Clinical and morphological features of undifferentiated monomorphous GH/TSH-secreting pituitary adenoma

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Abstract

A 41-year-old male presented with progressive visual defects, acromegaly and hyperthyroidism. After clinical evaluation a giant GH/TSH-secreting pituitary adenoma was diagnosed. Administration of the somatostatin analog octreotide at doses of 150 µg s.c. per day inhibited the secretion of both GH and TSH. A three-week treatment with octreotide prior to surgery led to slight visual improvement and CT scan showed some new necrotic areas within the tumor mass. Transcranial surgery was performed. By immunohistochemical analyses of the adenoma tissue GH, prolactin and β -chorionic gonadotropin were detected; TSH was negative. Electron microscopy revealed an undifferentiated, monomorphous adenoma with morphological features of an acidophil stem cell adenoma such as the presence of misplaced exocytoses, fibrous bodies and mitochondrial gigantism. However, the tumor cells contained small secretory granules (up to 250 nm) accumulated along the cell membrane characteristic of thyrotrope cells. Furthermore, some adenoma cells were fusiform with long cytoplasmic processes resembling thyrotropes.

Two months after the operation CT scan revealed a large residual tumor. Serum GH and TSH levels had increased again and the TSH level was even higher than before the treatment. The patient died suddenly, most probably of lethal arrhythmia. Specimens of the adenoma tissue obtained at autopsy confirmed the previous findings with the exception of positive immunostaining for TSH which was found in less than 1% of the adenoma cells.

This undifferentiated, monomorphous GH/TSH-secreting pituitary adenoma represents an entity that is unusual both in its ultrastructural features and clinical manifestations suggesting a cytogenesis from an early, undifferentiated stem cell.

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Introduction

Growth hormone/thyrotropin (GH/TSH)-secreting pituitary adenomas are very rare (about 0.5% of all pituitary adenomas) (1–4). These plurihormonal pituitary adenomas may produce hormones from different cell types in the tumor (bimorphous or plurimorphous types) or one cell may hypersecrete more than one hormone (monomorphous type) (4–10). Only a few monomorphous GH/TSH-secreting pituitary adenomas have previously been described (4, 9, 10). Descriptions of electron microscopical features of such adenoma cells range from thyrotrope-like to somatotrope-like, and also to acidophil stem cell adenoma-like.

Morphological characteristics, clinical behavior and the effect of octreotide therapy on undifferentiated, monomorphous GH/TSH-secreting pituitary adenomas are herein discussed.

Case report

A 41-year-old male was referred to the Department of Endocrinology, Clinical Hospital Centre Zagreb, because of progressive sight deficiency with visual field defects. The patient noticed increased size of his hands, feet and nose as well as 'swelling' of his lips over the 3-month period. He had a history of several years of alcohol abuse and severe smoking (40 cigarettes per day).

Clinical examination revealed a typical acromegalic face including deep nasolabial furrows, thick lips, broad nose and a prominent supraorbital ridge. A slight protrusion of the right bulbous and an asymmetrically enlarged thyroid gland were found. Gynecomastia was present. A lipoma (3 × 2 cm) of the left subscapular region was found. The sizes of his hands and feet were increased. The skin was warm and greasy. Blood pressure was 150/90 mmHg and sinus tachycardia (120/min) was found.

The fasting blood glucose level was 7.5 mmol/l. The serum value of triglyceride was 2.99 mmol/l (normal value <1.8 mmol/l). Antithyroglobulin and antimicrosomal antibodies were negative. Serum levels of GH and insulin-like growth factor (IGF)-I were 230 mIU/l (normal range <0.3–14 mIU/l) and 158.4 nmol/l (normal range 13–39 nmol/l) respectively. Serum free-tri-iodothyronine (T_3) was 13.6 pmol/l (normal range 3.6–7.8 pmol/l) and free thyroxine (T_4) was 37.1 pmol/l (normal range 8–23 pmol/l). Basal concentrations of TSH in serum varied from 3.4 to 4.99 mIU/l (normal range 0.32–4.1 mIU/l). Serum α -subunit of glycoprotein hormones (α -SU) was not measured. The serum concentration of prolactin (PRL) was 8.9 ng/ml (normal range 3.1–16.5 ng/ml), while the concentration of β -chorionic gonadotropin (β -CG) was <0.5 IU/l (normal values <6.15 IU/l). The serum level of testosterone was 2 nmol/l (normal range 8.5–63.6 nmol/l). An oral glucose load (100 g) failed to suppress plasma GH. Also GH did not respond to thyrotropin releasing hormone (TRH) stimulation (200 μ g i.v.). L-Dopa (0.5 g p.o.) had no effect on PRL release, while TRH (200 μ g i.v.) did not stimulate TSH or PRL secretion.

