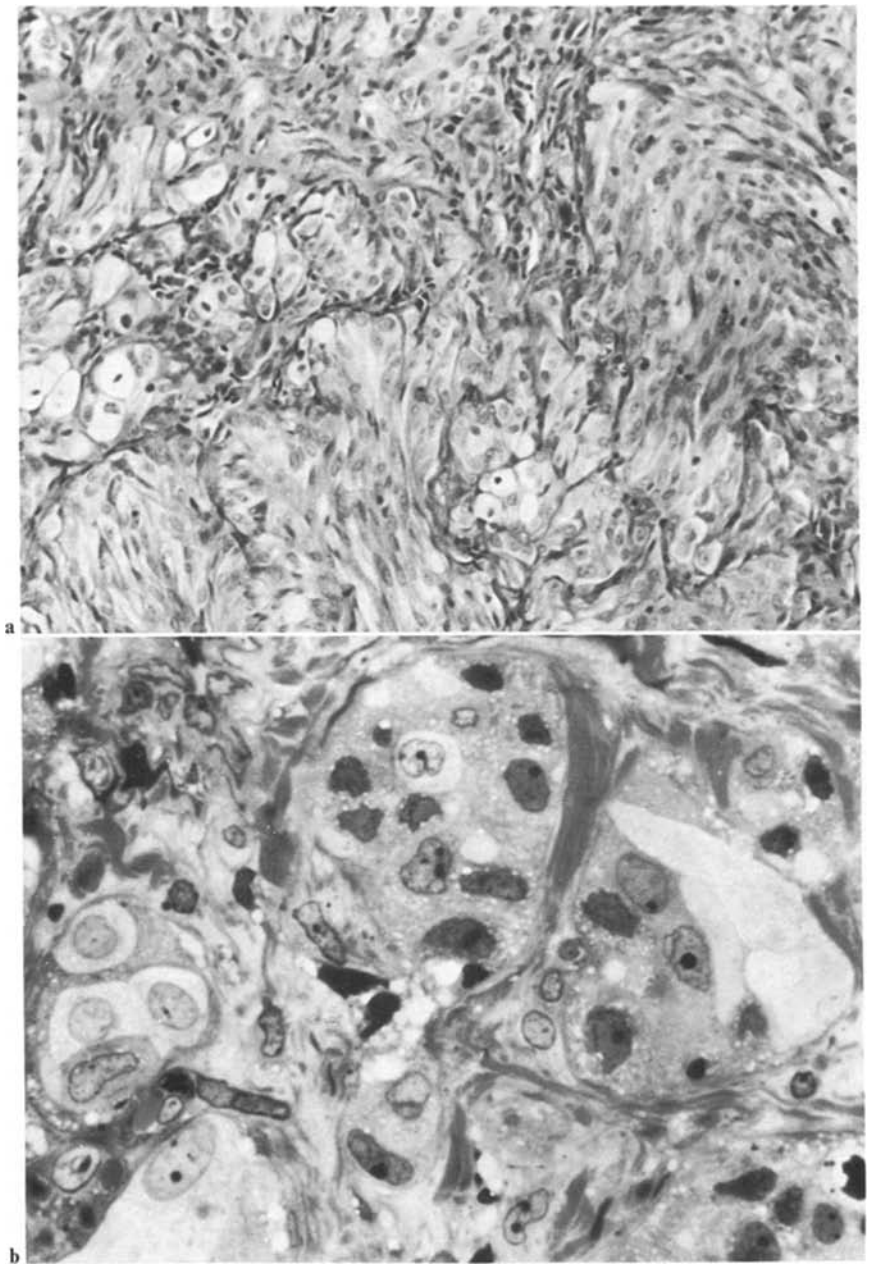

Fig. 1. a Solid tumour, arranged in nests, partly polygonal, partly spindle-shaped cells. Magnification ×180 haematoxylin and eosin. **b** Semithin section with dark and light tumour cells. Prominent nucleoli the oval nuclei. Magnification ×640

