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Light and Electron Microscopy of Parathyroid Carcinoma

Report of Three Cases*

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Summary. The morphology of three cases of parathyroid carcinoma is described, including the electron microscope findings in two of these cases. The clinical and morphologic points for the tentative diagnosis of parathyroid carcinoma are discussed. The malignancy of a parathyroid tumour is proved by lymphogenic or hematogenic metastases, by histological evidence of tumour infiltration into the surrounding tissues (including macroscopic adherence and sometimes vocal cord paralysis), and by cytologic evidence of mitoses. Nuclear atypism is often present but is neither a necessary nor an adequate proof of malignancy, because it is also seen in benign adenomas and in hyperplastic parathyroids. The ultrastructure of the carcinoma cells was also characterized by nuclear atypism and mitoses. In one carcinoma, the contents of cytoplasmic organelles varied in different cells, indicating various endocrine activity of the tumour cells. In another parathyroid carcinoma with low endocrine activity, copious cytoplasmic organelles and many secretory granules were found. There seem to be three possible causes of nonfunctioning parathyroid carcinomas: 1. lack of hormone synthesis, 2. impairment of cellular hormone secretion, 3. synthesis of a pathologic protein with defective endocrine activity.

Introduction

The clinico-pathological entity of carcinoma of the parathyroid gland (PTG) consists of a malignant PTG tumour mostly associated with the metabolic derangement of primary hyperparathyroidism (HPT). PTG carcinoma is a rare tumour. Its incidence seems to be 2–3% in patients suffering from primary HPT (Cope *et al.*, 1953; Dubost *et al.*, 1969). Geisbe (1966) has compiled 98 published cases of PTG carcinoma. Holmes *et al.* (1969), however accepted only 50 of those cases described in the literature as true PTG carcinomas. Points of discussion are the diagnostic criteria for malignancy of PTG tumours and the question whether malignant neck tumours which are histologically similar to PTG tumours but without HPT do actually originate from the PTG. Extensive reviews of PTG carcinomas including morphology and discussions of these problems have been given by Black (1954) and Holmes *et al.* (1969). The electron microscopy of benign PTG tumours is rather well known (Altenähr, 1972). Description of the ultrastructure of PTG carcinoma has been given only by Faccini (1970) in four cases. This paper intends to provide further information on the morphology of PTG carcinoma with special regards to the diagnostic criteria and to the ultrastructure.

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Abbreviated Case Reports

Case 1 (H. G.)

Male patient, aged 44 years, with severe HPT. Clinically, before the first operation the tentative diagnosis "metastasising PTG carcinoma" was made, as round foci looking like metastases were found on chest x-rays. During the first surgical neck exploration an encapsulated PTG tumour with a diameter of about 4 cm was removed. The primary histological diagnosis was "PTG ademona" because of its high cellular differentiation and its lack of infiltration, atypism and pleomorphism. Mitotic figures were not observed. After the surgical removal of the PTG tumour, HPT persisted. A lung biopsy performed 4 months later proved that the tentative diagnosis of lung metastases of the same histological type as the PTG tumour was correct. 15 months after the first neck exploration some of the lung metastases were removed surgically to mitigate HPT. Two months later a second neck exploration was done in which tumourous infiltration of the thyroid gland and the cervical soft tissues as well as metastases of the jugular and carotid lymph nodes were found. The patient died some months later of a hypercalcaemic crisis and acute pancreatitis. Unfortunately, autopsy was refused.

Case 2 (J. G.)

Male patient aged 45 years, with severe HPT and a palpable neck tumour. During the first surgical neck exploration a PTG tumour of 9 grams weight was found to originate from the left lower PTG. The tumour adhered to the surrounding soft tissues and had a hard consistency and greyish colour. The tumour has been resected totally with its surrounding soft tissues. Cervical metastases could not be detected at that operation. In an intra-operative frozen section as well as in the paraffin embedded tumour tissue, a PTG chief cell carcinoma was diagnosed because of its high-grade atypism, mitoses, and infiltrative growth. Two other parathyroids were removed at the same operation being somewhat enlarged and weighing 100 mg and 80 mg, respectively. The histological appearance of these glands was that of primary chief cell hyperplasia. After transitory recovery the HPT recurred, and a second neck exploration was necessary 14 months after the first operation. Multiple lymph node metastases in the lower neck region and in the upper mediastinum and a recurrent tumour in the cervical soft tissues were found. The tumourous tissue was hard and grey and as adherent as in the first operation. The patient was irradiated postoperatively. Ten months after this last operation, he is at present without relapse or symptoms of HPT.

Case 3 (F. B.)

Male patient, aged 50 years, no clear symptoms of HPT. The patient underwent hemithyroidectomy on the left side for a tumour thought to be of thyroid origin. This large tumour was diagnosed histologically as a "hyperplastic parathyroid gland". Five years later large bilateral recurrent neck tumours, big as a first on both sides, were removed surgically. Histologically these recurrent tumours also were of parathyroid type. One year later neck tumours developed again. At this time detailed studies on parathyroid function were made, including ^{47}calcium-kinetics (Montz *et al.*, 1972) and histomorphometric analysis of an iliac crest biopsy. Whereas no signs of HPT could be found in ^{47}calcium-kinetics, the histomorphometric analysis of bone showed a moderate HPT with increased osteoclastic bone resorption, osteoporosis, and slight osteomalacia. At the same time the histological slides of the previously removed tumours were also reexamined. They showed a tumourous tissue in full accordance with parathyroid tumours, but with criteria of malignancy in the primary as well as in the recurrent tumours. Consequently the third neck exploration was performed. On the right side a solitary recurrent tumour of 4 grams weight and on the left side multiple lymph node metastases were resected. The tumour tissue was hard in consistency, grey, and adherent to the surrounding tissues. The patient was irradiated after that operation. At present—fourteen months afterwards—the patient is well and without relapse.

Morphology

Macroscopical Findings

In one case the *primary tumour* macroscopically was well encapsulated and could be resected easily. In the other two cases the primary tumour infiltrated and adhered to the surrounding tissues, i.e. the thyroid gland, striated muscles, fatty tissue, and connective tissue. Surgical removal, therefore, was complicated. On the cut surface the colour of the tumours was greyish. In the one primary tumour seen macroscopically by the authors themselves (J. G.), the consistency was hard. All primary tumours were large and palpable at the time of detection and operation.

The *recurrent tumours* and all lymph node metastases had also a relatively hard consistency and a grey colour. As mentioned in the case reports, the recurrent cervical tumours were large in size. The lymph node metastases had developed as multiple tumourous nodules, which were often packed closely.