CT scan showed a giant adenoma causing compression of the optic chiasm as well as both carotid arteries (Fig. 1). Bitemporal hemianopia was recorded with a Goldmann perimetry. Thyroid ultrasonography confirmed the presence of multiple nodularity in an enlarged gland. Echocardiography revealed moderate, asymmetric hypertrophy of the left ventricle. Systolic and diastolic functions were preserved and there was no abnormality of the valves. Bone densitometry revealed osteopenia (bone mineral density: lumbar spine, L1–L4 40.92 g/cm², T-score –1.43; femoral neck 0.69 g/cm², T-score –2.16). Clinically, a pituitary adenoma secreting GH and TSH was diagnosed.

Octreotide administered at a dose of 50 mg s.c. 3 times a day was started and serum concentrations of GH and TSH were measured every 2 h during the 1st, 3rd and the 7th day of therapy (Fig. 2A,B). The normalization of serum peripheral thyroid hormones was achieved after ten days of treatment (total T_3 2.2 nmol/l, normal levels 1.3–2.8 nmol/l; total T_4 107 nmol/l, normal levels 58–161 nmol/l). After a three-week treatment (150 μ g s.c. daily for 16 days and 300 μ g s.c. daily for the next 5 days) CT examination was performed and new necrotic areas were found within the tumor mass (Fig. 3). Also examination of the visual field revealed slight improvement of the existing defect. Transcranial surgery of a pituitary adenoma was performed.

By light microscopy, the tumor was chromophobic. Immunohistochemistry showed immunoreactivity for GH, PRL and β -CG. Immunostaining was negative for TSH, adrenocorticotropin (ACTH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), β -LH and β -FSH (Fig. 4A,B). Electron microscopy showed that the tumor tissue was composed of monomorphous, polygonal epithelial cells (Figs 5–7). Some adenoma cells were elongated (fusiform) with long cytoplasmic processes. The tumor cells possessed oval, hyperchromatic nuclei. Small secretory granules measuring up to 250 nm were mainly aligned under the plasma membrane and scanty, large secretory granules measuring 800 nm were found in the cytoplasm. Sparse, immature haloed secretory granules measuring 150 nm were also seen. Misplaced exocytoses were frequent. Fibrous bodies or aggregates of filaments were recognizable. There was an increase in the number of mitochondria that were often unusually large, had irregular cristae and contained tubular structures. Endoplasmic reticulum, mostly saccular and granular, was well developed and widely dispersed. Golgi membranes were

Figure 1 Transversal CT scan showing a giant, solitary adenoma measuring 5 cm in antero-posterior diameter.

Figure 2 The levels of plasma TSH and GH over 24 h on the 1st, 3rd and 7th day of treatment with octreotide ($3 \times 50 \mu\text{g}$ per day). Arrows indicate the time of subcutaneous injections of octreotide. (A) Plasma TSH level (normal range $0.32\text{--}4.1$ mIU/l, dashed-dotted lines). (B) Plasma GH level (normal range $<0.3\text{--}14$ mIU/l, dashed-dotted line indicates the upper limit).

Figure 3 A coronal CT scan showing necrotic, hypodense areas within the tumor mass after treatment with octreotide (craniocaudal diameter of the tumor is 5 cm).

moderately developed. Sparse secondary lysosomes were found.

α -SU was significantly increased in the pituitary adenoma cell culture (> 100 IU/l, control value 0.2 IU/l).

Three weeks after the operation the patient was referred to the regional Rehabilitation Centre where physiotherapy was started. During the rehabilitation an episode of thyrotoxic symptoms including diarrhea, vomiting, fever and atrial fibrillation occurred, which was misdiagnosed as acute gastroenteritis and treated with 0.9% NaCl infusion and propafenon (2×150 mg/day). Subsequent hormonal examination revealed increased serum levels of GH (35.1 mIU/l, normal values < 0.3 –14 mIU/l) and TSH (4.44 mIU/l, normal values 0.32–4.1 mIU/l). Total T_3 was 6.6 nmol/l (normal range 1.3–2.8 nmol/l), while total T_4 was 315 nmol/l (normal range 58–161 nmol/l). Control CT scan showed residual adenomatous tissue. The patient died suddenly, most probably of lethal arrhythmia.

