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Light and Electron Microscopic Investigation of Parathyroid Carcinoma During Dedifferentiation

Survey and Study of a Case

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Summary. A case of parathyroid carcinoma in a 74-year-old female patient was studied by light and electron microscopy.

The malignancy of the parathyroid tumour was confirmed by local recurrence and infiltration of adjacent structures. The tumour was composed of uniform chief cells without mitoses. Ultrastructurally, the cells were characterized by tortuous plasma membranes, numerous secretion granules, an extensive rough endoplasmic reticulum and lack of lipid vacuoles, all indicating hyperactivity, but not malignancy.

At death, the autopsy revealed local recurrence of tumour tissue, but no distant metastases. Both light and electron microscopy showed that considerable dedifferentiation of the tumour tissue had occurred. The tumour cells were now characterized by a marked nuclear pleomorphism and a coarse clumping of the chromatin. The presence of secretion granules alone suggested a parathyroid origin.

Thus, at death there was unequivocal histological evidence of a carcinoma, whereas no such diagnosis could be made from the early biopsy. The clinical course alone indicated the malignant nature of the lesion.

Key words: Parathyroid carcinoma – Tumour progession – Ultrastructure.

Introduction

Carcinoma of the parathyroid gland is a very rare disease. According to the literature, it comprises only from 0.75% to 5% of cases with hyperparathyroidism (Häusler-Kolb et al., 1974).

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The clinician is often faced with a considerable diagnostic problem as the tumour tissue usually lacks the conventional cytomorphological criteria of malignancy, despite obviously malignant clinical behaviour. Thus, it is not uncommon that the disease on first admission is misdiagnosed as an adenoma.

Very few electron microscopic studies of parathyroid carcinoma have been reported (Faccini, 1970; Altenähr and Saeger, 1973; Thiele, Reale and Georgii, 1973; Murayama, Kawabe and Tagami, 1977). The following case report is a description of a carcinoma of the parathyroid in which the usual cytomorphological examination was supplemented with investigation of the ultrastructural details.

Methods

For light microscopic analysis conventional histological techniques were used, i.e., fixation in formaldehyde and staining with haematoxylin and eosin.

For electron microscopy, fragments of tissue, obtained at operation, were fixed by immersion in 2.5% glutaraldehyde in 0.1 M sodium cacodylate buffer, pH 7.3. Postfixation was carried out for 2 h in 1% osmium tetroxide. After dehydration in ethanol, the tissue was embedded in Vestopal. Sections were cut on an LKB ultramicrotome, mounted on copper grids with formvar membranes and stained with uranyl acetate and lead citrate. The sections were examined with a Philips EM 201 C electron microscope.

Case

A 74-year-old woman, who in 1944 had undergone partial resection of the thyroid due to hyperactivity of the gland, was admitted to the hospital in 1973 complaining of dyspnoea and swelling of the neck. X-ray showed a tumour that displaced the trachea to the left, and X-rays of the bones showed halisteresis. Serum calcium was considerably higher than normal (13.6 mg/100 ml) and an attempt to suppress serum Ca with prednisone was unsuccessful.

The patient was assumed to the suffering from primary hyperparathyroidism and was operated upon in March 1973. Histopathological examination showed a tumour composed of uniform well-differentiated parathyroid chief cells arranged in small trabeculae or follicular structures (Fig. 1 a and b). Mitotic figures were not observed. Conclusion: a benign parathyroid adenoma. Postoperatively the patient developed hypocalcaemia and was treated with calcium by mouth for the following 9 mth.

The patient was readmitted to the hospital in Apr. 1974 at which time Serum Ca was found to be a little above normal, Serum Phosphorus was subnormal. It was concluded that the patient had a small recurrence of the disease, but operation was not found necessary. In May 1975, Serum Ca was 11.2 mg/100 ml and Serum Phosphorus normal. In April 1976 the patient was again hospitalized. Serum ionized calcium had increased to 1.58 mmol/l (normal values 1.00–1.18 mmol/l). On this admission the histological specimen from the operation in 1973 was reviewed. Renewed examination revealed that the tumour tissue penetrated the capsule intermingling with bundles of the surrounding

