Acromegaly associated with a granular cell tumor of the neurohypophysis: a clinical and histological study

Case report

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Acromegaly is usually caused by a growth hormone (GH)–secreting pituitary adenoma, and hypersecretion of GH-releasing hormone (GHRH) from a hypothalamic or neuroendocrine tumor accounts for other cases. The authors report on the unusual association of acromegaly with a granular cell tumor of the neurohypophysis.

A 42-year-old woman with a 10-year history of acral enlargement, headache, and menstrual abnormalities was referred to our department for a suspected GH-secreting pituitary adenoma. The patient’s basal GH levels were mildly elevated at 4.8 μg/L, were not suppressed in response to an oral glucose tolerance test, and increased paradoxically after administration of thyrotropin-releasing hormone. The patient’s insulin-like growth factor–1 (IGF-1) level was elevated at 462 μg/L, whereas a magnetic resonance image of the sella turcica revealed an intra- and suprasellar lesion that was compatible with a diagnosis of pituitary adenoma. A transphenoidal approach to remove the lesion, which was mainly suprasellar, was successful after a second operative attempt, resulting in the clinical and biochemical regression of the patient’s acromegaly. Four months postoperatively, the patient’s basal GH level was 0.9 μg/L and her IGF-1 level was 140 μg/L. Histological analysis of the operative specimen demonstrated a granular cell tumor of the neurohypophysis, which when stained proved negative for pituitary hormones and GHRH.

This case represents the first reported association between a granular cell tumor of the neurohypophysis and acromegaly. Granular cell tumor of the neurohypophysis could be added to the restricted list of neoplastic causes of acromegaly secondary to hypersecretion of a GH-releasing substance.

KEY WORDS • acromegaly • pituitary tumor • neurohypophysis • granular cell tumor • growth hormone–releasing hormone

Abbreviations used in this paper: CRH = corticotropin-releasing hormone; FSH = follicle-stimulating hormone; GH = growth hormone; GHRH = GH-releasing hormone; GHRP = GH-releasing peptide; IGF-1 = insulin-like growth factor–1; LH = luteinizing hormone; MR = magnetic resonance; NSE = neuron-specific enolase; OGTT = oral glucose tolerance test; PAS = periodic acid–Schiff; PRL = prolactin; T3 = triiodothyronine; T4 = thyroxine; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone; UFC = urinary free cortisol.
A sagittal cell tumor was causally related to hypersecretion of GH. We report here such a case and suggest that the granular tumor of the neurohypophysis has never been described.

Her medical history was unremarkable. Her first symptoms of acromegaly had appeared 10 years earlier and consisted of progressive enlargement of hands and feet, menstrual disturbances (oligomenorrhea), headache, paraesthesia of both hands, and somnolence. The patient was admitted to the Department of Medicine of Ospedale di Lodi in 1987 for evaluation. Diagnosis of acromegaly was confirmed by the presence of an elevated GH level. A computerized tomography scan of the sella turcica revealed an enlarged sella occupied by a hyperdense lesion extending up to the optic chiasm; the inferior portion of the mass was hypodense and was considered to be a cystic area within a GH-secreting adenoma. Medical treatment with bromocriptine was begun and continued through 1992 at a mean dose of 7.5 mg per day, leading to partial improvement in the patient’s symptoms, even though her GH levels remained slightly abnormal. After a neurosurgical consultant did not advise surgery for unknown reasons, the patient was lost to follow-up review. In 1995 she presented again with headache, swelling of soft tissue, and worsened somnolence. Moreover, the patient had experienced nocturia and intermittent polyuria (approximately 3–4 L urinary output daily) for 3 years.

Endocrinological evaluation (see later section) confirmed the persistence of GH hypersecretion and normal pituitary function. Magnetic resonance images of the sella turcica revealed a mainly suprasellar lesion measuring 11 × 11 × 9 mm in the vertical, horizontal, and anteroposterior diameters, respectively, which was in close contact with the optic chiasm. The intrasellar portion of the mass was hypointense and a rim of flattened pituitary tissue appeared at the bottom of the sella turcica. Although not characteristic, the picture was considered compatible with that of a partially cystic pituitary adenoma. The patient was referred to our department for surgery.