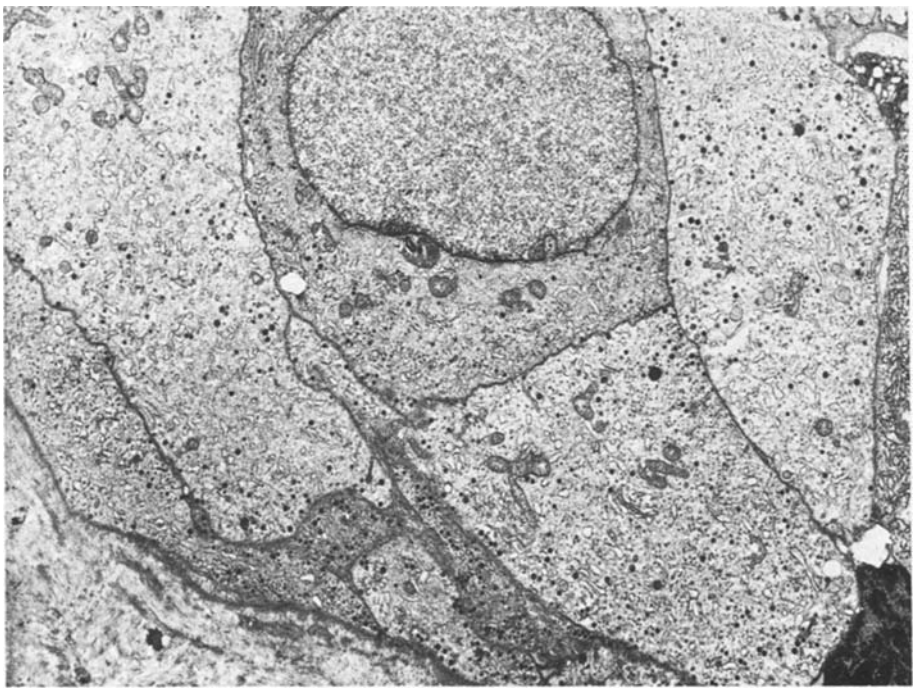

Fig. 2. Mosaic-like arranged cells of the tumour, varying electron-density of the hyaloplasm. Magnification ×12,960

close to the nuclei within dark cells. The mitochondria were rod-like or ovally shaped, and had an electron dense matrix and numerous cristae. The endoplasmic reticulum showed a preponderance of the smooth form with vesicular and tubular arrangement. Rarely rough endoplasmic reticulum was seen (Figs. 2–4). The cisternae of the golgi apparatus were usually located in the paranuclear region, and sometimes contained precursors of the secretory granules. They were the most important ultrastructural feature and were randomly distributed within the cytoplasm (Figs. 3 and 4).

Sometimes they accumulated close to the cytoplasmic membrane and occasionally discharged into the extracellular space by exocytosis (Fig. 5a). The spherical granules ranged in size from 100 to 160 mμ showing electron dense cores and a surrounding membrane separated from the content by a small halo (Fig. 3). Closely packed microvilli extended into the intracellular space (Fig. 5b). Within some tumour cells there were aggregates of secondary lysosomes, including a heterogenous electron dense component related to autophagic processes (Fig. 6b). There were also signs of heterophagic activity with macrophages of the adjacent stroma having phagocytosed single tumour cells (Fig. 6a). Here and there the tumour showed marked regressive changes with a heterochromatin pattern, pyknosis of the nuclei, swelling of the mitochondria and dilatation of the endoplasmic reticulum. These alterations were marked in a few tumour