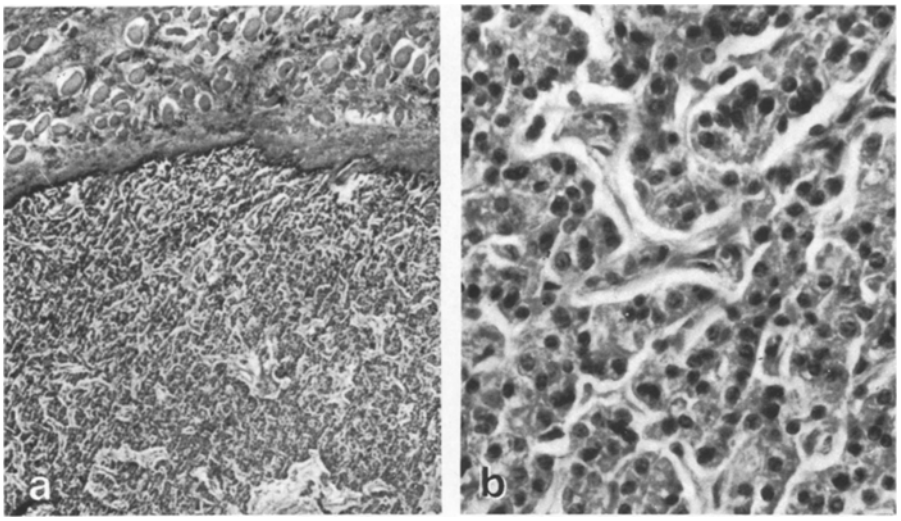

Fig. 1 a and b. Well-demarcated parathyroid tumour tissue with a tendency to alveolar arrangement, composed of uniform chief cells. Haematoxylin and eosin. × 30 and 120

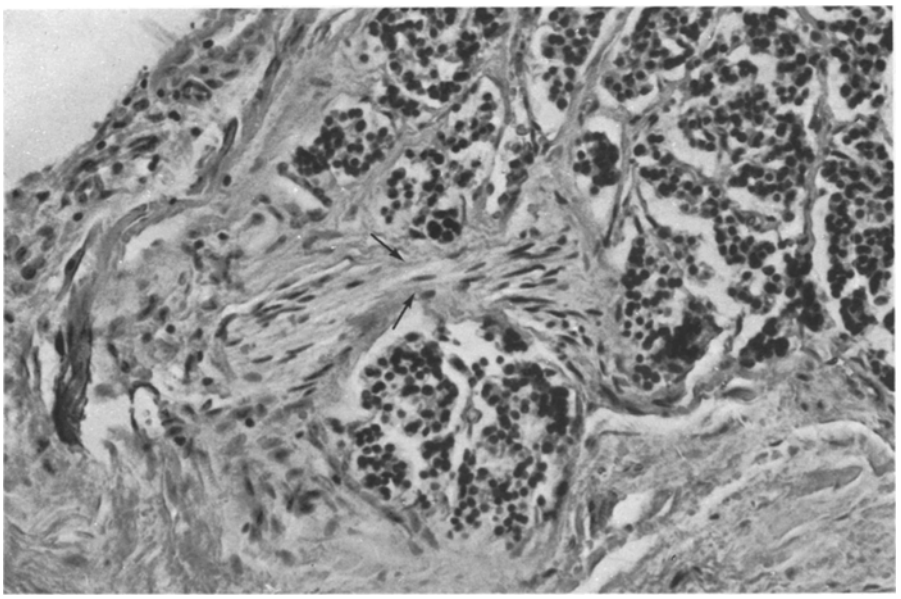

Fig. 2. Local infiltration of well-differentiated parathyroid tumour tissue with perineural infiltration (*arrows*). Haematoxylin and eosin. × 50

connective tissue and, in a few places, tumour cells invaded the perineural space. Taking the clinical course into consideration, it was now concluded that the patient suffered from a parathyroid carcinoma.