Histological Findings

Histologically all three primary tumours, their recurrent tumours and metastases presented a solid epithelial tumour tissue of an endocrine type with a more or less trabecular or lobular pattern formed by the tumour stroma (Fig. 1a). Extensive parts of the tumour had a sclerotic and hyalinised stroma responsible for their hard consistency (Fig. 1b). Regressive changes and tumour cell necroses were frequently seen. In case 3 (F. B.) there were central necroses within many of the lobules accompanied by needle-shaped crystalline deposits and multinucleated giant cells of the foreign body type suggesting cholesterol deposits. In case 2 (J. G.) there was a widespread calcification of hyalinised stroma as well as of parenchymal cords (Fig. 1b).

The cell type of all tumours corresponded to parathyroid chief cells (Fig. 1a). A few cells had a clear vacuolised or a somewhat oxyphilic cytoplasm similar to clear chief cells or oxyphilic chief cells. There were no typical waterclear or fully developed oxyphilic cells. The nuclei were somewhat enlarged compared to normal PTG cells, but individually they showed a large range of variations in sizes up to giant nuclei. Whilst the nuclei in general were round or ovoid, the larger ones and the giant nuclei were pleomorphic (Figs. 1, 3c). Mostly the chromatin content was moderate. A few large nuclei were hyperchromatic (Figs. 1a, 3c). Typically the chromatin was found as multiple clumps of various sizes dispersed throughout the nucleus (Fig. 3a). Nucleoli were frequently prominent and sometimes two or more nucleoli were present. A few multinucleated giant cells could be found (Fig. 3b). Emphasis must be laid on the presence of mitoses in PTG carcinomas (Fig. 3d). They were observed in all our tumours except in the primary tumour of case 1. This primary tumour is somewhat exceptional because of its intact capsule, its very regular cell structure, and its lack of atypism and mitoses. The recurrent tumour in the neck, the lymph node metastases, and the lung metastases in that case, however, had dedifferentiated markedly and were rich in atypias and mitoses. In all three cases lymphogenous spreading of the tumour could be observated within ectatic lymphatic vessels (Fig. 2a). Corresponding to that, in all cases lymph node metastases were present, and cords of tumourous tissue were observed within the

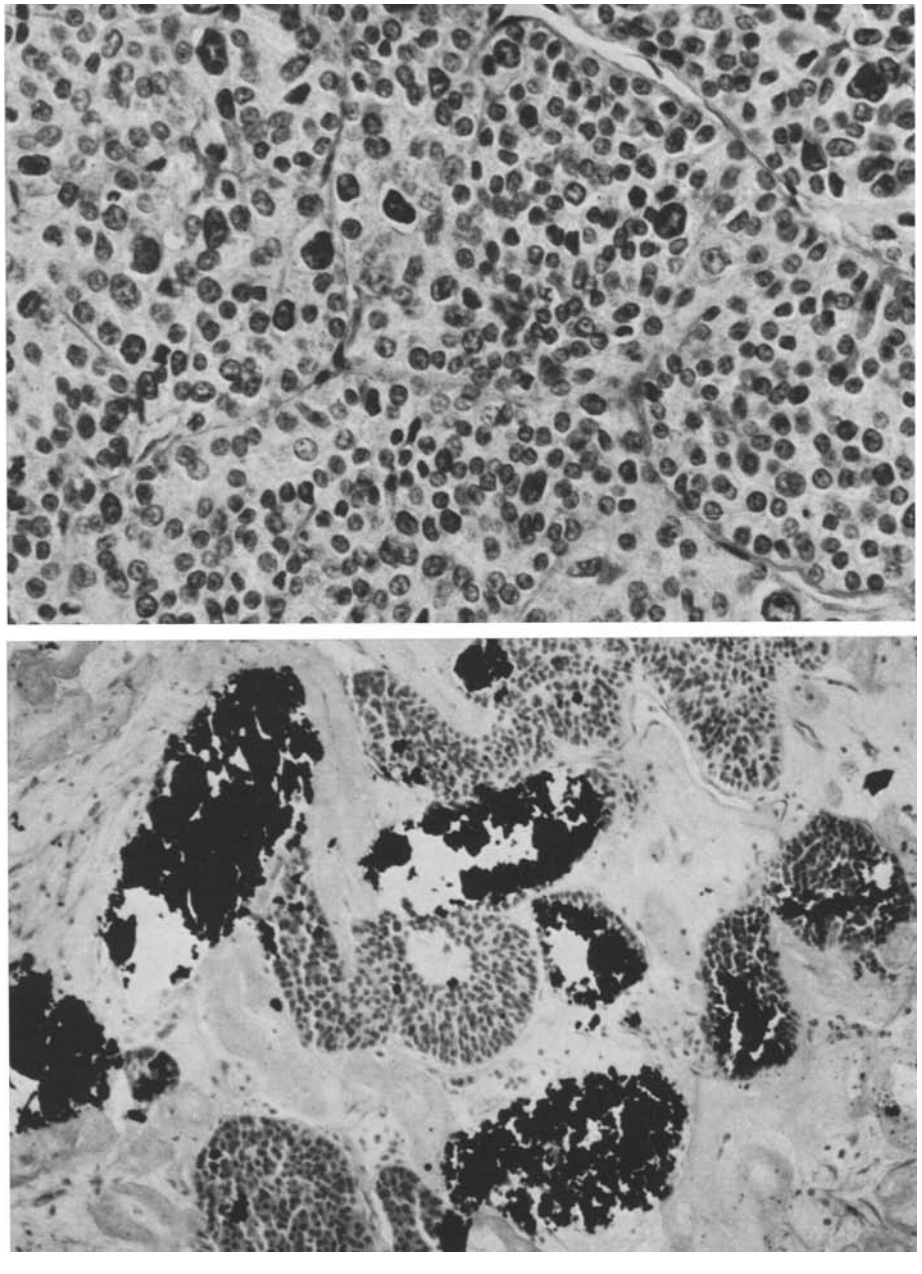
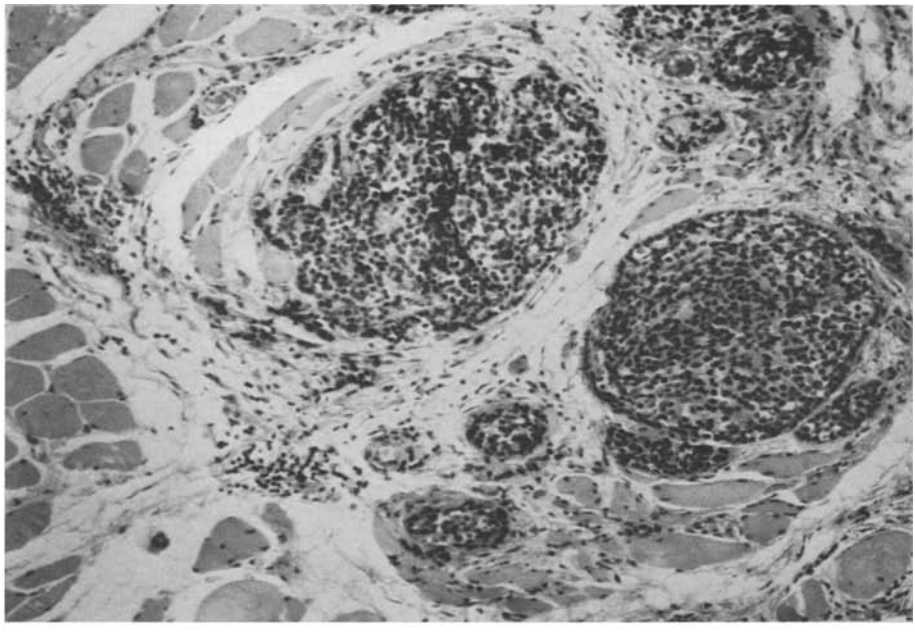


