

Spontaneous Remission of Functioning Pituitary Adenomas without Hypopituitarism following Infarctive Apoplexy: Two Case Reports

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Abstract. Functioning pituitary adenomas may exhibit spontaneous remission after pituitary apoplexy usually in association with hypopituitarism. We report two patients who presented with sudden headache and double vision, showed a ring-enhanced sellar tumor on MRI, underwent transsphenoidal surgery that revealed a coagulation necrotic adenoma without massive hemorrhage, and showed normal pituitary function after the surgery. Definitive diagnoses were made based on immunohistochemistry of the necrotic cells. The findings were consistent with the presence of selective infarct of a GH adenoma and a prolactinoma that had led to remission of acromegaly and menstrual disturbance, respectively, without pituitary insufficiency. In contrast to hemorrhagic apoplexy, infarctive apoplexy tends to affect only the tumor and thus presents with mild symptoms and lack pituitary deficiencies.

Key words: Acromegaly, Pituitary adenoma, Pituitary apoplexy, Pituitary infarction, Prolactinoma

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PITUITARY apoplexy is a rare clinical entity with abrupt neurological deteriorating conditions associated with fulminant expansion of the pituitary gland, caused by necrosis or hemorrhage [1]. Although it tends to be associated with large adenomas, particularly with prolactinomas, it can be associated with any adenomas and, rarely, with nonadenomatous pituitary gland and other lesions [1–3]. Despite its uncertain pathogenesis, pathological study has shown that nearly equal numbers have resulted from pure clot, hemorrhagic infarction, and bland infarction [4]. When apoplexy arises in functioning adenomas, it may result in spontaneous remission of symptoms by reduction of hypersecreted pituitary hormones usually with hypopituitarism. Cases with remission of acromegaly have been most frequently reported [5–12], whereas prolactinoma cases with remission of amenorrhea have been rarely reported [13]. Diagnosis of apoplexy without massive hem-

orrhage is often difficult since no specific CT or MRI findings of infarction have been reported [1, 14, 15], and the indications of surgery remain controversial [1]. We report two unique cases, one with acromegaly and another with prolactinoma, which showed spontaneous remission of symptoms without pituitary deficiency following infarctive apoplexy.

Case Reports

Case 1

A 57-year-old woman who had a 10-year history of diabetes mellitus suddenly developed frontal headache, slight left ptosis and slight double vision. When she was referred to her former hospital, 7 days after onset, mild left oculomotor nerve palsy was noted. In addition, she showed some physical features of acromegaly: thickening and oiliness of the facial skin, excessive sweating, and increased hand, finger and foot size. A heel pad thickness was 22 mm. A high basal GH level of 10.4 ng/ml, an enlarged sella turcica on craniography, a sellar tumor that showed ring enhancement with

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gadolinium on MRI (Fig. 1c) were found. The tumor was isointense and hyperintense on T1- and T2-weighted images, respectively (Fig. 1a, b). Her general condition was good, and no symptoms of hypopituitarism or

visual defect were noted. Basal levels of prolactin and gonadotropins were decreased, but basal levels of other hormones were within normal ranges (Table 1). Her tentative diagnosis was a cystic GH adenoma.