In 1977 a new attempt to suppress the hypercalcaemia with prednisone was made, but again without success. The concentration of the parathyroid

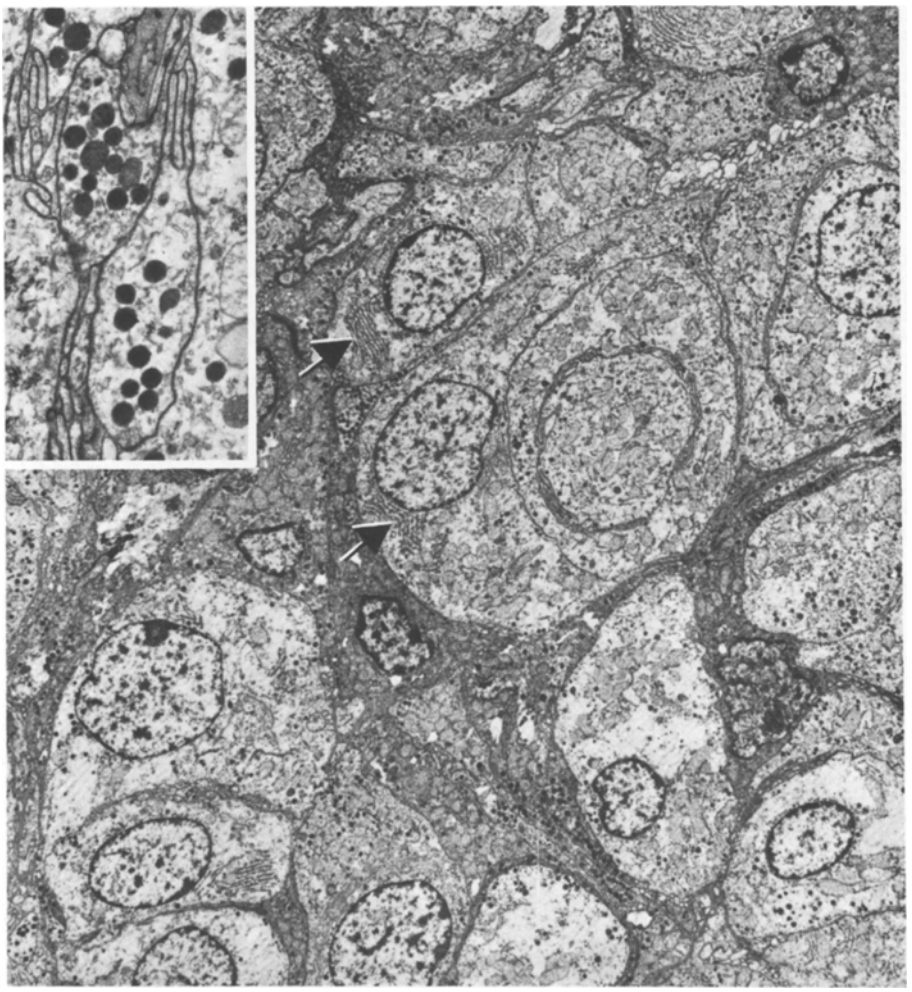

Fig. 3. Light cells with rounded and dark cells with shrunken nuclei. The plasma membranes are tortuous. Numerous secretion granules are seen. Well-developed rough endoplasmatic reticulae are present in some cells (*arrows*) (×3,800). *Inset:* Round secretion granules located partly inside the convolutions of the tortuous plasma membranes (×18,500)

hormone in the Serum (S-PTH) was considerably increased, 4000 pg/ml (normal values below 100 pg/ml).

Operation was performed in Oct. 1977, and a 3 × 3 × 4 cm locally infiltrating tumour (Fig. 2) was resected. The histological picture resembled that described previously.

Ultrastructurally, the tumour cells were seen to be fairly large, rounded or polygonal (Fig. 3). Most cells had a light, electron-lucent cytoplasm, and round or oval nuclei containing one or two prominent nucleoli. One of these was often located at the nuclear membrane. The chromatin was distributed in fine or coarse clumps with some tendency towards condensation at the nuclear