Fig. 1 a and b. a Recurrent tumour of PTG carcinoma, case 1: solid tumour tissue with lobular arrangement and septa of connective tissue stroma. Moderate pleomorphism of tumour cell nuclei. Haematoxylin-eosin. × 400. b Primary tumour of PTG carcinoma, case 2: tumour tissue with broad hyalinised sclerosis and calcifications. Von Kossa stain. × 175

a



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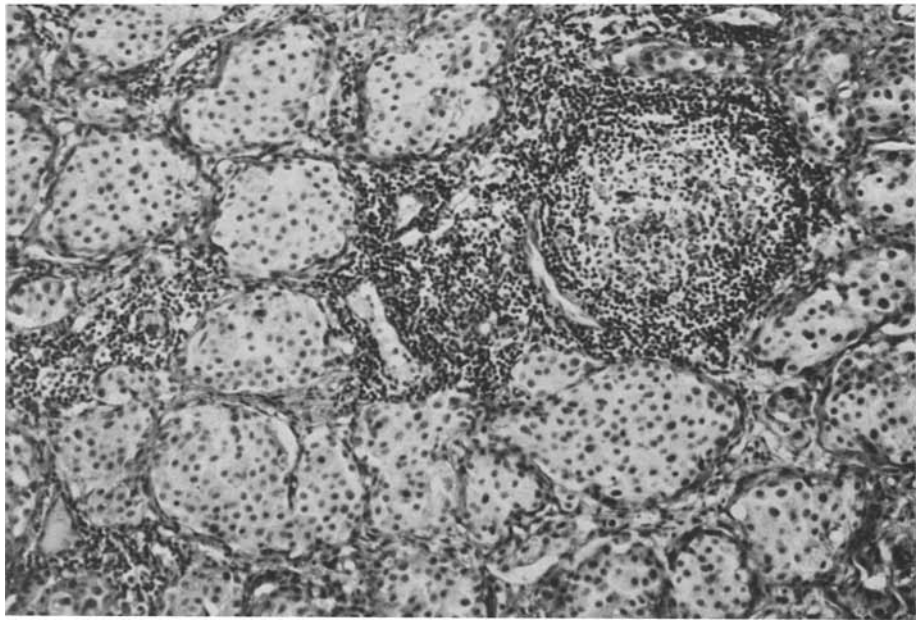


Fig. 2a and b. a Recurrent tumour of PTG carcinoma, case 2: muscular tumour infiltration via lymphatic vessels. Haematoxylin-eosin. × 175. b Lymph node metastasis of PTG carcinoma, case 3: nodular infiltration and tumour growth within ectatic lymph sinus. Haematoxylin-eosin. × 175