At autopsy a large residual tumor (4.5 cm in diameter) with destruction of the sella turcica was found. Pathohistological and immunohistochemical findings were identical to those obtained after the surgery with the exception of a few TSH-positive adenoma cells (less than 1% of cells) (Fig. 8). A renal cell carcinoma (3.5 cm in diameter) of the left kidney was found. Microscopical examination of the heart revealed changes of myocardium clearly related to ischemia.

Materials and methods

Hormone assays

Serum GH was determined by immunoradiometric assay (IRMA) (Sorin-Biomedica, Saluggia, Italy). The

sensitivity of the assay was 0.4 mIU/l, and the intra- and interassay coefficients of variation in our laboratory were 3.9% and 9.8% respectively.

IGF-I was measured by IRMA (Diagnostic Systems Laboratory, Webster, TX, USA). The detection limit was 0.104 ng/ml, and the intra- and interassay coefficients of variation were 3% and 3.7% respectively.

PRL was determined by IRMA (Diagnostic Products Corporation, Los Angeles, CA, USA). The detection limit was 0.1 ng/ml, and the intra- and interassay coefficients of variation were 0.8% and 5.3% respectively.

Serum TSH levels were measured by IRMA (Ortho-Clinical Diagnostics, Johnson & Johnson Company, Amersham, UK). The analytical sensitivity of the assay was 0.04 mIU/l, the functional sensitivity was 0.2 mIU/l and the intra- and interassay coefficients of variation were 1.6% and 2.7% respectively.

Serum β -CG was determined by immunoenzymometric assay with luminescent substrate (IEMA) (Vitros, Johnson & Johnson, Rochester, NY, USA). The sensitivity of the assay was 0.5 mIU/ml, and the intra- and interassay coefficients of variation were 3.5% and 5.5% respectively.

Serum free (f) T_3 and T_4 were determined by radioimmunoassay (RIA) (DYNO-test, Henning Berlin GmbH, Germany). Analytical sensitivity for f T_4 was 1.25 pmol/l, while functional sensitivity was 2.6 pmol/l. Analytical sensitivity for f T_3 was 0.73 pmol/l, while functional sensitivity was 1.5 pmol/l. The intra- and interassay coefficients of variation in our laboratory were 3.4% and 5.1% respectively for f T_4 , and 5.1% and 4.4% respectively for f T_3 .

Serum total T_3 and T_4 were measured by RIA (Diagnostic Products Corporation), and the detection limits were 0.1 nmol/l and 3.2 nmol/l respectively. The intra- and interassay coefficients of variation were 3.4% and 6.3% respectively for total T_3 , and 2.7% and 4.2% respectively for total T_4 .

Figure 4 Immunohistochemical staining of the biopsy specimens. (A) Most of the adenoma cells show positive reaction for GH. (B) Adenoma cells show negative reaction for TSH. PAP method, poststaining hematoxylin. Magnification $\times 400$.

α -SU was measured by IRMA (Immunotech International, Marseille, France). The detection limit was 0.025 IU/l. Intra- and interassay coefficients of variation were 6.8% and 18.6% respectively. Cross-reactions with LH, FSH and TSH were less than 0.1%.

Morphological studies

For light microscopy, pieces of tumor tissue were fixed in 10% buffered formalin and embedded in paraffin. Formalin-fixed, paraffin-embedded (FFPE) sections of

3 μ m thickness were stained with hematoxylin-eosin and the periodic acid Schiff method. The antigen retrieval procedure of Shi *et al.* (11) was used on FFPE sections before immunostaining. Primary antiserum samples were applied to detect the following hormones: GH (1:500 dilution), PRL (1:250 dilution), TSH (1:600 dilution), ACTH (1:250 dilution), LH (1:800 dilution) and FSH (1:150 dilution) (DAKO Corporation, Carpinteria, CA, USA); β -CG (1:200 dilution, DAKO A/S, Glostrup, Denmark); β -LH (1:20 dilution) and β -FSH (1:50 dilution, NIDDK, Pituitary Hormones & Antisera

Figure 5 Sparse secretory granules accumulating along the cell membrane and an increased number of mitochondria containing irregular cristae or tubular structures are seen. Near the right nucleus a fibrous body consisting of filaments is recognizable. Magnification $\times 12\,250$.