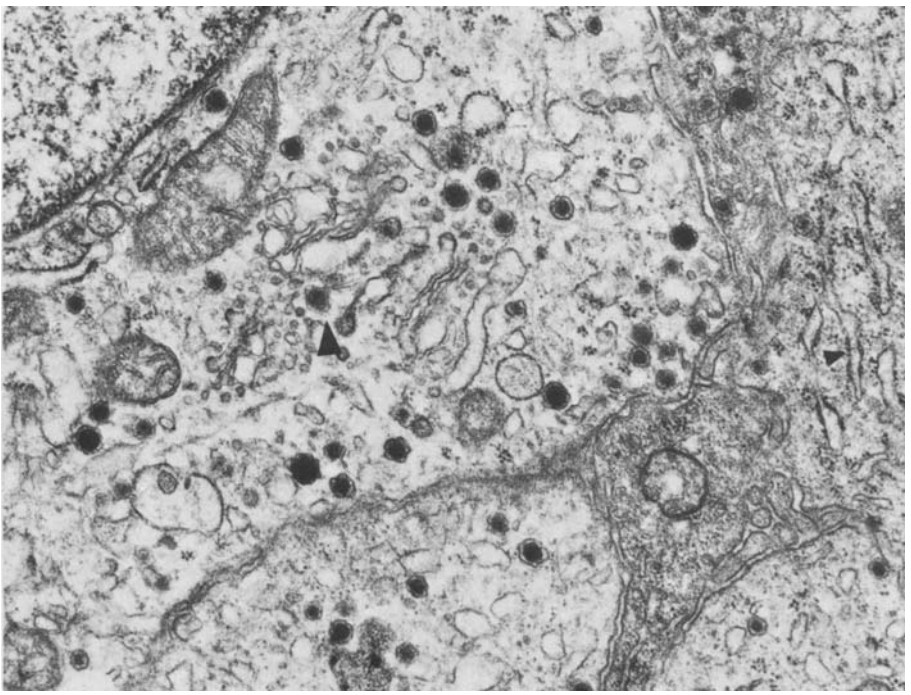

Fig. 3. Golgi-apparatus with precursors of specific granules (▲), occasionally rough endoplasmic reticulum of adjacent tumour-cell with rather dark hyaloplasm (▲). Magnification ×26,000

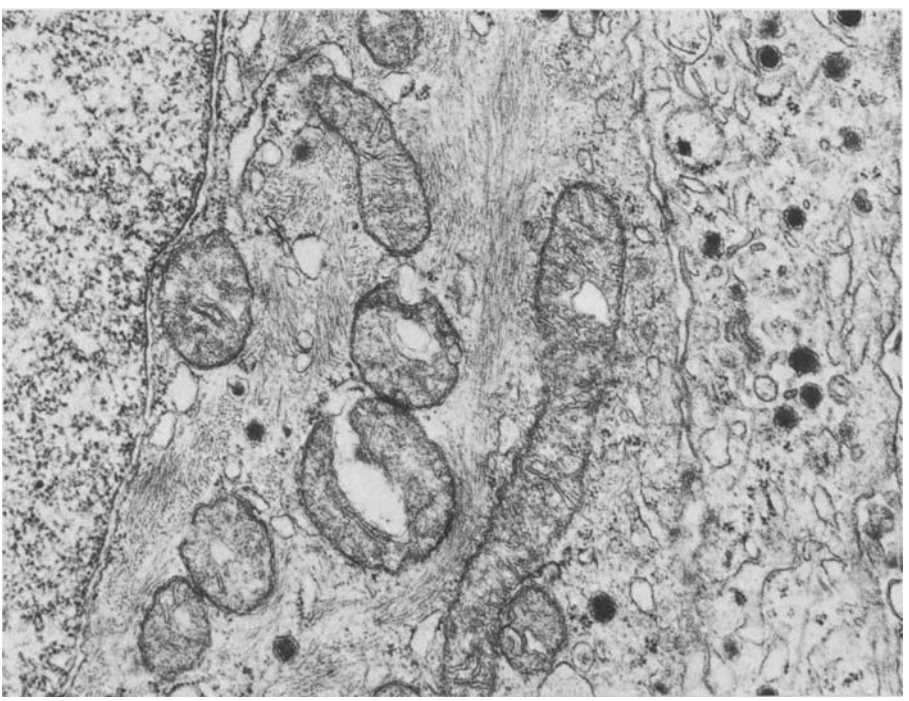

Fig. 4. Bundles of microfibrillae, rod-like mitochondria with electron-dense matrix, free ribosomes, vesicular smooth endoplasmic reticulum. Magnification ×25,600