Operation. In January 1996 the patient underwent surgery via the transsphenoidal approach. After opening the sellar floor, a normal pituitary gland appeared first and was incised on the midline to reach the lesion. Only a limited biopsy of the tumor was performed. The patient recovered uneventfully, but hormone testing showed persistence of her acromegaly. Histological analysis of the operative specimen revealed a granular cell tumor. Six months after surgery a repeated MR image (Fig. 1) confirmed the persistence of the suprasellar lesion which remained in close contact with the optic pathway, thus precluding the option of stereo-robotic radiosurgery. At this point an ectopic GHRH syndrome might have been considered in the differential diagnosis of our patient. However, we did not perform either abdominal and thoracic computerized tomography or MR imaging or octreotide scintigraphy because we had elected to proceed with another transsphenoidal operation. Knowing in advance the nature of the tumor and its relationships within the brain, we thought that complete removal of the mass was possible, even though we anticipated the likely destruction of the pituitary stalk and subsequent hypopituitarism. The second operation was performed in February 1997. By upwardly enlarging the opening of the sellar dura and dia...
Acromegaly due to granular cell tumor of the neurohypophysis

phragm, it was possible to expose the tumor directly, making its total removal feasible. Closure of the sellar floor was reinforced by placement of an autologous graft of adipose tissue.

Postoperative Course. The patient’s postoperative course was uneventful and she was discharged home on the 7th postoperative day. Five months after surgery the patient was doing well while receiving steroid replacement therapy. She denied the presence of headache, somnolence, and paresthesias of the hands; moreover, there was amelioration of her polyuria and nocturia. After surgery the patient reported experiencing amenorrhea and noticed slight fatigue, coldness, and dry skin. The latter symptoms disappeared after initiation of L-T4 substitution therapy. Endocrinological evaluation (see later section) revealed remission of the patient’s acromegaly and occurrence of panhypopituitarism, whereas MR images of the sella disclosed the absence of any residual suprasellar lesion (Fig. 1 lower). At the patient’s last follow-up examination, 29 months after the second transsphenoidal operation, she was still in clinical remission and a repeated MR image revealed no evidence of tumor recurrence.

Evaluation Methods

Endocrinological Studies

The following endocrine function tests were performed before and after neurosurgery: 1) synthetic TRH (200 µg) was injected intravenously and blood samples were collected before and 15, 30, and 60 minutes thereafter; 2) synthetic gonadotropin-releasing hormone (100 µg) was administered subcutaneously and blood specimens were collected before and 15, 30, and 60 minutes afterwards; 3) synthetic GHRH 1-29 (50 µg) was injected intravenously and blood samples were collected before and 15, 30, 45, 60, 90, and 120 minutes afterwards; and 4) oral glucose (100 g) was given and blood specimens were collected before and every 30 minutes thereafter for up to 2 hours. The serum was allowed time to clot at room temperature, separated by centrifugation, and stored at −20°C until assayed in duplicate.

Hormone Assays

Serum GH and cortisol were measured using immunofluorimetric assays and serum PRL, LH, and FSH were measured using immunoenzymatic assays. Serum IGF-1 was measured using a specific radioimmunoassay after acid extraction and serum free T4, free T3, and TSH concentrations were determined using an electrochemiluminescent assay. All assay supplies were commercially available (see Sources of Supplies and Equipment).

Histological and Immunohistochemical Analyses

The surgical specimen consisted of several small pieces of soft fragments, which were fixed in 10% buffered formalin and embedded in paraffin for light microscopy. Sections were stained using the hematoxylin and eosin, PAS, and PAS–diastase techniques. For electron microscopy other small tumor fragments were fixed in 2.5% glutaraldehyde in phosphate buffer at 4°C, postfixed in 1% osmium tetroxide, dehydrated, and embedded in epoxy resin. Ultrathin sections were stained with uranyl acetate and lead citrate, and were examined using an electron microscope.