Center, Harbor-UCLA Medical Center, CA, USA, donated by Dr A F Parlow). Sections were stained by the peroxidase-antiperoxidase (PAP) technique.

For electron microscopy, small pieces of tissue were fixed in 2.5% glutaraldehyde, postfixed in 1% osmium

tetroxide, dehydrated, and embedded in an epoxy resin mixture (Serva, Heidelberg, Germany). Appropriate areas were selected on toluidine blue semithin sections for the ultrastructural study. Ultrathin sections (15–20 nm) were stained with uranyl acetate and lead

Figure 6 Near the nucleus bundles of fibrillar material are evident. Secretory granules are scant and small (up to 250 nm). An increased number of mitochondria containing tubular structures (in cross section) and widely-dispersed saccular endoplasmic reticulum are seen. Magnification $\times 23\,750$.

Figure 7 Mitochondria containing bizarre cristae or tubular structures. Filaments and saccular endoplasmic reticulum are widely dispersed. Magnification $\times 23\,750$.

citrate and examined with an electron microscope 9S-2 (Carl-Zeiss, Oberkochen, Germany).

Cell culture

Pituitary adenoma tissue was collected in iced saline at the time of surgery. The suspension was prepared under

sterile conditions from mechanically and enzymatically disaggregated tissue. The number of live cells per ml medium was adjusted to 2×10^5 ; the cells were incubated in Dulbecco's modified Eagle's medium/Ham's F-12 medium supplemented with 10% fetal calf serum and cultured for 72 h at 37°C in humidified air atmosphere with 5% CO_2 . The same amount of medium

Figure 8 A few adenoma cells (arrows) show positive reaction for TSH in the autopsy specimen. PAP method, poststaining hematoxylin. Magnification $\times 400$.

was incubated without pituitary tissue as the control sample. Supernatants were collected for determination of hormones (12).

Discussion

The clinical and hormonal data led to the diagnosis of a GH/TSH-secreting pituitary adenoma. Although about 60% of acromegalic patients show a paradoxical increase in GH levels following intravenous administration of 200 μ g TRH (13), in our patient GH did not respond to TRH. As somatostatin is known to suppress the paradoxical GH response to TRH (14), it is suggested that endogenous hypothalamic somatostatinergic activity can suppress such response in some acromegalic patients (15). The higher hypothalamic somatostatinergic activity is most probably a result of a positive feedback by GH (15). It is possible that in our patient an extremely high autonomous secretion of GH from the pituitary adenoma caused the increase in somatostatinergic activity. Furthermore, it seems that the enhanced endogenous somatostatinergic activity also suppressed the TRH-induced TSH response. However, other factors apart from hypothalamic somatostatinergic activity might be involved in the genesis of these responses.

Surprisingly, negative immunostaining reactions for TSH in the biopsy specimens were obtained. The absence of specific TSH immunostaining may be due to low TSH concentration in the adenomatous tissue (16). The relatively low peripheral TSH levels in the presence of a large adenomatous mass are consistent with this suggestion (17). Alternatively, masked antigen determinants on the surface of the adenomatous cells could account for the negative TSH staining (17). According to Beck-Peccoz *et al.*, in only 5 out of 135 reported cases of all types of TSH-omas did immunostaining studies fail to show the presence of TSH β , free or combined (2). However, slight TSH-positivity (less than 1% of cells) was obtained in the autopsy specimens. It is possible that tumor phenotype had changed after the operation because serum TSH levels were higher in comparison with those before the operation. On the other hand, morphological characteristics of the biopsy and autopsy tissues were identical. Immunohistochemistry for PRL and β -CG was positive, but serum levels of these hormones were within the normal range. Furthermore, PRL did not respond to TRH and dopamine. The defect in PRL and β -CG secretion may be attributed to cellular immaturity (18). The levels of α -SU *in vivo* were not measured, but the concentration of α -SU in the adenoma cell culture was significantly increased. Therefore, we assume that the pituitary adenoma secretes α -SU *in vivo*. As has been documented in TSH-omas (2) and in somatotropinomas (19), α -SU is synthesized in molar excess compared with the TSH β -subunit, which could account for *in vivo* and *in vitro* co-secretion of free α -SU.