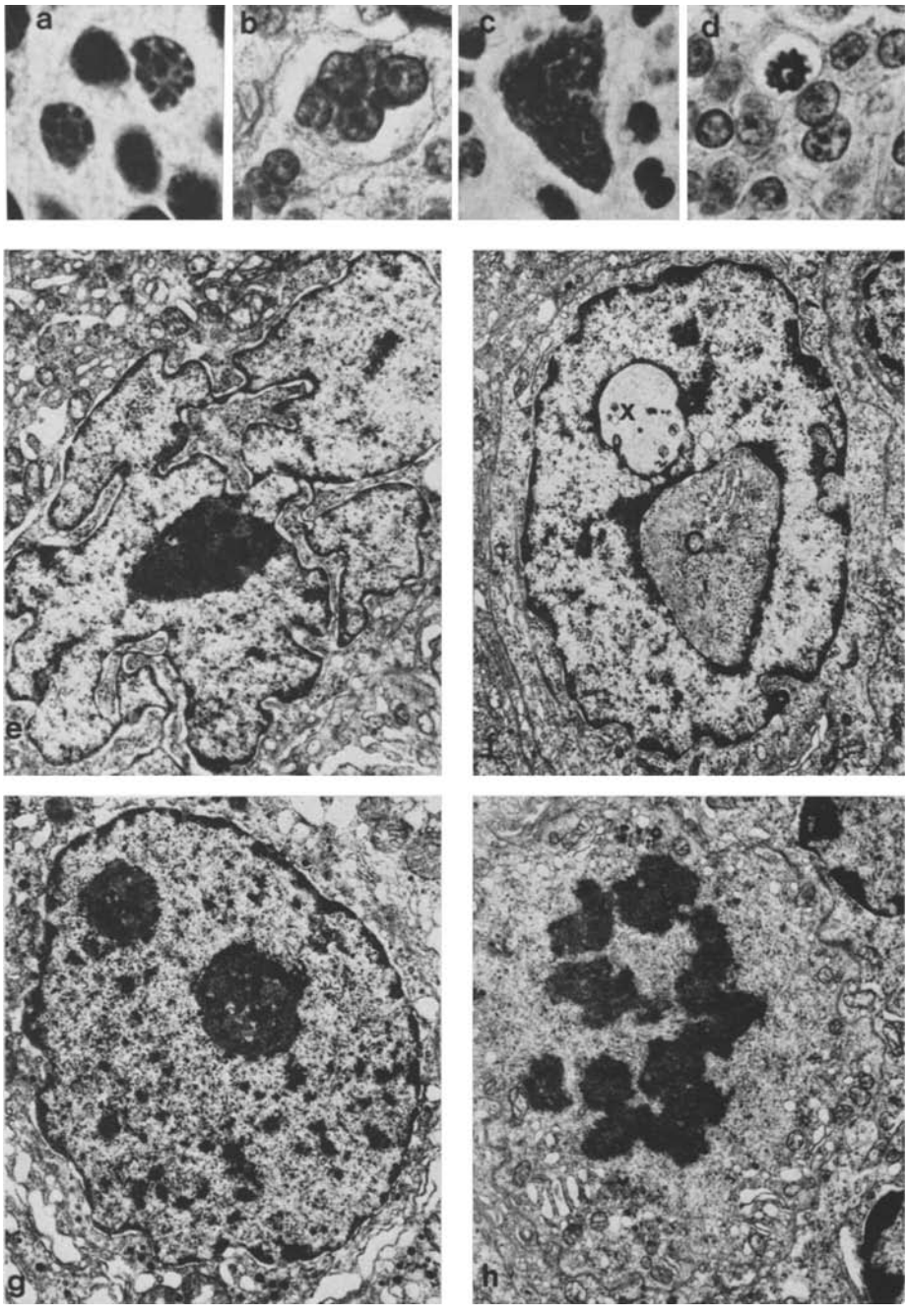


Fig. 3a—h. Various nuclear forms of PTG carcinomas: a Coarse clumps of chromatin dispersed throughout the nuclei, case 2. × 1500. b Multinucleated giant cell, case 1. × 800. c Hyperchromatic giant nucleus, case 2. × 800. d Mitosis, significant for malignancy, case 1. × 800. e Ultrastructure of a nucleus with deep bizarre invaginations and a large nucleolus, case 2. × 8600. f Ultrastructure of a nucleus with a vacuolar inclusion body (*x*), a cytoplasmic inclusion (*c*), and small superficial invaginations, case 2. × 6000. g Ultrastructure of a nucleus with a double nucleoli and finely stippled chromatin dispersed throughout the nucleus, case 3. × 13000. h Ultrastructure of a mitosis, case 2. × 6000

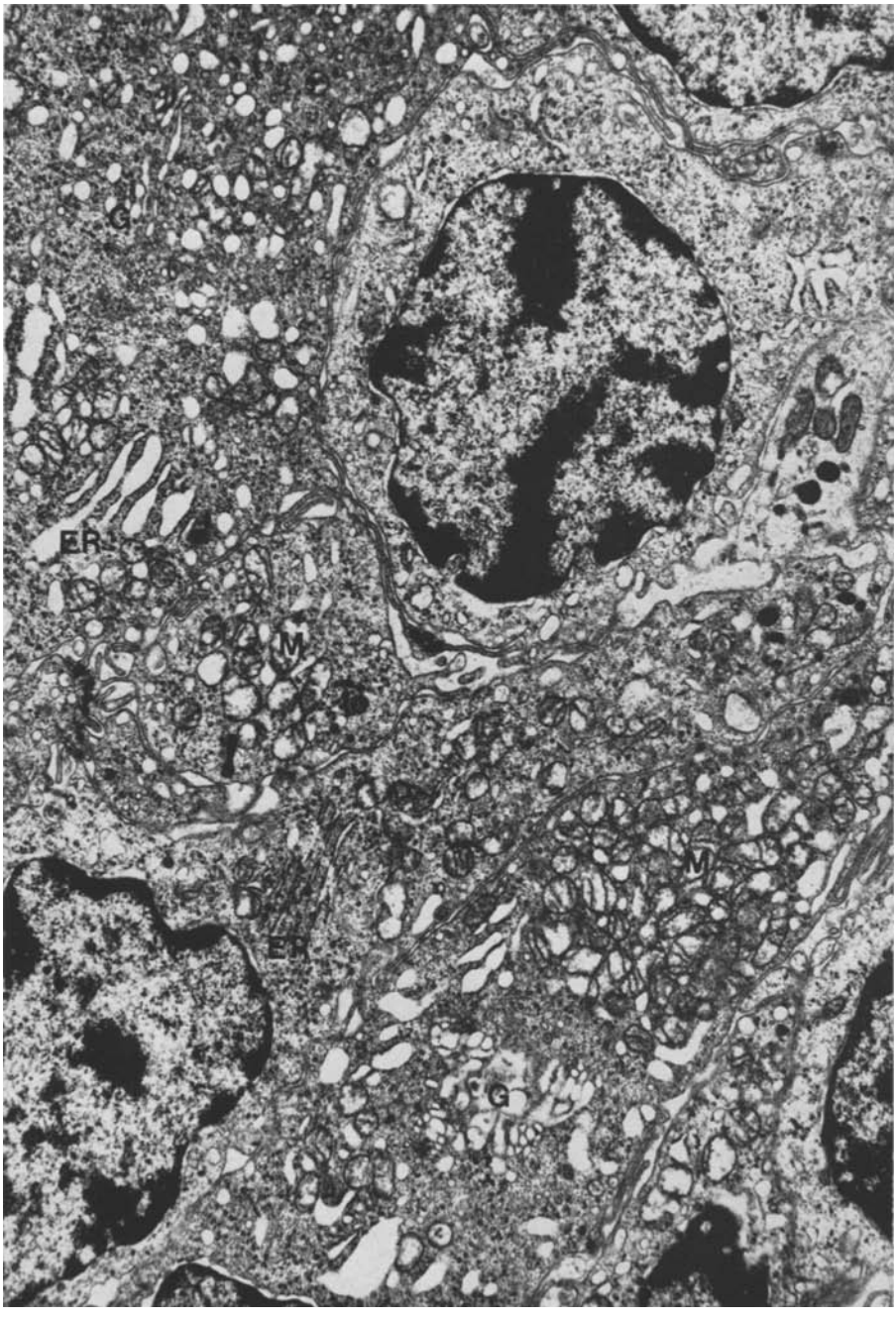


Fig. 4. Ultrastructure of PTG carcinoma, case 2: Part of the tumour with dark cells rich in organelles. Multiple mitochondria (*M*) and prominent Golgi fields (*G*). The endoplasmic reticulum (*ER*) is partly arranged in parallel arrays, partly dilated. Upper right another cell with few organelles. × 7800