Immunohistochemical studies were performed on 5-µm-thick paraffin sections using the streptavidin–biotin–peroxidase–conjugated detection system. Antisera were directed against the following: GH (monoclonal, diluted 1:1200), PRL (monoclonal, diluted 1:100), adrenocorticotropic (monoclonal, diluted 1:50), TSH (monoclonal, diluted 1:100), LH (monoclonal, diluted 1:200), FSH (monoclonal, diluted 1:200), α-subunit (monoclonal, diluted 1:100), GHRH (polyclonal, diluted 1:4000), CRH (polyclonal, diluted 1:300), galanin (polyclonal, diluted 1:100), S-100 protein (polyclonal, diluted 1:800), glial fibrillary acidic protein (polyclonal, diluted 1:300), neurofilament protein (monoclonal, diluted 1:30), NSE (monoclonal, diluted 1:150), epithelial membrane antigen (monoclonal, diluted 1:60), vimentin (monoclonal, diluted 1:50), keratin KL 1 (monoclonal, diluted 1:50), desmin (monoclonal, diluted 1:50), smooth-muscle actin (monoclonal, diluted 1:50), α1-antitrypsin (polyclonal, diluted 1:3000), and α1-antichymotrypsin (polyclonal, diluted 1:500).

Sources of Supplies and Equipment

Synthetic TRH and synthetic gonadotropin-releasing hormone were obtained from Ferring GmbH (Kiel, Germany), and synthetic GHRH 1-29 (GEREF) was obtained from Serono, Milan, Italy.

Tosoh (Tokyo, Japan) provided the supplies for the immunofluorimetric assays; Bayer S.p.A., Divisione Diagnostici (Milan, Italy) the supplies (Immuno 1) for the immunoenzymatic assays; Bioclone (Marrickville, Australia) the supplies for the radioimmunoassay; and Boehringer Mannheim Italia S.p.A. (Monza, Italy) the supplies for the electrochemiluminescent assay.

Sigma Immunochemicals (Steinheim, Germany) produced the antisera to GH; Immunotech (Hamburg, Germany) the antisera to PRL, TSH, FSH, LH, α1-subunit, and keratin KL 1; Dako (Hamburg, Germany) the antisera to adrenocorticotropic, S-100 protein, glial fibrillary acidic protein, neurofilament protein, NSE, epithelial membrane antigen, vimentin, desmin, smooth-muscle actin, α1-antitrypsin, and α1-antichymotrypsin; and Bioproducts (Bad Homburg, Germany) the antisera to GHRH and CRH; and ABC Serotex (Oxford, England) the antisera to galanin.

The CEM 902 electron microscope was purchased from Zeiss (Oberkochen, Germany).

Results

Hormone Evaluation

The main biochemical characteristics of the patient are summarized in Table 1. Before the first operation, her mean basal GH level was 4.8 µg/L and her IGF-1 was slightly increased at 462 µg/L (normal range 98–390 µg/L). Dynamic testing of GH secretion confirmed the diagnosis of active acromegaly: the patient’s GH level remained elevated during an OGTT (nadir 4.2 µg/L) and increased abnormally to a maximum of 21.9 µg/L following administration of TRH. In contrast, administration of GHRH elicited a nonsignificant rise in GH to 5.8 µg/L.
The PRL, free T<sub>3</sub>, free T<sub>4</sub>, TSH, UFC, and gonadotropin levels were all within normal ranges. One week after surgery, the patient’s GH level declined to 2 µg/L but it was not suppressed fully during an OGTT (nadir 1.2 µg/L). In April 1996 the patient’s basal GH level rose again to 6.3 µg/L and her IGF-1 level was still elevated (558 µg/L). Abnormal responses to TRH administration and an OGTT persisted (Table 1). One week after the second operation, her basal GH level was 2.5 µg/L, which increased after administration of TRH to a peak of 11.7 µg/L, and was incompletely suppressed during an OGTT to a nadir of 1.7 µg/L; however, at variance with the first postoperative period, the IGF-1 level normalized (245 µg/L). Four months after surgery, active acromegaly was no longer present: the patient’s basal GH level was 0.9 µg/L, which was further suppressed during an OGTT to a nadir of 0.7 µg/L, and her IGF-1 level was at the lower end of the normal range (140 µg/L). However, administration of TRH elicited a slight increase in GH to 5.2 µg/L. The free T<sub>3</sub> and free T<sub>4</sub> levels were markedly low, whereas the level of UFC was at the lower limit of the normal range. Considering the amenorrheic status of the patient, her gonadotropin levels were inappropriately normal, confirming the diagnosis of postoperative hypopituitarism. Twenty-nine months after surgery, the patient’s basal GH level was 2.5 µg/L and her IGF-1 level slightly increased to 313 µg/L, although it was still in the normal range.

