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Pituitary Adenomas with Hyperfunction of TSH

Frequency, Histological Classification, Immunocytochemistry and Ultrastructure *, **

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Summary. In a collection of 564 surgically removed pituitary adenomas, 4 cases were found to have had elevated TSH plasma levels. One of these tumors (case 1) could be classified as a highly differentiated mucoid TSH cell adenoma presenting histochemical reactions typical of, as well as electron microscopical features identical to, normal TSH cells. Immunoenzymatic studies failed to demonstrate TSH in the tumor cells. Two further adenomas (case 2 and 3) were similarly structured in many areas, but showed regions of poorer differentiation in which cells with distinct pleomorphism, irregular secretory granules, increased numbers of ribosomes and a well developed rough endoplasmic reticulum were present. In 10% of the tumor cells GH could be demonstrated immunoenzymatically, but there was no TSH. The fourth adenoma was an undifferentiated acidophilic adenoma showing pleomorphic cells having slight acidophil and partly mucoid granulations. The ultrastructure showed convoluted nuclei, increased numbers of free ribosomes as well as abundant rough endoplasmic reticulum and secretory granules which were different in size and number but distinctly of the TSH cell type. Immunoenzymatically, TSH was found in some cells, with GH in more cells. Endocrinologically, elevated levels of GH were measured in cases 2, 3 and 4 with LH being increased in case 1. Clinical and morphological correlations are discussed.

Key words: Pituitary – Adenoma – TSH – Ultrastructure – Immunocytochemistry.

Introduction

Pituitary tumors secreting TSH are very rare. They may develop from diffuse or nodular hyperplasia of TSH cells in long standing hypothyroidism, by means of chronic hyperstimulation of the pituitary TSH cells (Mösli and Hedinger

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** Dedicated to Professor Dr. Gerhard Seifert on the occasion of his 60th birthday

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1968; Phifer and Spicer 1973; Leong et al. 1976; Samaan et al. 1977; Katz et al. 1980). TSH producing adenomas can also grow in the pituitary without the stimulation of a primary thyroid defect. Such primary pituitary tumors can themselves induce a hyperstimulation of the thyroid gland, often resulting in hyperthyroidism (Jailer and Holub 1960; Lamberg et al. 1969; Linquette et al. 1969; Hamilton et al. 1970; Cure et al. 1972; Faglia et al. 1972; Hrubesch et al. 1972; Mornex et al. 1972; O'Donnell et al. 1973; Baylis 1976; Duello and Halmi, 1977; Tolis et al., 1978), while occasionally leaving the function of the thyroid normal (Gray et al. 1975; Heitz, 1979) or moderately decreased (Capella et al. 1979).

Some of the TSH producing adenomas described in the literature have been highly differentiated TSH cell adenomas (Mornex et al. 1972; Kovacs et al. 1977; Samaan et al. 1977; Afrasiabi et al. 1979; Capella et al. 1979; Waldhäusl et al. 1979; Katz et al. 1980), but other adenoma types have also been found to develop (Duello and Halmi, 1977).

Not to be neglected are GH secreting adenomas with acromegaly, occasionally leading to a goiter and mostly with a slight hyperfunction of the thyroid (Codaccioni et al. 1971; Hamilton and Maloof 1972; Kinnman 1973; Mukhtar et al. 1973; Quabbe 1978).

In view of these difficult pathophysiological correlations, it was our intent to study a large number of pituitary adenomas from surgically treated and endocrinologically examined patients, enabling the following questions to be answered:

1. What is the incidence of highly differentiated TSH cell adenoma in a large series of unselected, morphologically investigated pituitary adenomas?
2. Which types of morphological differentiation are found in the collection of endocrinologically examined cases having had elevated plasma levels of TSH?
3. Is it possible to demonstrate TSH immunoenzymatically, in TSH cell adenomas?
4. Does the ultrastructure of TSH producing adenomas correspond to the immunohistological findings?

Material and Methods

The TSH plasma levels of all patients undergoing adenomectomy of the pituitary since 1973, were measured by radioimmunoassay (Hehrmann 1974) in TRH test, before and after intravenous application of 200 µg TRH.

Four cases were found having elevated plasma levels of TSH. The patients had undergone a transsphenoidal adenomectomy, the operations being performed by different surgeons in the Neurosurgical Department (G. Grubel, R. Kautzky and R. Müke in cooperation with D.K.L.). Anamnestic data is listed in Table 1. Patient 3, having a residual tumor, had the test performed following the transsphenoidal operation. T3 and T4 were measured by radioimmunoassay as well (Hehrmann and Schneider 1974).