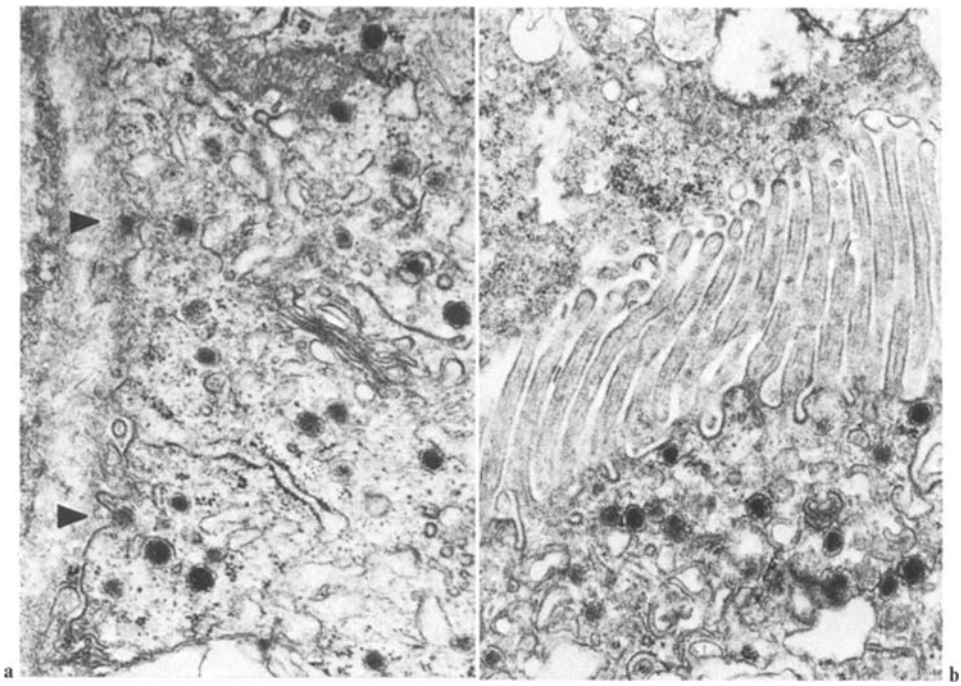

Fig. 5. a Exocytosis of secretory granules into the extracellular space (▲). Magnification ×28,500. **b** Microvilli of the cytoplasmic membrane. Magnification ×23,750