Electron microscopy showed that the tumor cells from the patient resembled those of an acidophilic stem cell adenoma. Monomorphous, immature cells with giant mitochondria, prominent fibrous bodies and misplaced exocytoses were diagnostic. However, the tumor cells revealed some features of thyrotropes such as the presence of small secretory granules (up to 250 nm) accumulated along the cell membrane and the elongation of some cells with cytoplasmic processes. To date, few papers have appeared describing the morphological features of monomorphous GH/TSH-secreting pituitary adenomas and no consistent results have been obtained (4, 9, 10). Clore *et al.* described a monomorphous adenoma containing TSH, α -SU and GH by immunohistochemistry (9). Blood levels of TSH and α -SU in their patient were elevated, while GH levels were normal. Electron microscopy showed well-differentiated adenomatous thyrotropes. In addition, some adenoma cells had, within their Golgi region, mostly spherical fibrous bodies indistinguishable from those seen in sparsely granulated growth hormone cell adenomas and acidophil stem cell adenomas (9). Furthermore, Trouillas *et al.* reported on another two GH/TSH-secreting adenomas, which were monomorphous and resembled sparsely granulated somatotrophic adenoma (4). The secretory granules measured 150–300 nm in diameter. Immunohistochemical reactions to TSH, GH and PRL were positive (4). These data suggest an earlier, oligopotent stem cell as the source of such neoplasms. Cells that express the transcription factor Pit-1 become committed to a cell line capable of further differentiation into either somatotropes, lactotropes, or thyrotropes (3).

The most important aspect of acidophil stem cell adenomas, as undifferentiated tumors, is their aggressive behavior. They appear to have a fast growth rate and a tendency to invade the surrounding bones. Because of their large size and occasional adhesions to neighboring tissue, their total removal may be impossible (18, 20). The sensitivity of an unusual GH/PRL-secreting acidophil stem cell adenoma to somatostatin has been described previously by Page *et al.* (21), where combined bromocriptine (7.5 mg daily) plus octreotide (100 μ g three times daily, s.c.) therapy suppressed GH and PRL release. We demonstrated that octreotide was able to inhibit GH and TSH secretion from a pituitary macroadenoma, causing an acute decrease in serum GH and TSH levels to 15% and 25% respectively of basal levels within 7 days of initiating therapy. Our findings were similar to those of several investigators who have previously reported on the efficacy of short and long term administration of a somatostatin analog (SMS 201–995) in patients with a TSH- and/or GH-secreting pituitary adenoma (13, 22–24). However, it is known that in all patients in whom treatment was temporarily interrupted or permanently discontinued, serum TSH, α -SU, and thyroid hormone levels returned to pretreatment levels (22). Furthermore, desensitization during

long term treatment with SMS 201–995 has been reported (2, 24). The inhibitory effect of somatostatin on GH secretion from GH/TSH-secreting adenomas seems to be more permanent and without 'rebound hypersecretion' (13, 22, 24). The same was found in our patient, whose serum TSH concentration after surgery was higher than before the octreotide and surgical treatment. Sudden death of the patient was most probably the consequence of lethal arrhythmia in thyroid crisis. Sleep apnoea as a cause of sudden death seems less probable, while no respiratory difficulties (cessations of breathing) during sleep were observed in the patient (13). Therefore, permanent postsurgical endocrine evaluation of patients with these unusual and invasive pituitary adenomas is important.

In our patient, the suppression of serum GH and TSH levels during octreotide treatment was associated with visual improvement and the appearance of some new necrotic areas within the tumor. However, necrotic areas were not found on the pathohistological examination probably due to neurosurgical procedures such as suction of necrotic parts of the tumor. A clear shrinkage of tumor mass was demonstrated in 52% of patients with TSH-secreting adenomas, while visual improvement was observed in 75% (2). On the other hand, Malarkey *et al.* did not find any reduction in size of a bimorphous GH/TSH-secreting adenoma after 3.5 months of therapy with SMS 201–995. Furthermore, no morphological abnormalities in the tumor were found (6). These findings raise questions about the mechanism of somatostatin action as well as somatostatin effects on cell morphology, which should be examined further (22, 26, 27).

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