In case 1, TSH was also determined by bioassay (personal communication by Prof. Dr. von zur Mühlen, Hannover).

Specimens of tumor and in part from paraadenomatous pituitary, were fixed in Bouin's solution. Small portions were separated for electron microscopy and fixed in glutaraldehyde. Paraffin sections were stained with haematoxylin-eosin, PAS and performic acid-alcian blue-PAS-orange G according to Adams and Swettenham (1958). Immunohistochemical studies were performed in 3 cases by the method according to Sternberger et al. (1970) with the peroxidase-antiperoxidase-complex in paraffin sections. Commercial anti-sera from rabbits (anti-TSH: Deutsche Kabi Vitrum GmbH, München, anti-GH: Deutsche Kabi Vitrum GmbH, München, anti-ACTH: Ferring Arzneimittel, Kiel, anti-Prolactin: Panchem Gesellschaft für chemische Produkte, Kleinwallstadt) were used and incubated for 24 h at 4° C. As a control of the method, other sections were incubated with normal rabbit serum. Glutaraldehyde-fixed specimens were postfixed in osmium tetroxyde and embedded in epon 812. Semi-thin sections were prepared specifically for electron microscopy. Ultrastructural examinations were performed with the Zeiss electron microscope EM9S2.

Table 1. Anamnestic, clinical and hormonal data of cases with TSH producing adenomas

	Case 1	Case 2	Case 3	Case 4
Number of specimen	S120/77, S26/78	S57/75	S56/72	S119/78
Sex	Male	Male	Female	Male
age (years)	58	64	39	59
Relapse of adenoma	1st operation 1977 2nd operation 1978	Not existent	1st operation 1963 2nd operation 1972	Not existent
Hyperthyroidism	Not existent	Moderate	Strong	Moderate
T3 (normal 0,72–1,47 µg/l)	1,00 (normal)	4,5 (strongly elevated)	2,0 (elevated)	2,1 (elevated)
T4 (normal 34–95 µg/l)	53,0 (normal)	210,0 (strongly elevated)	259,0 (elevated)	196 (elevated)
TSH (mU/l) (normal ≦0,6–7,4)	> 160 Not responsive to TRH	10–12 Not responsive to TRH	12.0 Not responsive to TRH (after operation). Decrease after irradiation	19.8 Not responsive to TRH
Acromegaly	Not existent	Moderate	Moderate	Moderate
GH (µg/l) (normal 4,4 µg/l)	1,2 (normal)	25	Basal 28.4 µg/l Decrease after irradiation	29
LH (µg/l)	> 50	Not determined	Not determined	6.6
Androgens	Elevated	Normal	Not determined	Orchiectomy because of cancer of the prostate

Results

Frequency of TSH Producing Adenomas

From a collection of 545 surgically resected pituitary adenomas, elevated levels of serum TSH were demonstrated in 4 cases (Table 1), giving a frequency of 0.73%.

Clinical and Hormonal Data

The most important clinical data are listed in Table 1. Hyperthyroidism was present in 3 of the 4 cases. The TSH levels in these 3 cases lie between 10 and 20 µU/ml. In the case lacking hyperthyroidism, TSH levels of more than 160 µU/ml were measured. This case also showed elevated levels of LH (278–300 µU/ml), and increased androgens.

Acromegaly was evident in the 3rd case with hyperthyroidism, GH levels lying between 25 and 30 µg/l (upper normal limit 4.4 ug/l).