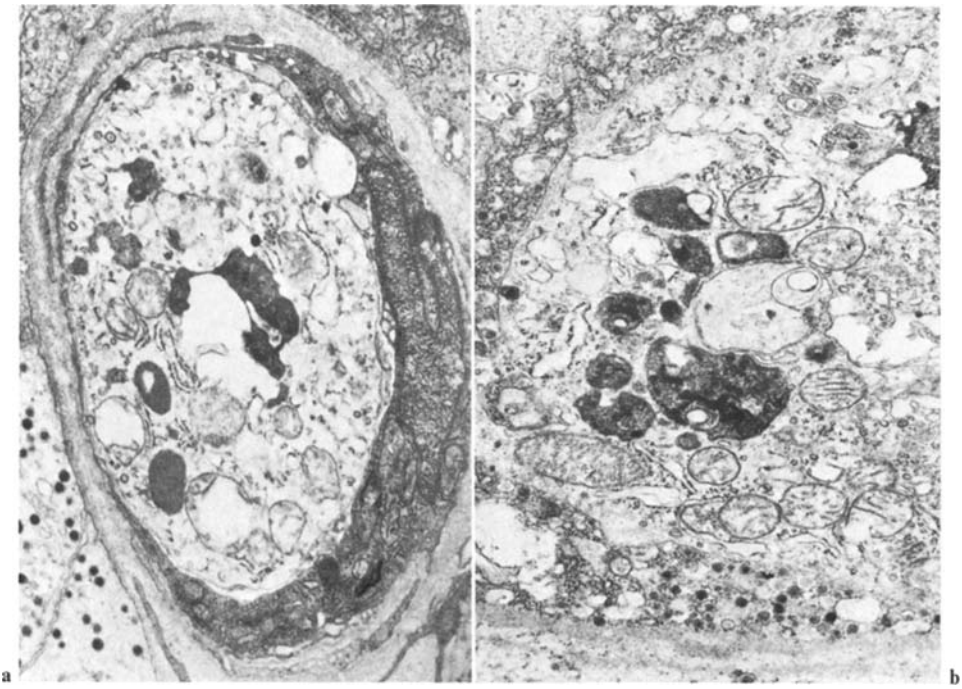

Fig. 6. a Signet-ring appearance of macrophage with cellular detritus of phagocytosed tumour cell. Magnification ×13,500. **b** Degenerate tumour cell with dilated mitochondria and accumulation of secondary lysosomes due to increased autophagic activity. Magnification ×13,500

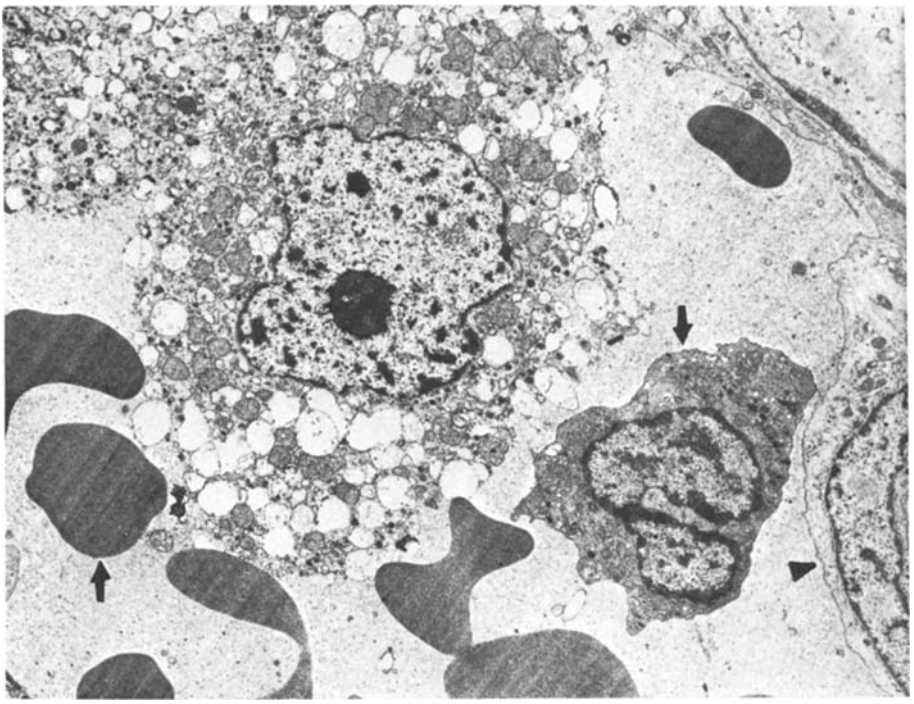

Fig. 7. Vascular invasion by tumour cells showing dilated vesicles of smooth endoplasmic reticulum. Endothelium (▲). Erythrocyte and leukocyte (↑). Magnification ×4700

