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Case reports

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Idiopathic prolactin cell hyperplasia of the pituitary mimicking prolactin cell adenoma: a morphological study including immunocytochemistry, electron microscopy, and in situ hybridization

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Summary. Prolactin cell adenoma is the most frequently found lesion in surgically removed pituitaries of patients with hyperprolactinemia. However, in several instances, instead of prolactin cell adenoma, other lesions are encountered by morphological investigation. We report here the morphological findings in a patient with hyperprolactinemia who underwent transsphenoidal pituitary surgery for suspected prolactin cell adenoma. A morphological diagnosis of tumor could not be confirmed and massive diffuse prolactin cell hyperplasia was identified. The aim of this publication is to describe the lesion by histology, immunocytochemistry, electron microscopy, and in situ hybridization and to call attention to primary prolactin cell hyperplasia which can mimic prolactin cell adenoma.

Key words: Hyperplasia – Pituitary – Pathology – Prolactin – Ultrastructure

The most common finding in patients with hyperprolactinemia is a prolactin cell adenoma of the pituitary. Elevated serum prolactin levels may, however, be encountered in a number of clinical states such as pregnancy, drug therapy, endocrine diseases, notably, hypothyroidism, and pituitary stalk compression or disruption [3, 5, 10, 13, 18, 20, 22, 23, 26, 28, 29]. In the present report we describe unusual pathological findings in a patient with hyperprolactinemia who underwent transsphenoidal pituitary surgery for suspected prolactin cell adenoma.

Case report

This 38-year-old woman with two children aged 11 and 17 years was investigated for headaches and irregular menses. The patient had had irregular menstruation in the preceding 11 years. About 4 years prior to this admission, there was a period of amenorrhea lasting 9 months. Her last menstrual period had been about 6 months prior to admission. There was no associated galactorrhea. The patient used no oral contraceptives or other medications.

Physical examination revealed a short statured woman in good health. Systemic examination including neurological assessment was within normal limits. There was no clinical evidence of thyroid disease or galactorrhea.

CT and MR scans of the head showed increased tissue on the left side in the adenohypophysis. The posterior gland appeared to be normally situated with no radiographic abnormalities.

The significant finding on biochemical studies was a serum prolactin level of 256 μg/l (normal range 0–20) with an exaggerated response to intravenous thyrotropin-releasing hormone (TRH) testing with a baseline of 199 μg/l increasing to 1101 μg/l. The baseline thyroid-stimulating hormone (TSH) was 6.8 mU/l (normal range 0.3–3.5) which increased on TRH administration to a level of 48.5 mU/l. The serum thyroxine level was 93 nmol/l (normal range 60–155) with the T3 resin uptake of 0.40 (normal range 0.25–0.35) and a free thyroxine index of 0.37. The total T3 level was 1.9 nmol/l (normal range 1.2–3.4). The serum levels of growth hormone (GH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), adrenocorticotropic hormone (ACTH), cortisol and testosterone were within normal limits.

One week prior to surgery, the patient had a menstrual period. Transsphenoidal exploration revealed no discrete adenoma. Except for a transient diabetes insipidus, the patient had an uneventful postoperative course. On the 1st, 2nd and 3rd postoperative days, serum prolactin levels remained at about double the upper limit of normal at 57, 52, and 50 μg/l; the TRH test showed a baseline of 50 μg/l with a peak which was very high around 170 μg/l. The patient also received 0.075 mg oral thyroxine daily for 2 weeks and 0.15 mg for another 2 weeks. This resulted in lowering of the serum TSH levels but there was persistence of the high serum prolactin levels in the postoperative range described above. A detailed workup to look for an ectopic source for prolactin release including CT scans of abdomen, lung, pelvis and neck was negative.

Pathology

Methods

Pieces of surgically resected tissue were fixed in 10% buffered formalin and embedded in paraffin. Sections, 4–6 μm thick, were stained with hematoxylin and eosin, Gordon-Sweet silver and the PAS methods. For immunocytochemistry, the avidin-biotin-perox-

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idase complex technique was applied as described elsewhere [2, 7, 8]. The following antibodies were used: anti-humanGH, anti-hPRL, anti-hACTH, anti-β hLH, anti-hFSH, anti-hTSH, and α-subunit; the dilutions and sources are as described elsewhere [12]. For electron microscopy, tissues were fixed in 2.5% glutaraldehyde, postfixed in 1% osmium tetroxide, dehydrated in ethanol, and embedded in Epon-Araldite mixture. Ultrathin sections were stained with lead citrate and uranyl acetate and studied with a Philips 410 LS electron microscope.

For the demonstration of GH and prolactin mRNA, in situ hybridization was used as described elsewhere [12].