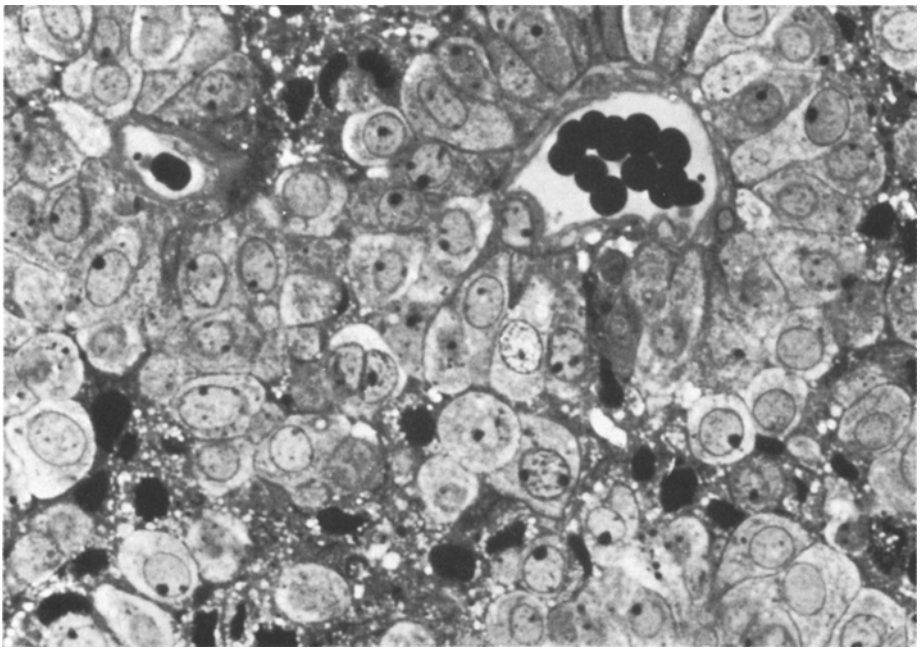

Fig. 1. Highly differentiated mucoid TSH cell adenoma (case 1): small to medium-sized medullarily arranged tumor cells with round nuclei and small nucleoli. Slightly granular structure of the cytoplasm. Some necrobiotically altered cells with shrinkage of the nuclei and vacuolization of the cytoplasm. Epon semi-thin section. Toluidine blue stain. ×700

Two operations were necessary in cases 1 and 3, but only case 1 allowed for examining the specimens of both operations.

Histology

A relatively large tumor was found in all four cases. The tissue structure was solid or pseudopapillary in case 1 and solid or medullary in cases 2 and 3 (Table 2). More connective tissue had developed in tumor 4. Necroses were sparse or intermediate. A somewhat higher degree of cellular and nuclear pleomorphism was seen in cases 2, 3 and 4. Sparse acidophil granulation of the cytoplasm was demonstrated in cases 3 and 4, but only case 4 had cells with more than very sparse granules. PAS positive granulation was found in 30% of the cells in case 1, and was extremely sparse in cases 2 and 3.

The relapsed tumor from a second operation in case 1 (Fig. 1) was structured identically to the specimen of the first operation.

Immunohistochemistry

In case 1, incubation with anti-TSH, anti-Prolactin and anti-GH gave negative results. ACTH was positive in a few cells (Table 2).

In case 2, reactions with anti-TSH and anti-ACTH were also negative, but

Table 2. Macroscopical and light microscopical findings in cases with TSH producing adenomas

	Case 1	Case 2	Case 3	Case 4
Size and consistency of tumor	Large, partly cystic	Large, solid	Large, solid	Large, solid
Expansion of tumor	Intra- and suprasellar	Intrasellar, suprasellar	Intrasellar	Intrasellar and slighly suprasellar
Tissue structure	Solid or pseudopapillary	Solid or medullary	Medullary	Solid, partly septated by sonnective tissue
Necroses	Medium	Sparse	Sparse, partly medium	Medium
Pleomorphism	Moderate, partly medium	Medium or increased	Medium, partly increased	Increased
Acidophil granulation	Lacking	Lacking	Very sparse in some cells	Very sparse in 35% of cells medium in 5% of cells
PAS positive granulation	Sparse granulation in about 30% of cells	Very sparse	Very sparse	Negative
PAP-immunohistology anti-ACTH	About 2% [b]	Negative	Not examined	Negative
anti-TSH	Negative	Negative	Not examined	About 10% [b]
anti-Prolactin	Negative	About 1% [b]	Not examined	Negative
anti-GH	Negative	About 5–10% [b]	Not examined	About 10% [c] about 50% [a]

[a] moderate reaction
[b] medium reaction
[c] strong reaction

some prolactin-positive and even more GH-positive cells could be demonstrated (Table 2).

In case 4, about 50% of all adenoma cells reacted slightly positively with anti-GH, 10% of the cells showing a strong reaction (Fig. 2).

TSH could be identified in approximately 10% of the cells, whereby the granular reaction products were intermediate in amount.

Electron microscopy

Case 1 (Figs. 3 and 4). The original and the relapsed adenoma were identically structured. All specimens showed relatively small cells with mostly round and only partly lobated nuclei. The nucleoli were small and peripherally localized.