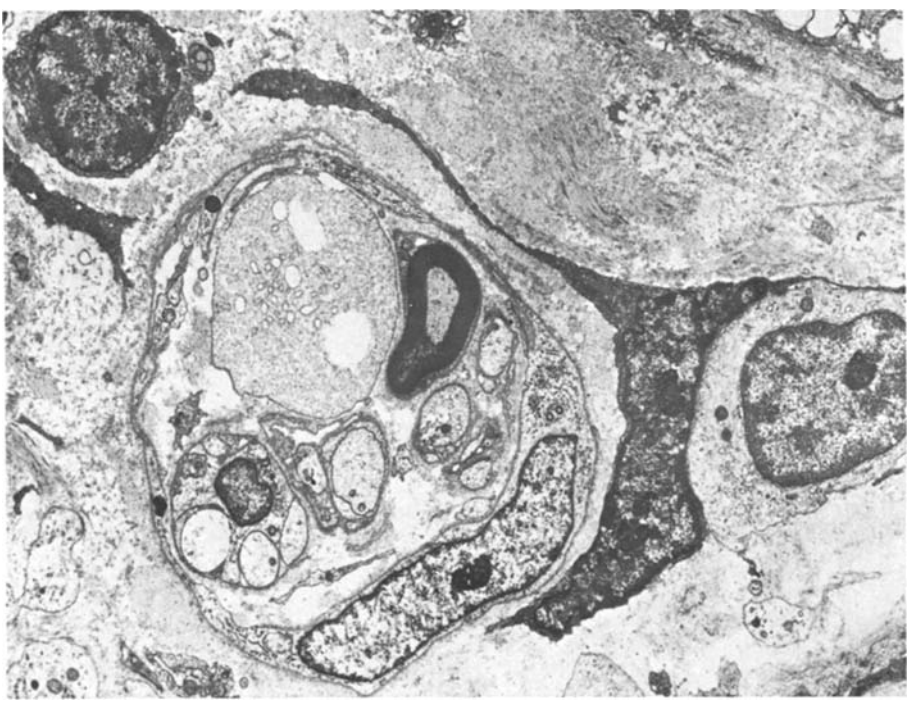

Fig. 8. Surrounding connective tissue with peripheral nerve, no contact with the tumour. Magnification ×4500

complexes found in the lumina of capillary blood vessels, following focal vascular invasion by the tumour (Fig. 7). Nerve endings in the stroma (Fig. 8) had no contact with the tumour, nor were sustentacular cells developed. These are a common feature in normal paraganglia, such as the carotid body.

Discussion

As the non-chromaffin paraganglia are believed to be chemoreceptors, their tumours, the non-chromaffin paragangliomas, were called chemodectomas by Mulligan (1950). This term is now well established. Recently more than 100 chemodectomas of the head and neck region were reviewed by Oberman et al. (1967) and Lack et al. (1977). They are mainly located in the upper parts of the 9th and 10th cranial nerves and arise from the carotid body, the vagal body and glomus jugulare. In contrast only 24 chemodectomas of the larynx, including the present case report, are found in the literature.

The clinical history and morphological aspects of the previously reviewed laryngeal chemodectomas (Vetters and Toner, 1970; Lawson and Zak, 1974; Lack et al., 1977) which are listed in Table 1, showed a slight preponderance of males over females (13♂: 10♀, 1 case without sex description). The age ranged from 14 to 67 years with a predominance in the 5th decade of life. The cardinal symptoms of laryngeal chemodectomas resemble those of other tumours in this region and consist of hoarseness, dysphagia, dyspnea of varying duration and occasionally pain radiating to the ear. Six of the operated patients suffered from local recurrence or metastases; some of these died with widespread dissemination (Vetters and Toner: personal communication from Prof. Thackray, 1970; Zachariah and Shah, 1972; Lack et al., 1977). Radical surgery, –if possible–, is the therapy of choice. Of the paragangliomas of the head and neck region, those arising in the larynx have by far the highest incidence of malignant behaviour and are resistant to radiation (Helpap and Helpap, 1966; Lawson and Zak, 1974; Lack et al., 1977). Malignancy is usually concealed by an apparently benign histological appearance. Thus the vascular invasion in our case was surprising and seemed to be in contrast with the generally benign histological appearance of the tumour. However, vascular invasion by the related chief cells of the more frequent carotid body tumours is well documented (Grimley and Glenner, 1967).