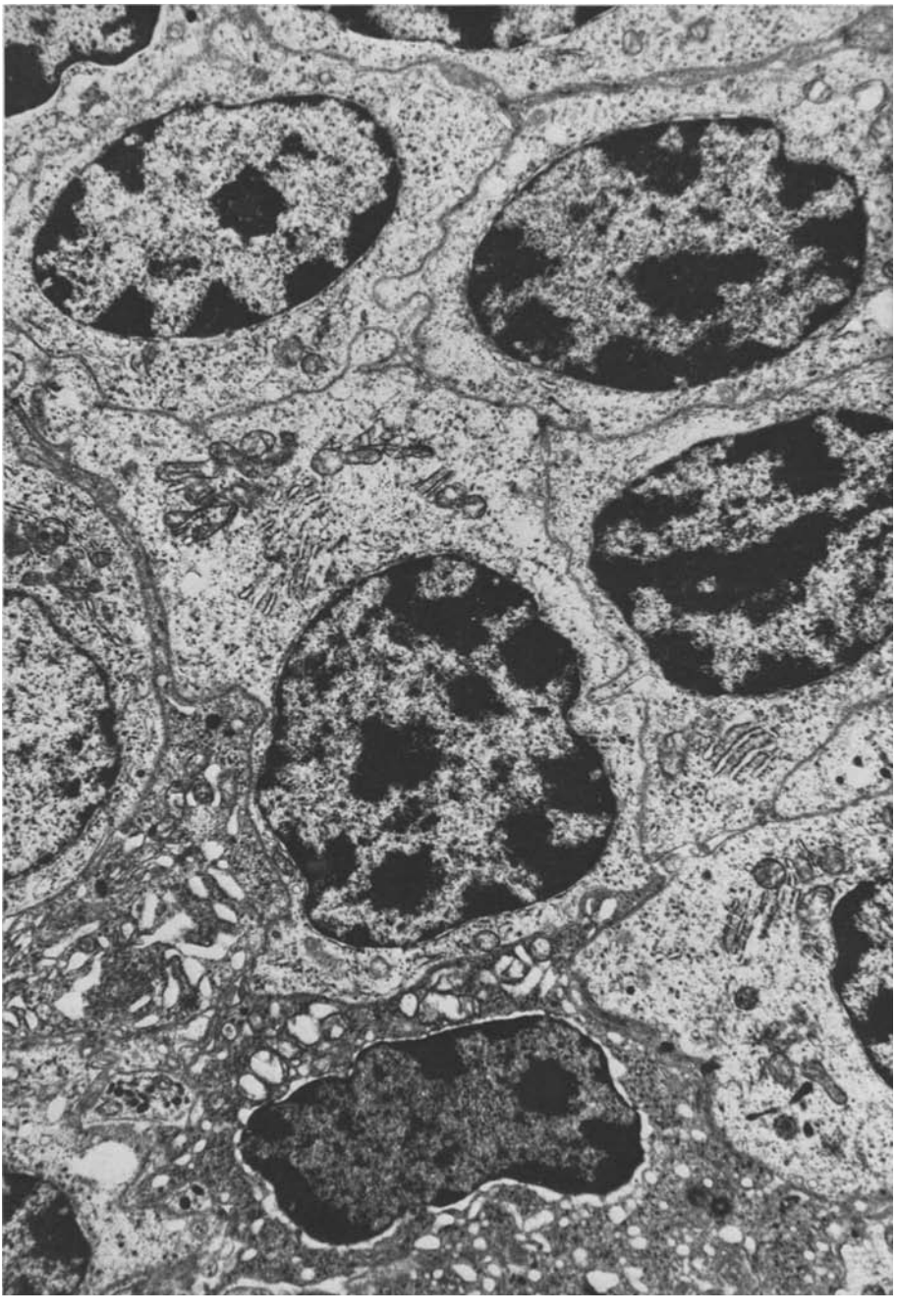
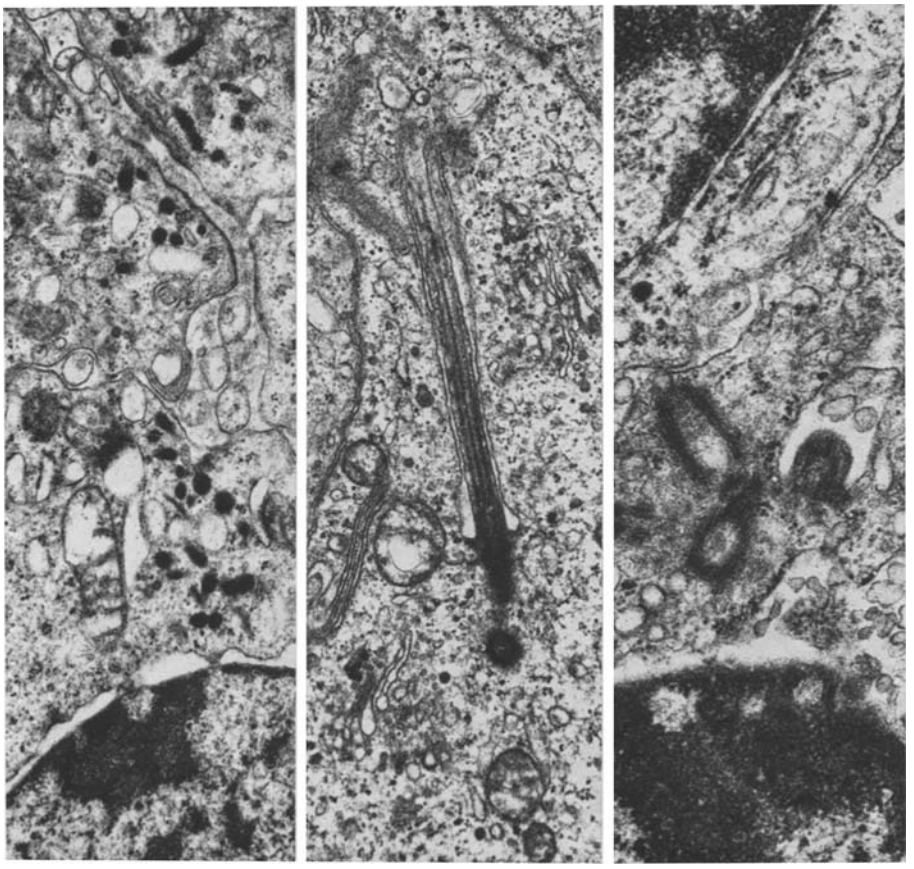


Fig. 5. Ultrastructure of PTG carcinoma, case 2: part of the tumour predominantly with light cells and few organelles. In the dark tumour cell below the perinuclear space is widened. The nuclear chromatin is present as corse clumps. × 6700



a b c

Fig. 6a—c. Ultrastructure of special cell constituents in PTG carcinoma, case 2: a Rare accumulation of small electron dense secretory granules underlying the plasma membrane near a widened intercellular cleft. × 18500. b Rare cilium invaginated within a tumour cell. × 16000. c Centrioles and a basal ciliary body in close vicinity. × 30000

lymph sinus (Fig. 2b). The hematogenic lung metastases in case 1 also showed lymphatic infiltration.