Morphological findings

The surgical specimen revealed sizeable fragments of non-tumorous adenohypophysis composed predominantly of chromophobic cells interspersed with acidophilic and scattered basophilic PAS-positive cells. The Gordon-Sweet silver stain revealed significant distortion of the reticulin network. Although the acinar architecture was still evident, marked enlargement of acini and even fragmentation of the reticulin fibers were noted (Fig. 1). By immunostaining, cells positive for GH were present throughout the specimen; their numbers, however, were markedly reduced (Fig. 2). The large majority of cells were immunoreactive for prolactin with a predominant Golgi-pattern of immunoreactivity, although a small contingent of larger, densely granulated cells were also positive for prolactin (Fig. 3). A varying number of scattered cells were positive for ACTH, TSH, FSH, LH, and α-subunit.

Electron microscopy revealed non-tumorous adenophypophysis with the large majority of cells representing prolactin cells with extensively developed rough endoplasmic reticulum and Golgi apparatus and variable granularity. Granule extrusions were mainly orthotopic. Corticotrophs, thyrotrophs and gonadotrophs were also encountered. Extracellular endocrine amyloid was found.

In situ hybridization revealed a large number of cells showing strong labelling with the prolactin probe (Fig. 4). Labelling for GH was in the normal range (Fig. 5).

Discussion

This unusual adenohypophysial lesion represents a massive diffuse hyperplasia of prolactin cells. The morphological study of a large number of human pituitaries has provided conclusive evidence that hyperplasia of various adenohypophysial cell types exists [1, 6, 11, 19, 24]. The investigation of hyperplasia in surgically removed pituitary specimens may be greatly hindered by several factors including variations in the regional distribution of some cell types and the often fragmented nature and poor quality of some surgical specimens. In the present case, the criteria for establishing the diagnosis of hyperplasia included lack of a visible discrete pituitary adenoma at surgery, and by histology, a diffuse proliferation of immunoreactive prolactin cells, a dif-

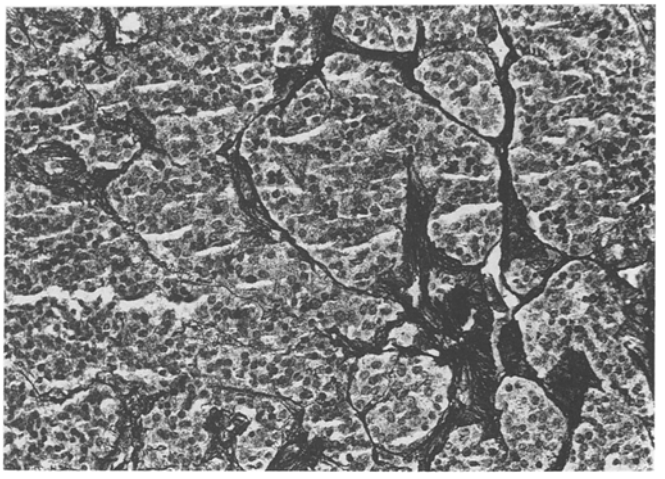

Fig. 1. Gordon-Sweet silver stain demonstrating distortion of reticulin fiber network with enlargement of acini. × 66

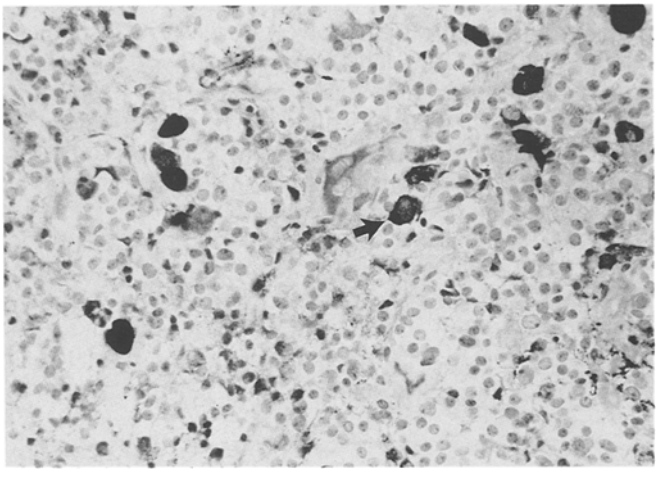

Fig. 2. Immunostaining for growth hormonal (GH) reveals scattered immunoreactive cells *(arrow)*. × 115