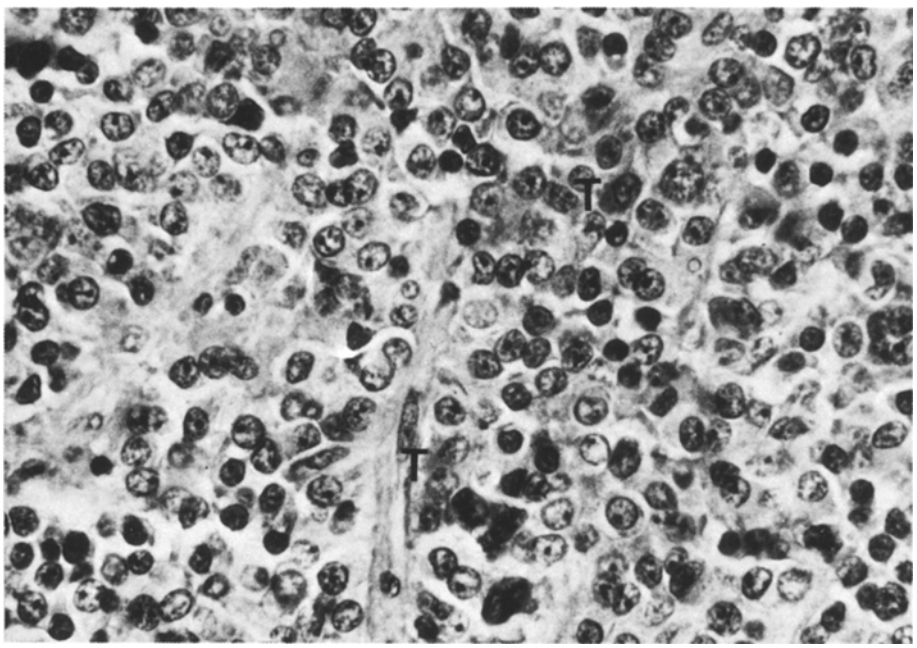

Fig. 2. Undifferentiated acidophil adenoma (case 4): medullarily arranged medium-sized to enlarged cells with moderately increased pleomorphism of cells. A few cells (T) with TSH-positive granules. TSH-anti-TSH-PAP after Sternberger et al. (1970), counterstain with haematoxylin. ×440

The rough endoplasmic reticulum was for the most part moderately developed, the membranes being short with an intermediate number of ribosomes. The ergastoplasm was focally increased in a few cells. The Golgi areas were small to medium-sized and had narrow cisterns. Very small secretory granules were found in evidently higher amount than was supposed from light microscopy, ranging in diameter from 20 to 100 nm and being very electron dense. An electron lucent halo between membrane and core was very rare. The mitochondria were mostly round and monomorphic, but some areas included pleomorphic forms with a fragmentation of cristae. Microtubules and cytofilaments were sparse. Lysosomes were from small to medium-sized and mostly showed a peripheral ring of pigment. The capillaries had normal walls.

Case 2 (Fig. 5). Large proportions of the tumor showed cells identical in structure to those of case 1. These areas had sparsely arranged, very small secretory granules in a relatively small cytoplasm. Other parts consisted of cells with a higher degree of pleomorphism. The nuclei were partially lobated, having a focally condensed chromatin. More free ribosomes were found than in case 1. The membranes of the rough endoplasmic reticulum were scattered and fragmented. Golgi complexes were often enlarged and increased in number. Secretory granules were sparse and pleomorphic, some being very small, others larger. The mitochondria were pleomorphicly structured, frequently elongated and greatly swollen in necrobiotically altered cells. Some oncocytic adenoma cells