Ultrastructural Findings

Electron microscopic studies could be performed in case 2 (primary tumour, local recurrent tumour and lymph node metastases) and in case 3 (second recurrent tumour in the neck and lymph node metastases).

Ultrastructurally, the nuclei were mostly round or ovoid as seen in the light microscope but showed a somewhat indented surface. Other nuclei—particularly in case 2—revealed deep invaginations which could not have been detected at the light microscopical level (Fig. 3e). Some of these nuclei showed a quite bizarre

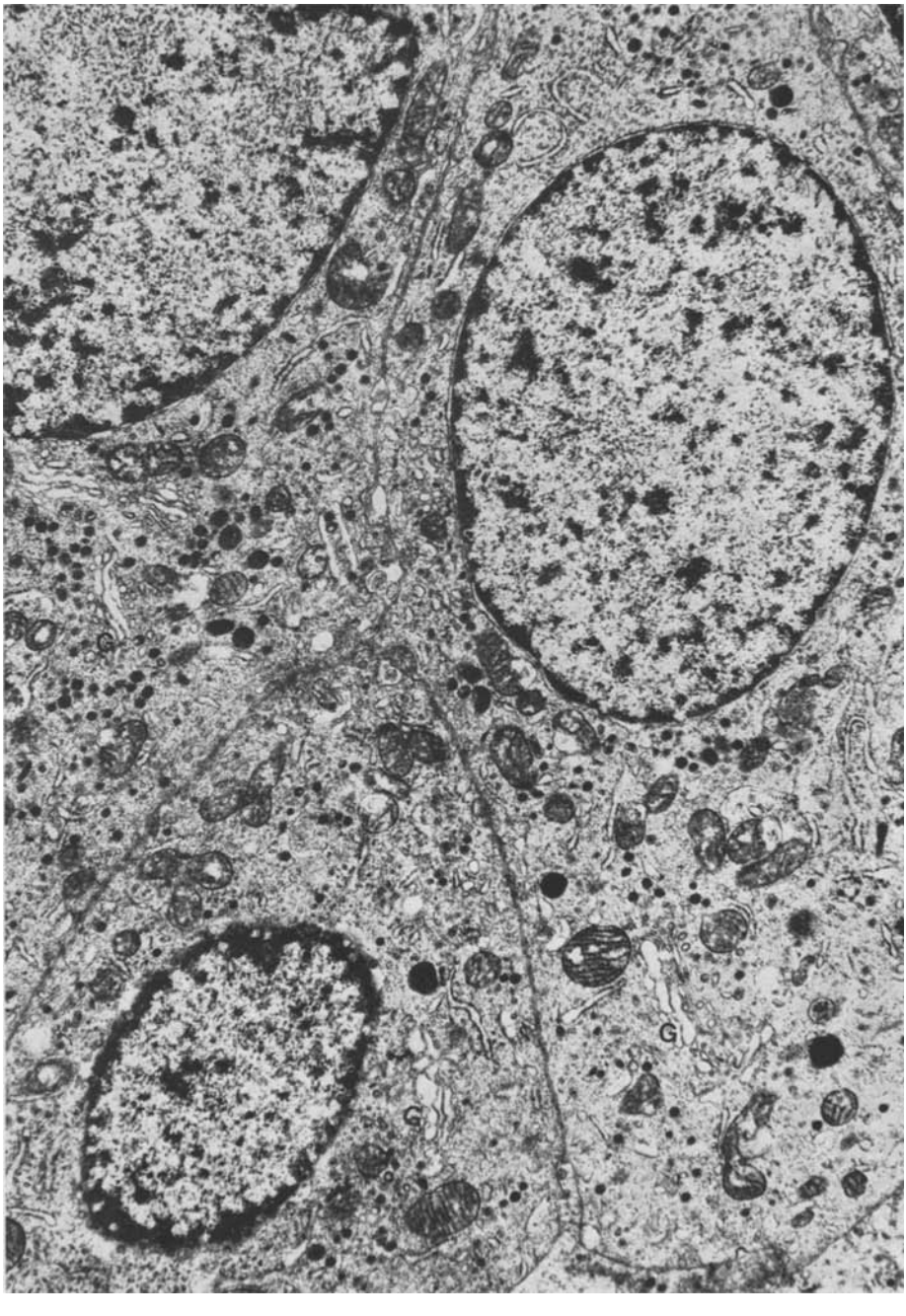


Fig. 7. Ultrastructure of PTG carcinoma, case 3: cytoplasm rich in organelles with large mitochondria, well-developed Golgi fields (*G*), and numerous electron dense secretory granules dispersed throughout the cytoplasm. Finely stippled nuclear chromatin. × 11000