The ultrastructure of normal laryngeal paraganglia has not been investigated, but there are two reports concerning the ultrastructure of laryngeal chemodectoma (Vetters and Toner, 1970; Adlington and Woodhouse, 1972). These authors found the appearances to be comparable with the ultrastructure of the chief cells of carotid body tumours, already described in detail (Grimley and Glenner, 1967; Toker, 1967; Macadam, 1969). Sustentacular cells, which are occasionally present in these tumours and which are common feature in the normal carotid body (Biscoe and Stehbens, 1966) were not present in the ultrastructurally investigated laryngeal chemodectomas of Vetters and Toner (1970), Adlington and Woodhouse (1972) or in our case.

Our observation of microvilli on the cell surface confirms the finding of

Table 1. Laryngeal chemodectoma

No.	Year	Author	Sex	Age	Symptoms	Site	Therapy	Recurrence/ metastases
1.	1955	Andrews	♂	27	hoarseness, dyspnea dysphagia	left aryepiglottic fold left false cord and ventricle	tracheostomy and thyrotomy	–
2	1955	Blanchard and Saunders	♂	38	hoarseness, dyspnea dysphagia	left aryepiglottic fold left false cord	tracheostomy and lateral pharyngotomy	–
3.	1955	Zeitlhofer	♀	56	hoarseness, dyspnea	left aryepiglottic fold left false cord	lateral pharyngotomy	–
4.	1958	Schall	♀	49	–	left aryepiglottic fold	extralaryngeal excision	–
5.	1960	Hartmann	♀	40	hoarseness, dyspnea	right arytenoid to glottic rim	tracheostomy intralaryngeal excision	–
6.	1962	De Barros	♀	44	spasmodic pain	supra glottic	?	?
7.	1965	Wöckel et al.	♀	56	hoarseness, dyspnea	right aryepiglotic fold	extralaryngeal excision	–
8.	1965	Wöckel et al.	♂	56	hoarseness, pain	right aryepiglottic fold	intralaryngeal excision and cautery	local recurrence
9.	1965	Baxter	♀	59	hoarseness, dysphagia	right aryepiglottic fold	tracheostomy and extralaryngeal excision	–
10.	1965	Gignoux et al.	♀	21	hoarseness	left aryepiglottic fold	tracheostomy and extralaryngeal excision	–
11.	1966	Otty	?	?	?	subglottic	?	?
12.	1967	Martinson	♂	14	hoarseness, dyspnea right neck mass	subglottic (below right true cord)	tracheostomy and laryngofissure	–
13.	1968	Azevedos-Gamas and Gloor	♀	36	dysphagia, voice weakness	right aryepiglottic fold	extralaryngeal excision	–
14.	1970	Vetters and Toner	♂	60	throat pain	supraglottic mass	partial laryngectomy	recurrence and regional metastases
15.	1971	Benevant et al.	♀	30	dysphagia, dysphonia dyspnea	right aryepiglottic fold	excision in toto	–
16.	1971	Ishida et al.	♂	19	hoarseness, dyspnea stridor	right ventricle	supraglottic partial laryngectomy	–
17.	1972	Hooper	♂	55	throat pain, hoarseness, dysphagia	left aryepiglottic fold, false cord	radiotherapy and right radical neck dissection	regional metastases

Table 1 (continued)