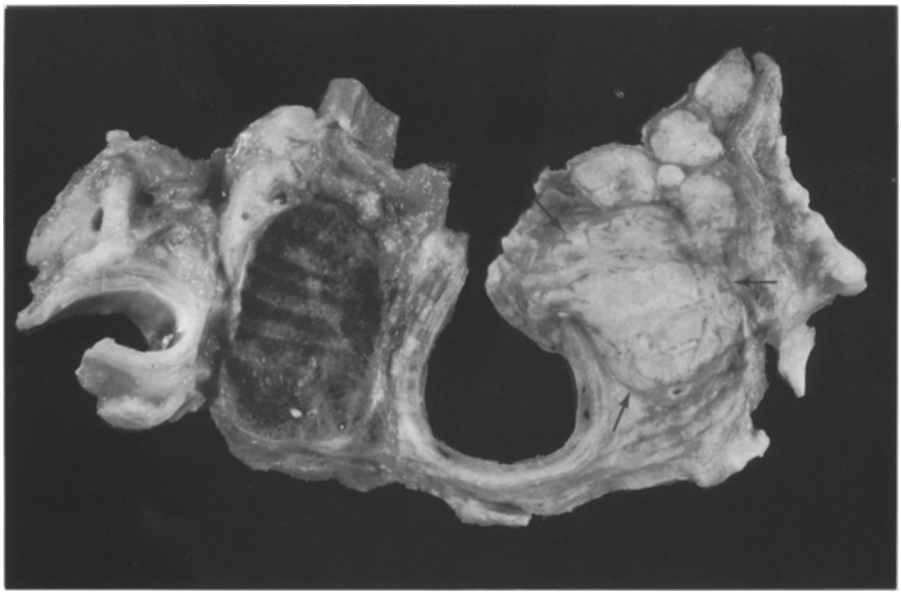

Fig. 4. Cross section of the larynx showing the dark normal thyroid and the white lobulated parathyroid tumour tissue (*arrows*)

membrane. The plasma membranes were conspicuously tortuous, often to an extreme degree, showing numerous complicated interdigitations (Fig. 3). Mitochondria were often unevenly distributed in the cell. Free ribosomes were inconspicuous. The Golgi complexes were well developed, usually several were present in the same cell. The rough endoplasmic reticulum was prominent, but not dilated, being arranged in close, parallel laminae (Fig. 3). Lysosomes were sparse. Lipid vacuoles or glycogen granules were not observed. Intercellular spaces were seen to contain a moderate electron-dense material in some areas. A striking feature was the occurrence of membrane-bound round structures with a strongly electron-dense core, interpreted as secretion granules. These were present numerously in the cytoplasm, mostly in the peripheral parts of the cell, often inside the tortuous interdigitations of the plasma membranes.

Some cells had a darker, more electron-dense cytoplasm and relatively small, indented nuclei; these cells are thought to represent degenerating forms.

In December 1978, the patient was readmitted to a local hospital with ischaemic problems of the left leg. A few days after admission she suddenly died, and the autopsy revealed that death was probably caused by septicaemia. At the posterior wall of the lower part of the larynx five hard, whitish and partly confluent tumours (Fig. 4), measuring $2 \times 3 \times 2$ cm, were found adhering to the adjacent wall of the larynx and prominating under the surface of the oesophagus, but without apparent invasion. Behind the oesophagus, located about 9 cm below the level of the vocal cords, a small tumour was found which was thought to be a metastasis to a lymph node. Metastases were not detected in other organs.

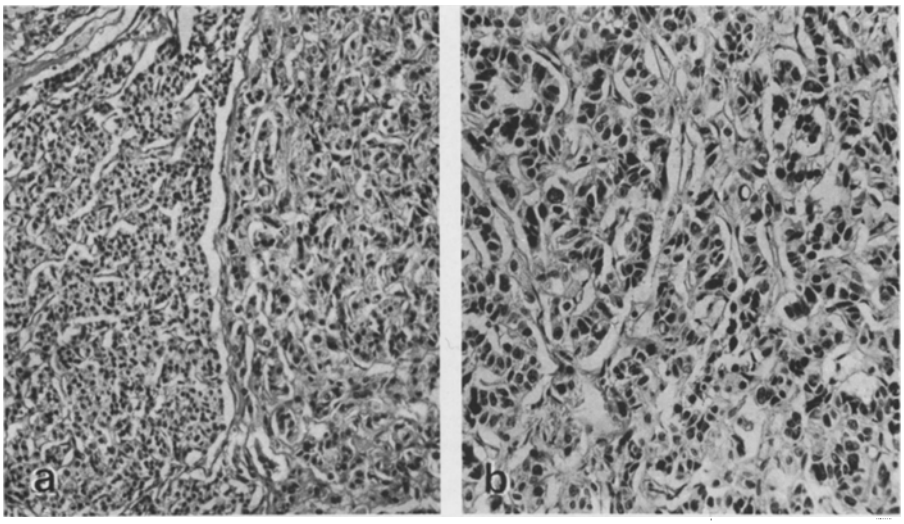

Fig. 5a und b. Photomicrograph showing both the well-differentiated parathyroid tumour and the dedifferentiated tumour tissue characterized by marked cellular pleomorphism. Haemotoxylin and eosin. × 50 and 100