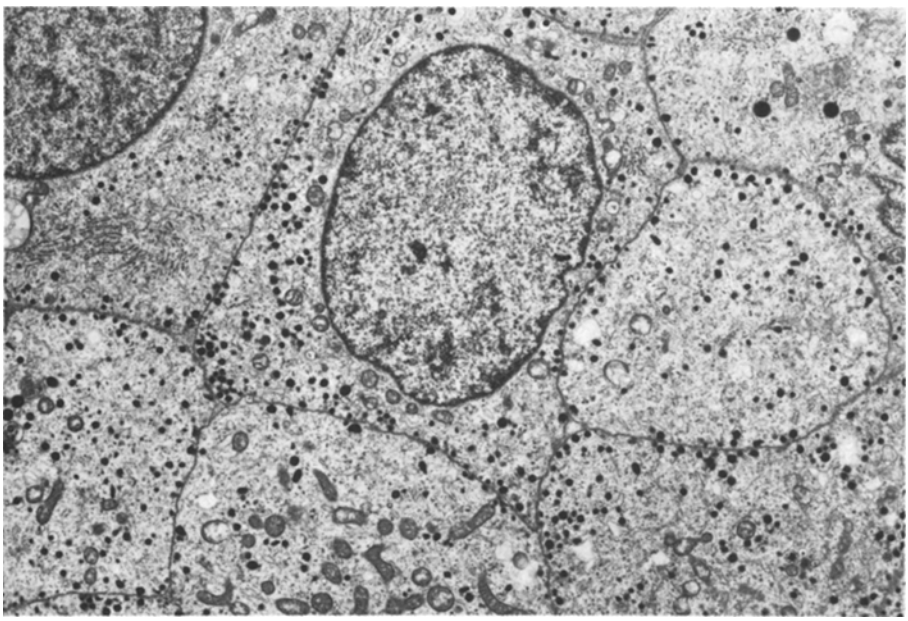

Fig. 3. Highly differentiated mucoid TSH cell adenoma (case 1): small tumor cells with round nuclei and narrow cytoplasm, sparse partly densely arranged small secretory granules, poorly developed only focally increased rough endoplasmic reticulum, relatively many free ribosomes, a few partly pleomorphic mitochondria and some medium-sized lysosomes. Epon ultra-thin section. Uranyl acetate, lead citrate. ×4,100

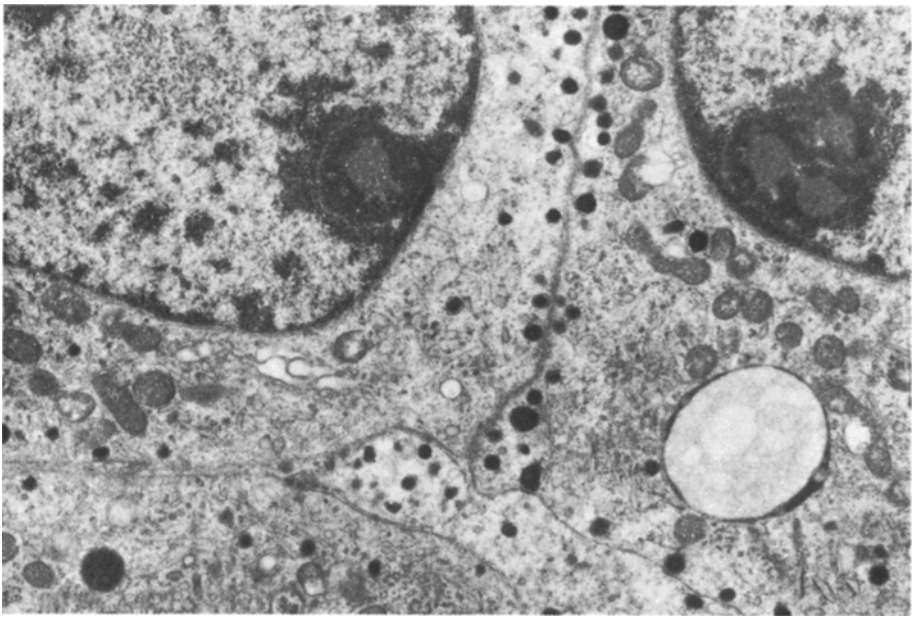

Fig. 4. Highly differentiated mucoid TSH cell adenoma (case 1, relapsed tumor): round nuclei with peripheral nucleoli, small to medium-sized secretory granules, small Golgi zones, poorly developed rough endoplasmic reticulum, and a medium-sized lipid-rich lysosome. Epon ultrathin section. Uranyl acetate, lead citrate. ×12,800

