Panhypopituitarism due to Rathke's Cleft Cyst Associated with Pituitary Oncocytoma

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A 38-year-old male with panhypopituitarism due to Rathke's cleft cyst associated with a pituitary oncocytoma is reported. The presenting signs were general myalgia and slight fatigue. Endocrine examinations revealed panhypopituitarism. Magnetic resonance imaging disclosed a suprasellar cystic lesion of the pituitary gland. Cytological examination demonstrated ciliated cells in the mucinous fluid flowing from the cyst during the pituitary operation. A pituitary oncocytoma with randomly scattered S-100 immunoreactive cells was found upon histologic examination of the nodular tissue curettaged from the internal wall of the cyst. These results suggest that the pituitary adenoma was derived from folliculostellate cells included in the Rathke's cleft wall.

Introduction

The epithelial portion of the pituitary originates from the evagination of the stomodeal ectoderm, Rathke’s pouch. A Rathke’s cleft cyst is derived from the remnant of Rathke’s pouch, which is a slit-like space within the substance of the pituitary (1). Usually the size of a Rathke’s cleft cyst is small and non symptomatic. Its incidence has been reported to be 2–26% in normal pituitary glands (2). Symptomatic Rathke’s cleft cyst has been reported to be rare (2–4), but was recently reported to be associated with deficits in pituitary function in a series of patients presenting for pituitary surgery (5). Symptomatic Rathke’s cleft cyst with panhypopituitarism is uncommon, as is the co-existence of Rathke’s cleft cyst and pituitary adenoma (6). We report a patient with Rathke’s cleft cyst with pituitary oncocytoma, showing panhypopituitarism.

Case Report

A 38-year-old male consulted Matsunami General Hospital complaining of general myalgia in July 1994. A muscular and/or connective tissue disease was suspected. Routine laboratory examinations and immunological tests revealed no remarkable findings except for eosinophilia which was probably due to allergic rhinitis. He was observed for 3 months with no abatement of symptoms. The administration of 1.5 mg betamethasone daily and an antihistamine for allergic rhinitis for 5 days induced dramatic improvement of the myalgia. After improvement of these symptoms, the patient complained for the first time that he had no ejaculation on sexual intercourse for six months, prompting further examination for hypopituitarism. Plain X-ray films of the head showed ballooning of the sella turcica without suprasellar calcification. The patient was admitted on January 31, 1995 for further studies.

Upon admission, he complained of slight fatigue, but headache, vertigo and visual disturbance were not noticed. He was 167 cm in height and weighed 60 kg. The testes were soft. Axillary and pubic hair was slightly decreased and a slight decrease of the hair over the lower extremities had also been noticed by the patient. Pulse rate was 72/min and blood pressure was low, 84/50 mmHg. No other abnormalities were found by physical examination. Routine laboratory data on admission were unremarkable: serum sodium, 143 mmol/l; serum potassium, 3.7 mmol/l; serum total cholesterol, 4.58 mmol/l; serum triglycerides, 0.82 mmol/l; fasting plasma glucose, 4.9 mmol/l; eosinophil count, 3.6 × 10^9/l. Examination of visual field and visual acuity was normal.

Plasma corticotropin (ACTH) level was at the lower limit of the reference range, 1.1 pmol/l (reference range, 1.1–12.1 pmol/l), but increased to only 2.0 pmol/l after the intravenous administration of 100 μg of corticotropin-releasing hormone (Fig. 1a). Plasma cortisol level was less than 27 nmol/l (refer-
ence range, 110–505 nmol/l) and showed a blunted increase to only to 155 nmol/l after the intravenous administration of 250 µg 1-24 ACTH. Urinary excretion of free cortisol was low, less than 303 nmol/day (reference range, 828–2,759 nmol/day). Serum testosterone level was less than 0.2 nmol/l (reference range, 9–38 nmol/l). Basal plasma luteinizing hormone (reference range, 1.8–5.2 IU/l) and follicle-stimulating hormone (reference range, 2.9–8.2 IU/l) were 0.8 IU/l and 3.9 IU/l, respectively, and their peaks after 100 µg gonadotropin-releaseing hormone administration were low, being 2.3 IU// and 6.0 IU//, respectively (Fig. 1b). Serum thyroid hormone levels were low: free triiodothyronine (reference range, 3.8–6.7 pmol/l) and free thyroxine (12.4–23.0 pmol/l) were 3.7 pmol/l and 7.2 pmol/l, respectively. Serum thyrotropin (reference range, 0.34–3.5 mU/l) and plasma prolactin levels (reference range, 1.5–14 µg/l) were normal, 2.0 mU/l and 13 µg/l, respectively, but their responses to thyrotropin-releasing hormone were depressed, at 4.2 mU/l and 21 µg/l, respectively (Fig. 1c). Plasma growth