The histological examination revealed a tumour tissue composed mostly of "normal" chief cells with the same morphology as that previously described. Tumour tissue was found to infiltrate between the tracheal rings and to penetrate to oesophageal wall to, but not through, the squamous epithelial lining. However, the tumour now contained areas characterized by a conspicuous cellular pleomorphism, large hyperchromatic nuclei with a highly variable chromatin structure and scattered multinucleated cells (Fig. 5a and b). Again no mitotic figures were observed.

The tumour situated behind the oesophagus and assumed to be a metastatic lymph node was composed of neoplastic tissue of the same histological appearance. However, no lymphatic tissue was demonstrated and it must remain an open question whether it was a true metastasis, or simply the result of implantation during the surgical procedure.

Discussion

A number of features have been considered to be suggestive of parathyroid carcinoma (Schantz and Castleman, 1973): adherence to surrounding structures, a clinically palpable tumour, a thick capsule with fibrous trabeculae intermingling with the tumour, penetration of tumour through the capsule, invasion of venous blood vessels and mitotic figures.

According to these criteria, five out of 53 studied cases (Kay and Hume, 1973) of primary hyperparathyroidism were carcinomata. However, in none

of these patients did a follow-up examination reveal any sign of malignancy and the authors suggested, in accordance with Castleman (1952) that apart from verified metastases the presence of mitoses seem to be the only reliable malignant criterion. However, mitotic figures may also be present in adenomata (Black, 1958; Kleinfeld, 1959). The difficulties are further illustrated by the fact that carcinoma without mitoses has also been described (Stephenson, Jr., 1950; Altenähr and Saeger, 1973).

The present case of parathyroid carcinoma was initially misdiagnosed as a parathyroid adenoma. However, at the second operation the macroscopically infiltrative and aggressive appearance left no doubt as to the malignant nature of the tumour.

The cytomorphological features of the tumour removed at the operation were unchanged, i.e. there were no definite malignant characteristics.

However, at the autopsy the tumour was found to be composed of fairly normal parathyroid chief cells, but also contained tumour tissue with very little resemblance to the tissue of probable origin. Although wide variations in nuclear size, nuclear hyperchromatism bizarre nuclei and giant cells have been observed in 25% of reported adenomata (Norris, 1948), this tumour component most likely represents a malignant and dedifferentiated variant of the primary tumour, and thus reflecting progression of the disease.

Ultrastructurally, as in light microscope, the cells in the primary tumour of our case were chief cells. Features like the numerous secretion granules, the extensive rough endoplasmic reticulum, the well-developed Golgi complexes, the tortuous plasma membranes and the lack of lipid vacuoles, indicate that the cells were hyperactive and clearly different from normal chief cells (Nilsson, 1977). These features of hyperactivity are seen in both chief-cell hyperplasia and adenoma, which consequently cannot be differentiated by electron microscopic examination (Nilsson).

In the tumour tissue removed at autopsy, the cells could no longer be identified as parathyroid cells with certainty. Only the presence of secretion granules suggests a parathyroid origin. With regard to the diagnosis of malignancy, electron microscopic investigation did not add significantly to light microscopy.

The ultrastructural appearance of parathyroid carcinoma has been described in few reports: Faccini (1970) (four cases), Altenähr and Saeger (two cases), Thiele et al. (1973) (one case) and Murayama et al. (1977) (one case). We find our case to be similar to those of Faccini and Murayama et al. in that they describe an extreme variation in nuclear size and form, features which were also observed in the later tumour of our patient. On the other hand, round or oval nuclei, as in the primary tumour, were reported by Altenähr and Saeger and Thiele et al., presumably as an expression of a high degree of differentiation of the tumour.

Thus, the electron microscopic examination of parathyroid tissue can differentiate between the normal and the hyperactive chief cell. No safe differentiation can at present be made between chief cell hyperplasia and adenoma, or carcinoma – at least when the carcinoma is well-differentiated.

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