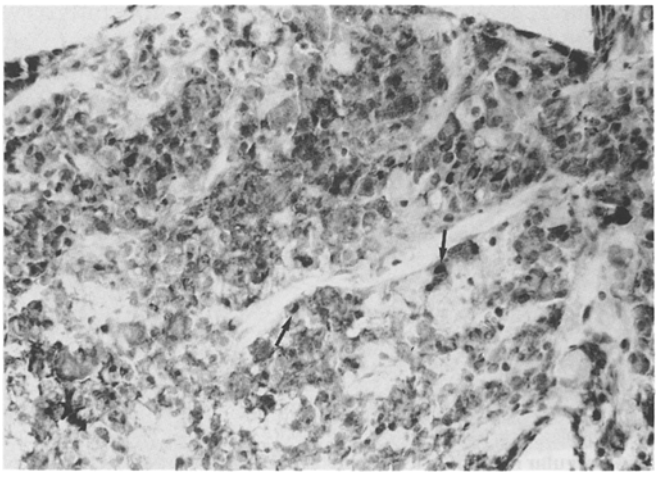

Fig. 3. Immunostaining for prolactin reveals positive immunoreactivity in many cells with a Golgi pattern of staining *(arrows)*. × 115

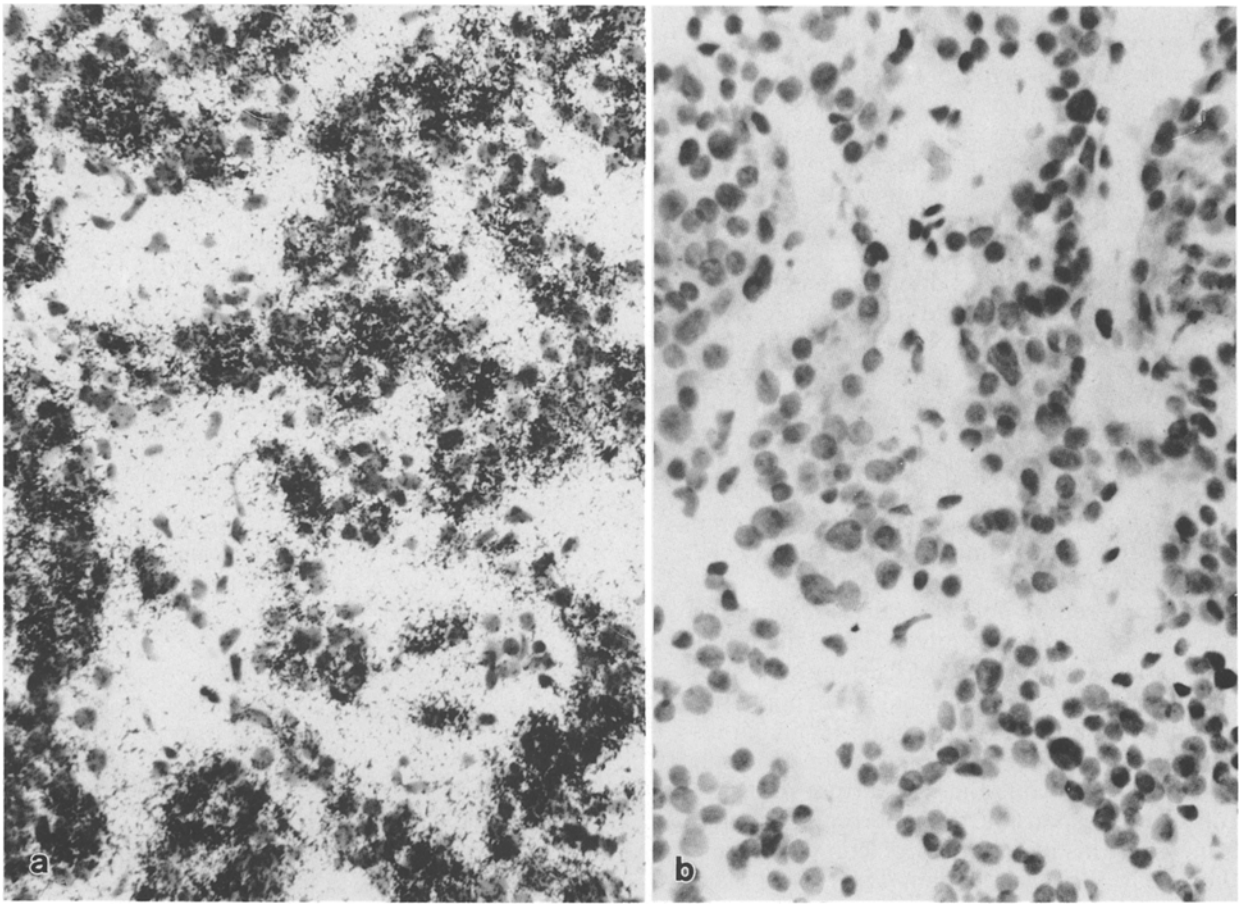

Fig. 4. **a** Strong expression of prolactin mRNA is demonstrated by in situ hybridization. **b** negative control. **a, b** × 225