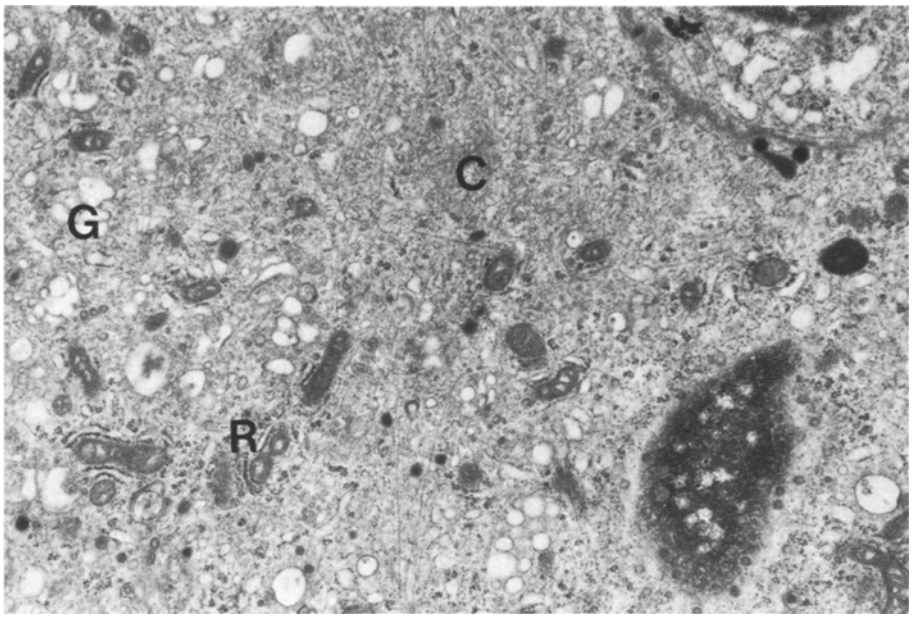

Fig. 5. TSH cell adenoma with undifferentiated parts (case 2): 2 undifferentiated cells with few very small to medium-sized irregular secretory granules, fragmented rough endoplasmic reticulum (*R*), a large Golgi complex (*G*), many microtubules and cytofilaments (*C*), moderately pleomorphic mitochondria. Epon ultrathin section. Uranyl acetate, lead citrate. ×6,700

were also found. Single cells were found to have increased numbers of condensed cytofilaments and microtubules. The lysosomes were partly enlarged but contained much pigment. Necrotic cell organelles and erythrocytes could often be found in the intercellular spaces.

Case 3 (Fig. 6). This adenoma showed lack of homogeneity in its differentiation which was similar to case 2. Most sections of the tumor were highly differentiated, appearing like normal TSH-cells. These had round monomorphic nuclei, the chromatin being partially condensed peripherally. The nucleoli were small. A few cells possessed double nuclei. The cytoplasm was small or intermediate in breadth. The rough endoplasmic reticulum showed short or medium-long membranes with a moderate number of ribosomes, being enlarged and increased in only a few cells. The Golgi areas were small. Secretory granules were sparse and very small, mostly being arranged along the cell membrane. Evidence for an exocytosis into the intercellular spaces could seldom be found. The round or moderately pleomorphic mitochondria were in part, focally accumulated, with some mitochondria having whirl-like structured cristae. Free ribosomes were focally increased. Some cells had a few small lysosomes with much pigment.

A high degree of pleomorphism was found in a small proportion of tumor cells, the nuclei of these cells having an increased or decreased amount of chromatin as well as an increased number of free ribosomes in the cytoplasm. The rough endoplasmic reticulum was fragmented. The Golgi areas seemed

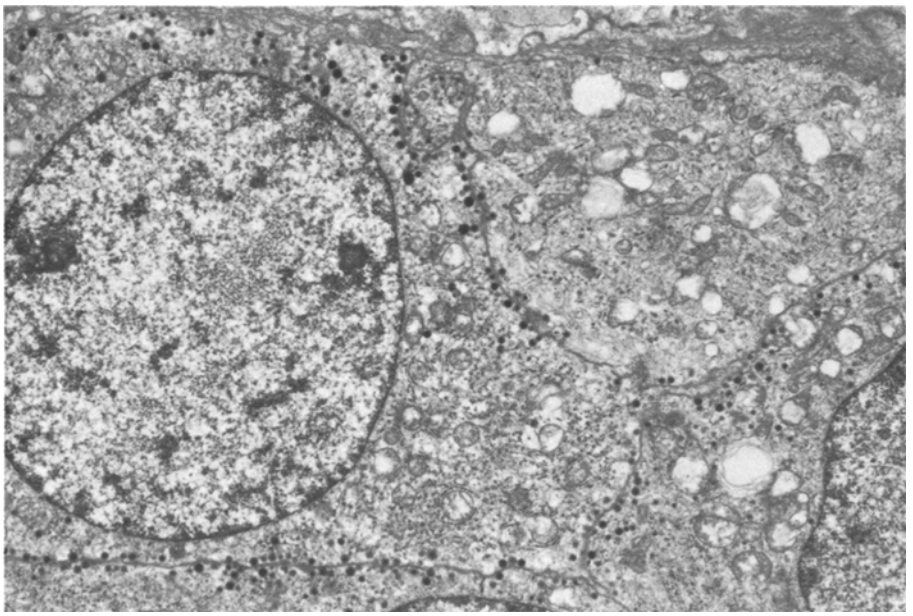

Fig. 6. TSH cell adenoma with undifferentiated parts (case 3): small secretory granules of TSH cell type, focally increased rough endoplasmic reticulum with many ribosomes, pleomorphic mitochondria and sinuous cell membranes. Epon ultra-thin section. Uranyl acetate, lead citrate. ×6,800

to be enlarged. The secretory granules were different in number, size and arrangement. The mitochondria were also more pleomorphic.