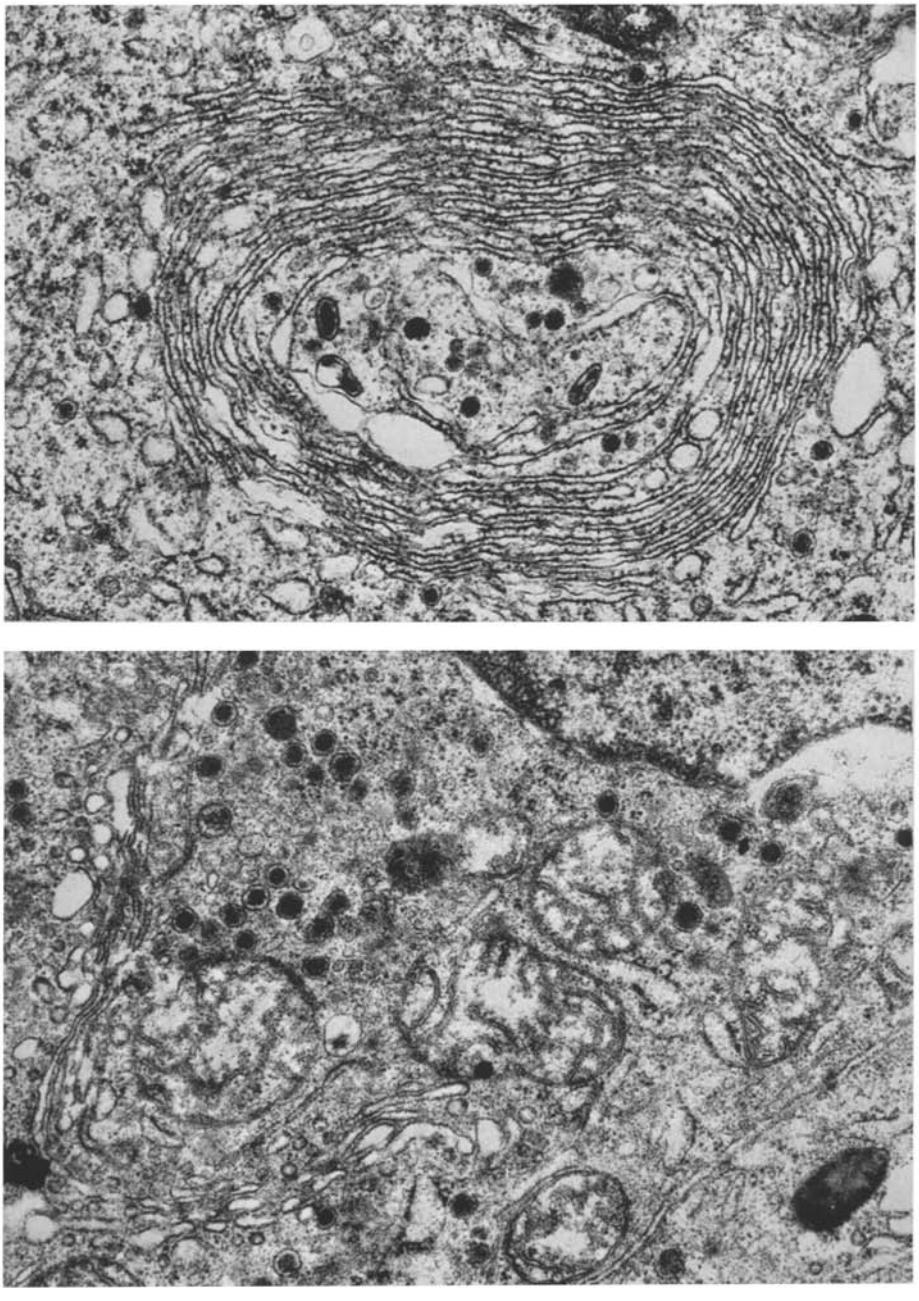


Fig. 8a and b. Ultrastructure of cytoplasmic constituents in PTG carcinoma, case 3: a Rough endoplasmic reticulum arranged in concentrical parallel arrays enclosing some secretory granules. × 26000. b Numerous membrane bound secretory granules near a prominent Golgi field. Large Mitochondria. × 29000

structure and a few nucleoli had real inclusions, most probably arising from cytoplasmic invaginations by vesicular lysis and destruction of cytoplasmic organelles (Fig. 3f). The chromatin displayed a stippled pattern with multiple small or coarse clumps of chromatin throughout the cytoplasm, not only underlying the nuclear membrane but also dispersed in the inner parts of the nuclei (Figs. 3g, 4, 5, 7). Large nucleoli were observed frequently with an enlarged pars amorpha, and often more than one nucleolus was present (Fig. 3e, g). In some areas the nuclear membrane seemed to be lost, but that could possibly be caused by tangentional sectioning (Figs. 4, 5). Mitoses could also be observed in the electron microscope (Fig. 3h) and the presence of multinucleated tumour giant cells was confirmed ultrastructurally.

There were some differences in the cytoplasmic organelle pattern of case 2 and case 3. — In case 2 the number of mitochondria and the extension of the rough surfaced endoplasmic reticulum and the Golgi apparatus varied to a high degree (Figs. 4, 5). The structure of mitochondria was variable, some of them being enlarged, ovoid, longish, y-shaped, or vacuolised. In some cells the rough endoplasmic reticulum was well developed and stacked in parallel arrays. Frequently the cisternae were widened and dilated with widening of the perinuclear space. The Golgi apparatus mostly consisted of small Golgi complexes with short and narrow Golgi profiles. Prosecretory and secretory granules were sparse (Fig. 6a). Cilia and centrioles were rarely present (Fig. 6b, 6c). Many cells showed degenerative, necrobiotic, and necrotic lesions with autophagic vacuoles, focal cytoplasmic degradation, cytolysis, and pycnotic nuclei. The primary tumour and the recurrent tumour as well as the metastases had identical ultrastructural features.

In case 3 the cytoplasm of the tumour cells was very rich in organelles (Fig. 7). There were larger mitochondria. The rough endoplasmic reticulum was well developed, its cisternae frequently being arranged concentrically (Fig. 8a) or in parallel arrays. An impressive feature distinguishing this tumour from case 2 were the prominent Golgi fields and many membrane bound prosecretory and secretory granules dispersed throughout the cytoplasm (Figs. 7, 8b). An accumulation of secretory granules at the cell periphery was not apparent. A few tumour cells contained abundant lipid droplets besides the secretory granules. Cellular autophagy, focal cytoplasmic degradation and cytolysis were to be seen as in case 2.

The plasma membranes in both cases were moderately tortuous. The intercellular space was mostly narrow but sometimes widened and contained microvillus-like cell processes. Desmosomes were sparse.

Comments

In PTG tumours the morphological signs of malignancy are problematic. Some highly differentiated tumours without distinct atypias were considered as adenomas and turned out to be recurrent and metastasising carcinomas (Black, 1954) as in our case 1. On the other hand a few parathyroid tumours were primarily regarded as malignant because of their atypias (Alexander *et al.*, 1944), but did not metastasise nor relapse after removal and therefore could not be retrospectively acknowledged as carcinomas (Woolner *et al.*, 1952).

Clinically the tentative diagnosis of PTG carcinoma can be made in hyperparathyroid patients with a large palpable PTG tumour and in patients suffering from very severe HPT or recurrent HPT after removal of a PTG tumour. But these conditions are by no means diagnostic. Only a unilateral vocal cord paralysis accompanying HPT is sufficient proof for a malignant and infiltrating PTG tumour if other causes are excluded. The surgeon is therefore compelled to diagnose a carcinoma during the operation mainly on account of the macroscopical findings. The result of the operation and the prognosis depend decisively on the total removal of the carcinoma at the first operation in which a hemithyroidectomy and neck dissection should be performed. Operations of relapsed PTG carcinomas bring about no definite healing in most cases (Holmes *et al.*, 1969).