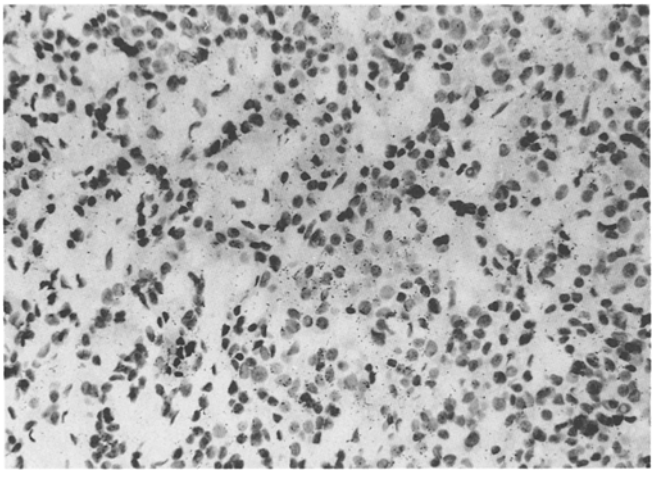

Fig. 5. Normal labelling for GH is demonstrated by in situ hybridization. × 115

fusely abnormal reticulin pattern suggesting a cellular overgrowth and fusion of adjacent acini, and an admixture of cytologically normal secretory cells of other hormonal types.

While the most common cause of hyperprolactinemia is a prolactin cell adenoma, elevated serum prolactin levels may be encountered in a number of situations [5, 10, 13, 18, 20, 22, 23, 26, 28, 29]: e.g., pregnancy, lactation, disruption of the hypophysial stalk, and organic lesions in the hypothalamus and hypophysial stalk. This stalk section effect is attributed to diminished synthesis, release, or adenohypophysial transport of dopamine, which is considered to be the main hypothalamic prolactin inhibiting factor. Hyperprolactinemia may be apparent in patients with primary long-standing hypothyroidism [3, 5, 13, 18, 21, 26, 28], Cushing's disease, and following treatment with several hormones and drugs such as estrogens and dopamine antagonists and in patients with liver cirrhosis presumably related to elevated estrogen levels associated with hepatic dysfunction [9, 29]. Prolactin cell hyperplasia in primary hypothyroidism may result from excess TRH which stimulates prolactin cells with resultant hyperprolactinemia or from reduced hypothalamic dopamine, thereby facilitating prolactin secretion [21].

Prolactin cell hyperplasia is hardly ever the sole cause of pituitary disease. Scanlon et al. [20] described a patient with hyperprolactinemia/amenorrhea-galactorrhea syndrome and an enlarged pituitary fossa who had a thyrotroph adenoma with surrounding lactotroph hyperplasia. McKeel and Jacobs [15] noted diffuse prolactin cell hyperplasia in five hyperprolactinemic patients initially suspected of harboring discrete pituitary adenoma. Subsequently, they also reported prolactin cell

hyperplasia in 9/33 patients who underwent transphenoidal surgery for hyperprolactinemia [16].

Adenohypophysial cell hyperplasia as a cause of a clinical syndrome associated with pituitary hormone excess has been recognized recently. Hyperplasia of GH cells has been documented in acromegalic patients and that of corticotrophs in association with Cushing's syndrome secondary to corticotropin (ACTH)-releasing hormone producing tumors [4, 14, 17, 19, 27]. In several patients with pituitary Cushing's disease the endocrine abnormalities have been attributed to idiopathic corticotroph hyperplasia [24]. Thyrotroph cell hyperplasia is known to occur in patients with long-standing primary hypothyroidism [6]. Mice transgenic for growth hormone-releasing hormone become giant and develop massive pituitary GH cell hyperplasia [25]. These examples clearly show that diffuse hyperplasia should be regarded as a distinct pathological entity. In some patients, the hyperplasia is primary but the cause of cell proliferation remains obscure.

In the patient presented here the causes resulting in hyperprolactinemia remain unresolved. The patient was not pregnant and had no evidence of Cushing's disease, or of organic lesions in the hypothalamus-hypophysial stalk area, and was not treated with hormones and drugs which could account for the elevation of serum prolactin levels. Thus, it is conceivable that the diffuse prolactin cell hyperplasia was responsible for hyperprolactinemia. The mechanism of this idiopathic prolactin cell hyperplasia is not clear. While the serum TSH levels were above the normal range and became normal after oral thyroxine therapy, the serum prolactin levels remained unchanged. Thus, it may be that abnormal receptors or some intracellular defects, or undisclosed prolactin-stimulating peptides or growth factors were responsible for the proliferation of prolactin cells and hyperprolactinemia. Further studies are required to clarify the mechanisms of prolactin cell proliferation in this form of pituitary disease.

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