![Graphs showing hormone levels over time](image_url)

Figure 1. Pituitary function of the patient. a) the response of plasma ACTH and cortisol to intravenous administration of 100 µg corticotropin-releasing hormone, b) the response of plasma luteinizing hormone (LH) and follicle-stimulating hormone (FSH) to intravenous administration of 100 µg gonadotropin-releasing hormone, c) the response of serum thyrotropin (TSH) and plasma prolactin (PRL) to intravenous administration of 100 µg thyrotropin-releasing hormone, and d) the response of plasma growth hormone (GH) to intravenous administration of 100 µg growth hormone-releasing hormone.
hormone was increased from 0.31 μg/l only to 4.7 μg/l by the administration of 100 μg growth hormone-releasing hormone (Fig. 1d). Serum antidiuretic hormone level and serum and urinary osmolality after overnight water restriction increased normally from 1.3 pmol/l (reference range, 0.3-3.2 pmol/l), 283 mmol/kg and 622 mmol/kg to 3.1, 288 and 982, respectively, indicating intact function of the posterior lobe of pituitary gland. Based on these findings, supplementation with thyroid hormone, glucocorticoid and testosterone was started and the patient was discharged. The symptoms of hypopituitarism improved.

Magnetic resonance imaging (MRIs) of the head were performed twice, in November 1994 and in March 1995. Both MRIs revealed a suprasellar lesion 3.0 x 3.0 x 2.2 cm in size which extended almost to the optic nerve. The image showed extremely high intensity both in T1- and T2-weighted images and the signal was not suppressed by a fat suppression sequence (Fig. 2). Within the lower part of the high intensity image, a small low intensity area was visible. No change of the intensity of the lesion between MRIs indicated a cystic, rather than hemorrhagic, lesion.

In March 1995, although the subject was complaint free, re-examination of the visual field revealed bitemporal upper quadranopsia. One month later he began to complain of visual disturbance and was re-admitted.

On April 19, 1995, transsphenoidal pituitary surgery was performed. The bone of the floor of the sella was eroded and, upon incision of dura matter ventral to the pituitary, yellowish brown mucinous fluid flowed out and was removed by suction. Nodular tissue was found in the lower part of the internal wall of the cyst. The nodular tissue was resected and curettage of the internal wall of the rest of the cystic lesion was done until no more could be removed. Visual defects improved after surgery.

**Pathological findings**

Fresh smears were prepared from the cyst fluid and fixed in 95% ethanol. The Papanicolaou-stained smears showed clusters or sheets of loosely arranged cells, most of which had round or ovoid, small to middle sized nuclei with abundant cytoplasm. A few large macrophages and ciliated columnar cells were also observed within the thick mucus-laden background (Fig. 3). Staining for iron revealed its presence within some macrophages. Histologic sections of formalin-fixed paraffin-embedded mate-

![Figure 2. MRI without enhancement demonstrated a pituitary lesion (black arrow) which was extended suprasellarly and showed extremely high intensity on both T1- and T2- (not shown) weighted images. The relatively lower intense part in the bottom of the lesion might have been the pituitary adenoma (white arrowhead).](image)

![Figure 3. The Papanicolaou-stained smears of the mucinous fluid of the pituitary cystic lesion (×1,000). A few large macrophages (large arrows) and ciliated columnar cells (small arrow) were observed within the thick mucus-laden background.](image)
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Result

The nodular tissue consisted of polygonal cells arranged in sheets or rosette formation (Fig. 4). Most of the cells had abundant eosinophilic, but poorly granulated cytoplasm and mildly hyperchromatic nuclei with minimal pleomorphism, consistent with a pituitary adenoma. Immunohistochemical stains of the tissue for ACTH, luteinizing hormone, follicle-stimulating hormone, growth hormone, prolactin, and thyrotropin were negative, but S-100 protein was positive in some of the cells. No foamy macrophages or ciliated columnar cells were found in the paraffin-embedded sections.

Ultrastructurally, adenoma cells were polygonal with round or ovoid nuclei and crowded with hyperplastic mitochondria. Some mitochondria were enlarged, others were elongated and relatively dense. The endoplasmic reticulum was scanty (Fig. 5). Rare to few secretory granules ranging from 200 to 250 nm in diameter were found, but no tonofilaments were present.

In summary, Rathke’s cleft cyst associated with a pituitary oncocytoma was diagnosed histopathologically.