No.	Year	Author	Sex	Age	Symptoms	Site	Therapy	Recurrence/ metastases
18.	1972	Hooper	♂	64	throat pain	left aryepiglottic fold	lateral pharyngotomy, radical neck dissection	local recurrence and metastases (Adlington and Woodhouse 1972)
19.	1972	Hooper	♂	54	throat pain	right aryepiglottic fold	total laryngectomy	–
20.	1972	Tobin and Harris	♂	67	hemoptysis, hoarseness	right aryepiglottic fold	supraglottic laryngectomy	–
21.	1972	Adlington and Woodhouse	♂	51	anosmia, throat-pain, ear pain	right arytenoid to right ventricular band	partial laryngectomy, right cervical block dissection	general dissemination
22.	1972	Zachariah and Shah	♂	61	right throat pain, ear pain, dysphagia, hoarseness	right supraglottic region, right vocal cord, subepiglottic space	right partial laryngectomy	local recurrence and general dissemination
23.	1977	Lack et al.	♀	57	hoarseness, dyspnea	right aryepiglottic fold	?	–
24.	1977	Hohbach and Mootz	♂	64	hoarseness, dysphagia, ear pain, pains on pressure to the right larynx	right aryepiglottic fold and dorsal false cord	excision from right pharyngotomy tracheotomy	–

Completed as per Vetters and Toner (1970), Lawson and Zak (1974)

Vetters and Toner (1970). According to Adlington and Woodhouse (1972) this ultrastructural characteristic, suggesting an epithelial origin, exists in metastases as well as in the primary tumour. There is general agreement that the predominant ultrastructural feature of all chemodectomas, and of chemoreceptor cells in intact paraganglia, is the presence of numerous secretory granules. Vetters and Toner (1970) demonstrated histochemically catecholamines in their case of laryngeal chemodectomas, correlating with clinical evidence of enhanced catecholamine secretion. In our case, in contrast to this we found evidence of discharge of secretory granules by exocytosis, but there were no corresponding clinical symptoms.

One probable site of origin of laryngeal chemodectomas is the pair of superior and inferior laryngeal glomera described by Watzka (1963) and Kleinsasser (1964). Lawson and Zak (1974) found further aberrant or ectopic non-chromaffin paraganglionic tissue at other sites in the larynx. Another possible parent cell is the Kultschitzky-type cell of normal human bronchial mucosa, first described by Bensch et al. (1965, 1968). In ultrastructure they closely resemble the intestinal

argentaffin cells, showing argyrophilia in the fetus and newborn, but argyrophobia in adults (Feyrter, 1969; Bensch, 1976; Heitz, 1977).

The immunocytochemical and histochemical properties of the specific granules of laryngeal chemodectoma and of their presumptive precursor cells are typical of a group of cells, present in different organs with widely different functions. They are collectively known as APUD-cells by Pearse (1974). (APUD = *A*mine content and/or *A*mine *P*recursor *U*ptake and *D*ecarboxylation). Frequently the tumours arising from APUD-cells, the apudomas, exhibit the functional and structural characteristics of the APUD-series more distinctly than the cells from which they arose (Pearse, 1975). Ultrastructurally, in addition to the granules, Pearse and his coworkers have described further properties of the APUD-cells and apudomas. All of these characteristics are evident in the ultrastructurally investigated laryngeal chemodectomas (Vetters and Toner, 1970; Adlington and Wood-House, 1972; our own case report) and include: 1. low levels of rough endoplasmic reticulum, 2. high levels of smooth endoplasmic reticulum in form of vesicles, 3. high content of free ribosomes, 4. electron dense mitochondria, 5. fixation labile mitochondria, 6. bundles of protein microfibres – especially when neoplastic (Pearse, 1969; Pearse and Welbourn, 1973). Thus the laryngeal chemodectomas can be included with the apudomas, whose presumptive parent cells are very likely to have their origin in the neural crest (Pearse, 1975).

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