Case 4 (Fig. 7). The electron microscope revealed cells with greater pleomorphism than the other three. The cell size seemed to be greater. Relatively many cells were necrotic, showing shrunken nuclei with a vacuolization of the cytoplasm. The nuclei, often irregularly structured and lobated, contained a high amount of chromatin along with nucleoli which were partly increased or doubled. In the cytoplasm, we were able to observe an intermediately developed, partly fragmented rough endoplasmic reticulum. Free ribosomes were increased and accumulated focally. The Golgi areas were not prominent. Many secretory granules had a size and structure of TSH-type but many others were differently structured. The granules were irregularly arranged and had a diameter of up to 300 nm. Mitochondria were sparse and pleomorphic. The lysosomes were partly increased in number or in size, and possessed much pigment. Some myelin-like bodies were observed. The cytofilaments were focally increased and condensed.

Classification of Adenomas

In view of the structures described in detail above, as well as histochemical and immunocytochemical evidence, the classification of the WHO (1980), and our own classification (Saeger 1981) were used to diagnose the first tumor

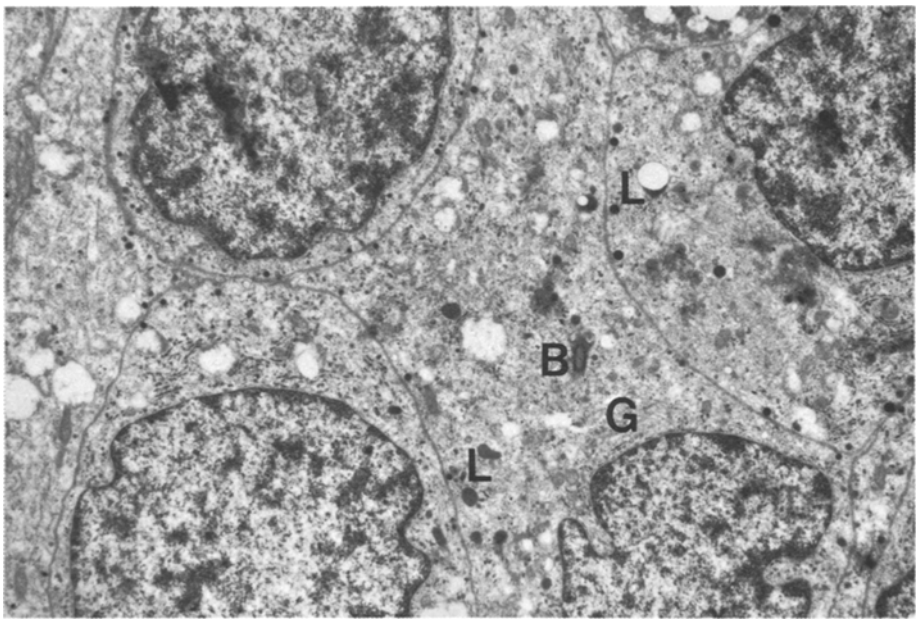

Fig. 7. Undifferentiated acidophil (case 4): lobated nuclei, short membranes of rough endoplasmic reticulum, small Golgi complex (*G*), only very few small secretory granules, some small lysosomes (*L*) with pigment, a ciliary body (*B*). Epon ultra-thin section. Uranyl acetate, lead citrate. ×7,500

as being a highly differentiated mucoid TSH cell adenoma, the second and the third cases as TSH cell adenomas, with undifferentiated parts, and the last case as an undifferentiated sparsely granulated acidophil adenoma.

Discussion

TSH producing adenomas were thought to be very rare, because hyperthyroidism was seldom observed in patients with pituitary adenomas. Our first case demonstrates the existence of TSH production by a pituitary adenoma but not resulting in hyperthyroidism. We should therefore not necessarily equate the rarity of hyperthyroidism in non-acromegalics to the rarity of TSH secretion of pituitary tumors. Gray et al. (1975) proposed that the frequency must be higher than was generally assumed, following their ultrastructural studies on the size of secretory granules in chromophobe adenomas, a theory supported by Heitz (1979) and his immunocytochemical studies of clinically silent adenomas.