Discussion

It is frequently impossible to determine the origin of large pituitary cysts. Furthermore, cystic spaces associated with tumorous tissue must be differentiated from degenerative follicles observed within adenomatous glands. Since only curettage, not total resection of the lesion, was performed in this patient, a single layered columnar epithelium of the cyst wall was not demonstrated in histological specimens. However, ciliated cells found in the mucinous fluid on cytological examination strongly suggested that the cystic lesion was a Rathke’s cleft cyst. The MRI character of the pituitary lesion, which showed extremely high intensity in both the T1- and T2-weighted images, was also consistent with Rathke’s cleft cyst, although some variations of image character on MRI have been reported (4, 7). The relatively low intensity area within the larger high intensity area of the pituitary lesion on the MRI in this patient was probably the pituitary adenoma confirmed by

Figure 4. Histological sections stained with HE (×400). The nodular tissue consists of polygonal cells arranged in sheets or rosette-like formation. Most of the cells have abundant eosinophilic but poorly granulated cytoplasms and mildly hyperchromatic nuclei with minimal pleomorphism.

Figure 5. Electron-microscopic findings of the pituitary adenoma (×2,500). Adenoma cells were polygonal with round or ovoid nuclei and filled with crowded hyperplastic mitochondria, some of which were enlarged and others were elongated and relatively dense. The endoplasmic reticulum was scanty.
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histopathology. The presence of macrophages ingesting hemosiderin in the cyst fluid suggests a previous small hemorrhage from cystic wall as has been described by Oka et al (4), especially in large cysts.

Several patients with Rathke’s cleft cysts accompanying pituitary adenoma have been reported (6, 8, 9). In a large series of 464 patients with pituitary adenoma 1.7% were associated with Rathke’s cleft cyst (6). Among these cases (6, 8–11), the relationship between the adenoma and Rathke’s cleft cyst is controversial. It has been reported that the association of these lesions is only occasional and coincidental (10, 11) and that pituitary adenomas containing elements of both the fetal Rathke’s pouch and differentiated adenohypophysial cells are extremely rare (9). Kepes (8) reported an autopsied patient with Rathke’s cleft cyst with an accompanying transitional cell tumor comprised of cells which were very rich in both tonofilaments and secretory granules. Pearl et al (9) reported a variant form of transitional cell adenoma, in which interspersed mucin-filled cysts were present. The adenoma was clearly seen at surgery to be attached to the cystic wall in our patient. Immunoreactive S-100 cells are seen in normal pituitary glands, pituicytes, folliculostellate cells, and marginal cells along the hypophyseal cleft (12, 13), but only rarely in pituitary adenomas (14). The presence of immunoreactive S-100 cells supports the possibility that the origin of the pituitary adenoma of this patient was folliculostellate cells of the Rathke’s cleft cyst wall (15).

Pituitary oncocyoma in this patient was indicated by the negative immunohistochemical findings for anterior pituitary hormones and the electron-microscopic findings of mitochondria-rich cells with few cytoplasmic secretory granules. According to a review by Miyagi et al (11) the most frequent pituitary adenomas accompanying Rathke’s cleft cyst were prolactinoma and plurihormonal adenoma which have secretory granules of prolactin, growth hormone and/or thyrotrpin. A case of Cushing’s disease with an ACTH producing pituitary adenoma accompanying Rathke’s cleft cyst (16) was reported. A putative non-functioning pituitary adenoma also was reported in association with a cyst (17), but its detailed character was not clear because of the lack of either immunohistochemical or electron-microscopic examination. We have searched, but not found another report of a pituitary oncocyoma associated with Rathke’s cleft cyst.

It is conceivable that panhypopituitarism and visual disturbance in this patient were induced by the compression of normal pituitary tissue and the optic nerve by the cystic lesion. Pain and stiffness in this patient were induced by the compression of normal pituitary tissue and the optic nerve by the cystic lesion. Pain and stiffness of the muscles, the chief and presenting complaints of this patient, were probably secondary to thyroid and/or adrenocortical insufficiency. Myalgia and stiffness are common in hypothyroidism (18). Though unusual is adrenocortical insufficiency, myalgia has also been reported in some patients with glucocorticoid deficiency due to isolated ACTH deficiency (19, 20).

In a review of Japanese patients with Rathke’s cleft cyst (21), some degree of hypopituitarism was found in 19 out of 23 patients, indicating that pituitary dysfunction is more common in patients with Rathke’s cleft cyst than previously reported. However, in this review (21) and another by Eguchi et al (5), only 2 of 23 and 2 of 19 patients had evidence of panhypopituitarism associated with Rathke’s cleft cyst. Accordingly, panhypopituitarism in patients with Rathke’s cleft cyst is not common. In our patient, six hormones of the anterior pituitary were disturbed to a greater or lesser degree.

In summary, we reported an extremely rare case of panhypopituitarism due to Rathke’s cleft cyst associated with a pituitary oncocyoma.

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References