**Histological Evaluation**

The surgical specimens obtained at the second operation constituted approximately 1 cm<sup>2</sup> of whitish, firm material. Histological sections of the mass revealed a highly cellular tumor (Fig. 2). The neoplastic cells were large and elongated, with abundant cytoplasm filled with eosinophilic granulations; the cells were strongly positive for PAS staining and were diastase resistant. The cells were arranged either in columns or in well-demarcated alveolar nests. The nuclei were small, oval, or elongated, and did not contain abundant chromatin. Mitoses were not observed. Blood vessels were infrequently found and demonstrated a normal wall structure.

Electron microscopic examination disclosed oval nuclei that were low in chromatin and without evident nucleoli; poorly developed rough-surfaced endoplasmic reticula; well-developed Golgi apparatuses; no secretory granules; and many complex lysosomal structures, ranging from small and round to large and irregular, that had variable electron density, sometimes with a partially multilamellar inner structure (Fig. 3). The cytofilament bundles were short and sparse and the mitochondria were rare, oval, and without specific characteristics. Cell membranes showed some blunt processes, which were similar to Schwann cell projections.

**Immunohistochemical studies for pituitary hormones, GHRH, galanin, and CRH were all undetected. Glial fibrillary acidic protein, NSE, keratin, desmin, and smooth muscle actin also were undetected. Staining for epithelial membrane antigen, α<sub>1</sub>-antitrypsin, and α<sub>1</sub>-antichymotrypsin was strongly positive; staining for vimentin was weakly positive, and staining for S-100 protein was focally positive.**

**Discussion**

The histological, immunohistochemical, and ultrastructural features of the lesion removed from our patient were diagnostic of a granular cell tumor of the neurohypophysis. The histogenesis of this rare tumor is still controversial, even though a particular cell of the posterior hypophysis, the granule pituicyte, the characteristics of which grossly resemble that of the tumor cell, is the most likely cell of origin. In a recent study of 100 pituitary glands examined at autopsy, 9% of cases harbored a granular cell tumor, the existence of which had not been suspected during the patients’ lifetimes. Moreover, in three cases there was a small coexisting pituitary adenoma. However, in all cases the granular cell tumor was small. The clinical manifestations of a granular cell tumor of the neurohypophysis or of the pituitary stalk are usually nonspecific, such as headache and hypopituitarism. Compression of the optic pathways, causing loss of visual acuity, visual field defects, and optic atrophy, frequently occurs. Despite the involvement of the neurohypophysis and the pituitary stalk, diabetes insipidus is not a typical feature of granular cell tumor of the neurohypophysis, and it has been reported in only one patient. Although we did
not formally evaluate our patient by using a water deprivation test, slight polyuria that had continued for 3 years suggests that our case may represent the second reported association between diabetes insipidus and granular cell tumor.