TSH producing adenomas had a frequency of 0.73% in our collection. All tumors of this series were large adenomas, not enabling their total surgical removal, as was reported in the studies of TSH secreting microadenoma presented by Tolis et al. (1978) and by Barbarino et al. (1980).

The classification of TSH secreting adenomas has been variously described throughout the literature. The tumors have most frequently been classified as chromophobe adenomas (Nyhan and Green 1964; Lambert et al. 1969; Hamilton et al. 1970; Hrubesch et al. 1972; Jackson 1975; Baylis 1976). Others were histochemically identified, then as acidophil (Horn et al. 1976) or as TSH cell

adenomas (Linquette et al. 1969; Tolis et al. 1978; Afrasiabi et al. 1979). Simple embedding and staining methods would lead to the diagnosis of chromophobe adenomas in our 4 cases, as light microscopy failed to demonstrate distinct granulation. Semithin sections and special differentiating staining enabled light microscopical demonstration of secretory granules both of the TSH cell types, in 3 cases and of the acidophil type, in the last case.

Immunohistochemical studies of TSH secreting adenomas have been performed by Duello and Halmi (1977), Tolis et al. (1978), Capella et al. (1979), and Waldhäusl et al. (1979). Waldhäusl et al. (1979) found additional tumor cells reacting with anti-GH, anti-ACTH and anti-MSH. Duello and Halmi (1977) and Tolis et al. (1978) also demonstrated cells containing prolactin. Capella et al. (1979) described TSH- and GH-positive tumor cells.

Two of our tumors were TSH-negative, two had some GH-positive cells and one had a few prolactin-positive cells. The adenoma of Katz et al. (1980) was also TSH-negative.

Electron microscopical studies of 3 cases showed tumor cells of exclusively the TSH cell type. This corresponds with the investigation of Mornex et al. (1972), Duello and Halmi (1977), Kovacs et al. (1977), Afrasiabi et al. (1979), Kovacs and Horvath (1979) and Waldhäusl et al. (1979), but some deviations from our results have to be mentioned. Kovacs et al. (1977), Kovacs and Horvath (1979) and Katz et al. (1980) emphasized the lack of exocytoses which we could rarely find, and the frequent halo of the secretory granules which was also very rare in our tumors. Waldhäusl et al. (1979) found a marked development of the rough endoplasmic reticulum in contrast to our results, Cure et al. (1972) demonstrated peculiar tubular inclusions in the endothelial cells of their TSH cell adenoma. Larger and irregular cells were observed by Capella et al. (1979). The adenoma of Duello and Halmi (1977) was very comparable with two of our cases since these authors emphasized two types of differentiation: a TSH cell type and a pleomorphic type.

The TSH secreting adenomas which develop from a long standing hypothyroidism seem to be structurally nearly identical to the adenomas of primary TSH hyperfunction as demonstrated in studies using immunohistochemistry (Phifer and Spicer 1973) and those using electron microscopy (Leong et al. 1976; Samaan et al. 1977; Katz et al. 1980).

Our study clearly shows that pituitary adenomas secreting TSH are not uniformly differentiated. Only one case is exclusively composed of cells with a structural identity similar to normal TSH cells. This patient (case 1) suffered from an adenoma which secreted large amounts of TSH and LH (Table 1), with GH not being elevated. The combined elevation of TSH and LH can be explained by the structural resemblance of the molecules. The pecularity of this case is the lack of goiter and thyroidal hyperfunction, leading us to suppose that either the adenoma produced a radioimmunologically active but biologically inactive hormone of TSH type, or that the thyroids do not react upon the highly elevated TSH, especially since the bioassay of TSH showed no elevated levels. It seems to be of great interest that an immunohistological demonstration of TSH in the tumor cells of this case (Table 1) gave negative results.

The patient in cases 2 and 3, suffered from a combined hyperfunction of

TSH and GH which resulted in hyperthyroidism and acromegaly. Since both adenomas showed regions with a differentiation similar to highly differentiated TSH cell adenomas, yet smaller areas with undifferentiated cells, we assume that TSH was secreted in the one part and GH in the other past of the tumors.

The fourth patient (Table 1) also had hyperthyroidism and acromegaly. Both TSH and GH were elevated. Immunohistology also revealed both hormones to be in the tumor, but the structural differentiation was relatively poor. We know from earlier studies (see Saeger (1981)) that adenomas with poor differentiation are more inclined to secrete hormones of a single nature, than those of higher degree of differentiation. We therefore conclude that the combined secretion of TSH and GH in this fourth case, was caused by the low grade of differentiation.

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