A hard consistency and a greyish or white colour are typical for PTG carcinomas and give contrast to the mostly soft consistency and the yellow or tan colour of PTG adenomas. These macroscopical findings depend on the frequent scleroses and calcifications in PTG carcinomas but are neither indispensable nor a sufficient proof of malignancy. Sclerosis and infiltration cause the almost diagnostic adherence of PTG carcinomas to the adjacent tissues, while benign adenomas can be dissected easily (Castleman, 1952; Holmes *et al.*, 1969). Adhesiveness and sclerotic induration bear macroscopical resemblance to chronic sclerosing inflammation (Barnes and Cope, 1961). Malignancy is proved if the tumourous tissue surrounds or infiltrates the recurrent laryngeal nerve corresponding to the clinical vocal cord paralysis. Histological rapid frozen sections under the operation should only be performed when the tumour is totally resected for avoidance of implantation of tumour cells or tumour tissue that could give rise to recurrence of carcinomas—and possibly also of adenomas (Black and Ackerman, 1950).

Histologically atypism of nuclei, tumour invasion of the capsule and tumour cells lying free within the blood vessels are not sufficient proof of malignancy in PTG tumours (Black, 1954). Nuclear atypism is also frequently present in adenomas, chiefly in the so-called "adenomas with giant nuclei". The cells of these adenomas reveal an exceptional hyperchromasia and pleomorphism of nuclei and a typical oxyphilic granulation of cytoplasm (Woolner *et al.*, 1952; Altenähr and Dammann, 1971). Contrary to these adenomas most PTG carcinomas are of the chief cell type with faint eosinophilic cytoplasm. Atypical, pleomorphic, and polyploidic nuclei may be present as described in our cases but are not compulsory (Castleman, 1952). In our PTG carcinomas it seemed to be typical that the chromatin was finely stippled or dispersed in coarse clumps throughout the nuclei as emphasised also by Tange (1958). The statement of Castleman (1952) coincides with our experience that the most relevant and diagnostic cytological criterion for PTG carcinoma is the presence of mitoses.

However, this symptom is not indispensable as seen in the primary tumour of our case 1 and in the case reported by Stevenson (1950). It is obvious that tumour infiltration into the surrounding tissues and metastases establish malignancy. Capsular infiltration, however, cannot be accepted as a valuable criterion because it can be pretended by sclerotic stroma with parenchymal cords or by atrophic rim of PTG adenomas.

The metastases of PTG carcinomas are found predominantly in the regional lymph nodes of the neck and mediastinum. Hematogenic metastases have been

Table 1. Symptoms suggesting the tentative diagnosis of a malignant parathyroid tumour

Clinical	Severe hyperparathyroidism Recurrent hyperparathyroidism Palpable parathyroid tumour (50% of cases)
Macroscopic (surgical)	Hard consistency of the tumour Thick capsule Adherence to surrounding tissues Greyish or white colour
Histological	Profuse sclerosis of the tumour Calcifications Infiltration of the capsule Tumour cells within the tumour vessels
Cytological	Atypism of the nuclei Prominent nucleoli

Table 2. Evidences for malignancy in parathyroid tumours

Paresis of recurrent laryngeal nerve (other causes excluded)
Metastases regional lymph nodes (32%) lungs (26%) liver, skeleton, pancreas, adrenal glands
Tumour infiltration into the surrounding tissues
Mitoses (no matter how in frequent they are)

described mostly in the lungs and in the liver, rarely in other organs (Holmes *et al.*, 1969). Because of the above mentioned facts it seems practical to differentiate between suspicious symptoms of PTG carcinoma and conclusive criteria for malignancy (see Table 1 and 2).

Nonfunctioning PTG carcinomas have been described sporadically (Guy, 1929; McQuillan, 1938; Armstrong, 1938; Sieracki and Horn, 1960). Although there is no doubt that nonfunctioning PTG carcinomas really exist, its proof in a single given case on the basis of histology alone is difficult, as thyroid and thymic tumour may reveal a similar histological picture. In our case 3 HPT was not evident clinically. Only histomorphometric evaluation of an iliac crest biopsy showed a stimulated osteoclastic bone resorption. The histology of the carcinoma in that case was equal to PTG tumours but not to typical thyroid or thymic tumours. It may be speculated whether the presence of cholesterol deposits with foreign body giant cells as seen in our case 3 and in the inactive carcinoma described by Sieracki and Horn (1960) bears some relevance. Probably in the future PTG carcinomas with low endocrine activity will be established with more accuracy by more refined techniques, e.g., histomorphometric analysis of bone biopsies, ^{47}calcium-kinetics, or radioimmunoassay of parathyroid hormone.

The ultrastructure of PTG carcinomas has hitherto not been described except by Faccini (1970) who investigated four cases with high endocrine activity. His

findings coincide with ours to a high degree. However, we could not find signs of increased cellular activity as a general rule, as they are established in the experimental and in the human PTG hyperplasia (Altenähr, 1970; Black, 1970; Altenähr and Seifert, 1971). In case 2 cells rich in organelles and with apparently high endocrine activity were present just as well as cells with few organelles and low activity. In case 3 all organelles concerned in hormone synthesis and package were well developed and many secretory granules were dispersed throughout the cytoplasm. This seems to be paradoxical in view of the low endocrine activity of this tumour. It may be supposed that the accumulation of secretory granules in that case indicates an impairment of hormone secretion. A similar intracellular storage of granules has been observed in experimentally suppressed PTG cells of low (Capen, 1971) as well as in other proteohormone producing cells, e.g., the parafollicular cells of the thyroid (Lietz, 1970), the eosinophilic (Smith and Farquhar, 1966) and the mucoid cells (DeCicco *et al.*, 1972) of the anterior pituitary. The numerous lipid vacuoles observed in some tumour cells may be presumably interpreted as residual bodies of autophagic hormone desintegration. As a second explanation it has to be considered that the cells may have synthesised and stored a pathological protein with defective endocrine activity. This means that three different causes for endocrine activity of PTG tumours may exist which have to be considered: 1. lack of hormone synthesis, 2. impairment of cellular hormone secretion, 3. synthesis of a pathological protein with defective endocrine activity.

The clinical data of the presented cases were kindly provided by Prof. Dr. Kuhlencordt and Dr. Hehrmann. ^{47}calcium kinetics were studied by Dr. Montz and Dr. Hehrmann. Histomorphometric analysis of undecalcified bone sections was done by Dr. Delling. The operations of the parathyroid tumours were performed by Prof. Dr. Zuckschwerdt, Prof. Dr. Bay, Prof. Dr. Schreiber, and Dr. Farthmann. We are gratefully indebted to all these colleagues for their kind cooperation. A detailed clinico-pathological study of our case 1 is being prepared by Prof. Dr. Kuhlencordt and Prof. Dr. Kracht.

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