Our case represents the first reported association between a granular cell tumor of the neurohypophysis and acromegaly. We believe that the two conditions were causally related—the granular cell tumor induced GH hypersecretion from the normal pituitary gland by producing a GH-releasing substance—and was not merely an association of two distinct and independent lesions, despite the reported coexistence at autopsy of a pituitary adenoma and a granular cell tumor in the same cadaver. It should be noted that granular cell tumors detected at autopsy are very small lesions, whereas clinically relevant granular cell tumors of the neurohypophysis are an exceptional finding, only 43 cases having been described thus. On the other hand, acromegaly is a rare disease; its incidence in the general population is estimated to be three or four cases per 1 million each year. Therefore, the occurrence of two rare and unrelated conditions in the same patient is extremely unlikely from a statistical point of view. Even more important, the patient’s acromegaly resolved after the second operation, when all visible tumor could be removed, although it had persisted after the first operation, when only partial resection of the tumor was achieved.

A very similar situation occurs in patients with ectopic GHRH syndrome; resolution of acromegaly follows complete removal of the tumor, in most cases bronchial carcinoid, whereas persistence of GHRH-secreting tissue, such as in the case of metastatizing lesions, does not allow remission of GH hypersecretion. In our patient, resolution of acromegaly after removal of the granular cell tumor also excluded the theoretical possibility of acromegaly secondary to ectopic GHRH secretion.

What was the mechanism of acromegaly in this patient? Direct production of GH by the granular cell tumor seems rather unlikely because immunostaining detected no GH in the tumor cells. Moreover, the patient consistently showed a paradoxical GH response to TRH stimulation, which, in the usual setting of a GH-secreting pituitary adenoma, is due to aberrant expression of intact and functional TRH receptors in adenomatous tissue. Although it is plausible that during the process of tumorigenesis, tumors originating from the anterior pituitary may acquire functional characteristics of progenitor elements, it is much more difficult to envision such an occurrence in a tumor that has a completely different histogenesis, such as the granular cell tumor of the neurohypophysis.

The only alternative explanation is that the granular cell tumor secreted a GH-releasing substance. The logical candidate for this role was GHRH, but surprisingly immunohistochemical staining for GHRH proved nondiagnostic. However, we cannot completely exclude the possibility that GHRH hypersecretion was actually the cause of acromegaly in our patient, despite the negative result of immunohistochemistry. In fact, GHRH may have been produced by the granular cell tumor at such a low level that it escaped detection by immunostaining, or GHRH may have been continuously released without being stored in the neoplastic cells. Alternatively, another substance with GH-releasing properties may have been produced by the granular cell tumor. Galanin, a peptide predominantly found in the hypothalamus and whose physiological function in normal man is not completely known, was another likely candidate because it can stimulate GH release in healthy volunteers when intravenously infused continuously for 30 minutes. However, immunohistochemical analysis failed to reveal the presence of galanin in the tumor. Another substance with GH-releasing activity, GHRP, has been shown to stimulate GH secretion in healthy volunteers by modulating the somatostatinergic tone and the GHRH receptor on somatotrophs. Even though an endogenous ligand for GHRP has been postulated to exist, it has not yet been identified, thus preclud-
ing the possibility of testing the hypothesis of GHRP hypersecretion by the granular cell tumor.

Normalization of GH secretion did not occur immediately after complete removal of the granular cell tumor, as demonstrated by the lack of GH suppression during OGTT. Moreover, the paradoxical GH responsiveness to TRH persisted 4 months after surgery, despite normalization of basal GH and IGF-1 levels. Although not universally accepted, postoperative persistence of an abnormal GH response to TRH is not by itself a sufficient criterion to establish failure of surgery in cases of acromegaly.11,12 It is noteworthy that persistence of abnormal GH responsiveness to TRH has been described in two patients with ectopic GHRH syndrome, even after complete removal of GHRH-secreting tumors and remission of acromegaly.4,5

It is likely that hyperplastic somatotrophs do not lose aberrant characteristics immediately after the decline of elevated GHRH levels.

Conclusions

We suggest that granular cell tumor of the neurohypophysis could be added to the restricted list of neoplastic causes of acromegaly secondary to hypersecretion of a GH-releasing substance, either GHRH or another unidentified peptide.

References


M. Losa, et al.