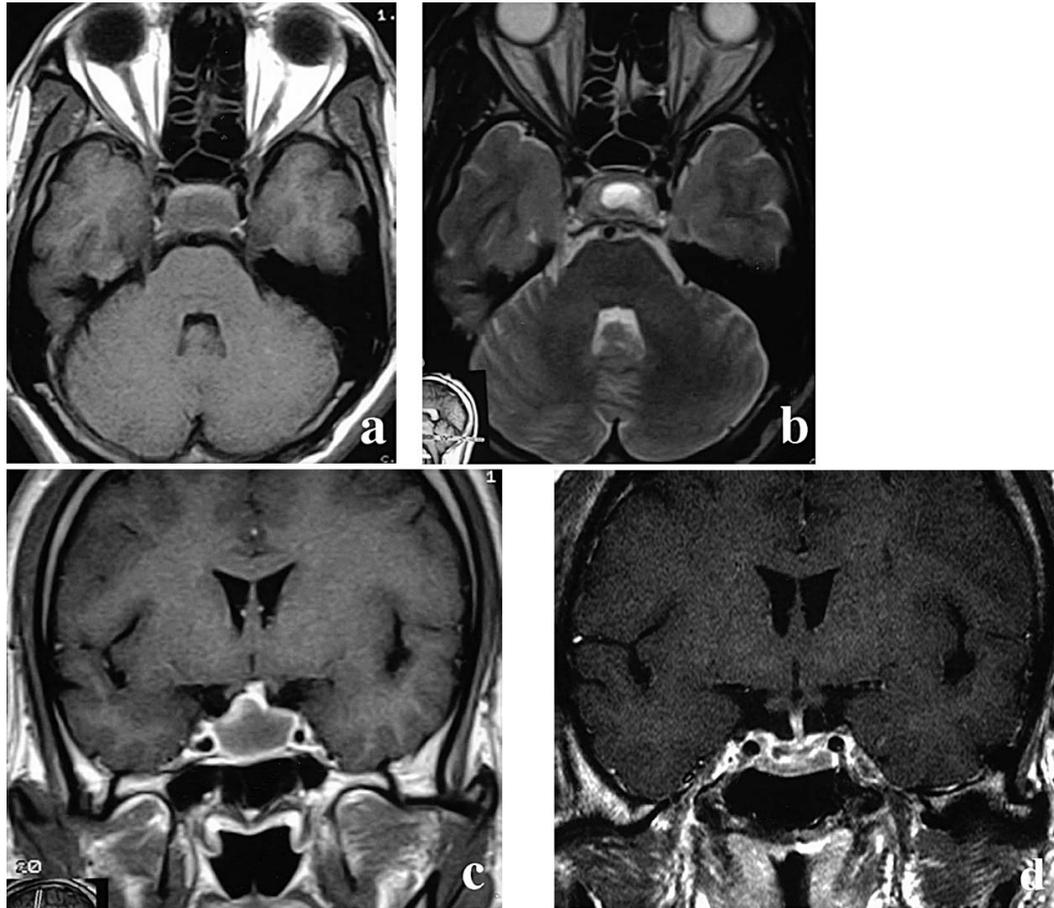


Fig. 1. MR imaging obtained 10 days (a, b, c) and 50 days (d) after apoplexy. The tumor was isointense and hyperintense on axial T1 (a)- and T2 (b)-weighted images, respectively. Coronal gadolinium-enhanced T1-weighted image demonstrated a ring-enhanced sellar lesion (c). Note the prominent shrinkage of the tumor on follow-up coronal T1-weighted image with gadolinium (d).

Table 1. Chronological changes in pituitary and target organ hormone levels in case 1

Time after onset of apoplexy	7 days (at her former hospital)	51 days (before surgery)	6 months (after surgery)	normal range
GH (ng/ml)	10.4	2.75*	1.91* (18.4)	0.66–3.8
IGF-1 (ng/ml)	N.E.	180	120	37–266
Prolactin (ng/ml)	1.3	2.6 (6.5)	5.0 (22.9)	1.4–14.6
ACTH (pg/ml)	62.8	17.8 (60.4)	29.2 (49.2)	9–52
Cortisol (μg/dl)	16.7	17.6 (34.9)	15.7 (36.1)	3.8–18.4
TSH (U/L)	1.19	1.30 (19.0)	1.56 (11.0)	0.35–4.94
Free T3 (pg/ml)	1.54	2.58	2.50	1.71–3.71
Free T4 (ng/ml)	0.88	0.94	1.23	0.70–1.48
LH (IU/L)	0.6	1.6 (4.0)	9.0 (52.0)	8.7–38.0
FSH (IU/L)	6.3	10.2 (12.8)	28.3 (44.9)	26.2–113.3

N.E.: not examined; *: nadir GH after oral glucose <1.0; (): peak level after provocation test

When she was referred to our hospital, 50 days after onset, she only complained of a minor headache. Her oculomotor nerve palsy had fully improved. Repeat endocrine tests showed a normal basal GH level (2.75 ng/ml) and IGF-1 level (180 ng/ml). Nadir GH during oral glucose tolerance test was below 1 ng/ml and GH showed no response to TRH test. Other pituitary hormones beside gonadotropins showed normal basal levels (Table 1). The response of serum prolactin to TRH, and LH and FSH to LH-RH was decreased. In addition, repeat MRI demonstrated prominent shrinkage of the cyst (Fig. 1d). After informed consent was obtained, the patient underwent transsphenoidal surgery. The tumor was a yellow, elastic soft mass surrounded by a thin fibrous wall. The tumor was totally removed with preservation of the surrounding normal pituitary gland.

Histological examination revealed an adenoma with massive coagulation necrosis surrounded by granulation tissue and inflammatory cell infiltration (Fig. 2a). No intact adenoma cells were present. On immunohistochemistry, most of the necrotic cells were positive for GH (Fig. 2b) and some cells were weakly positive for prolactin. However, ACTH, alpha-subunit, FSH-beta, LH-beta, and TSH-beta were negative. These findings yielded a diagnosis of bland infarction of a GH

adenoma.

The patient did well postoperatively and no pituitary deficiency developed (Table 1). Diabetes mellitus showed improvement and thus the insulin dose was reduced. In addition, there was a dramatic regression of the acromegalic features: excessive sweating, oiliness of the facial skin had improved, and hand, finger and foot size had decreased.

Case 2

A 27-year-old woman who had been suffering from severe dysmenorrhea for a few years suddenly developed severe frontal headache and double vision. On admission, right abducens nerve palsy and bitemporal superior quadrantanopsia were noted. CT demonstrated an isodensity sellar tumor. On MRI, the tumor showed suprasellar extension compressing the chiasma. The tumor showed predominantly slightly low intensity on T1-weighted image and high and iso mixed-intensity on T2-weighted image (Fig. 3a, b), and showed ring enhancement with gadolinium (Fig. 3c, d). The basal PRL level was 28 ng/ml. Basal levels of other hormones apart from cortisol and gonadotropins were within normal ranges (Table 2). The response of serum GH to GRF, prolactin to TRH, and LH and FSH to

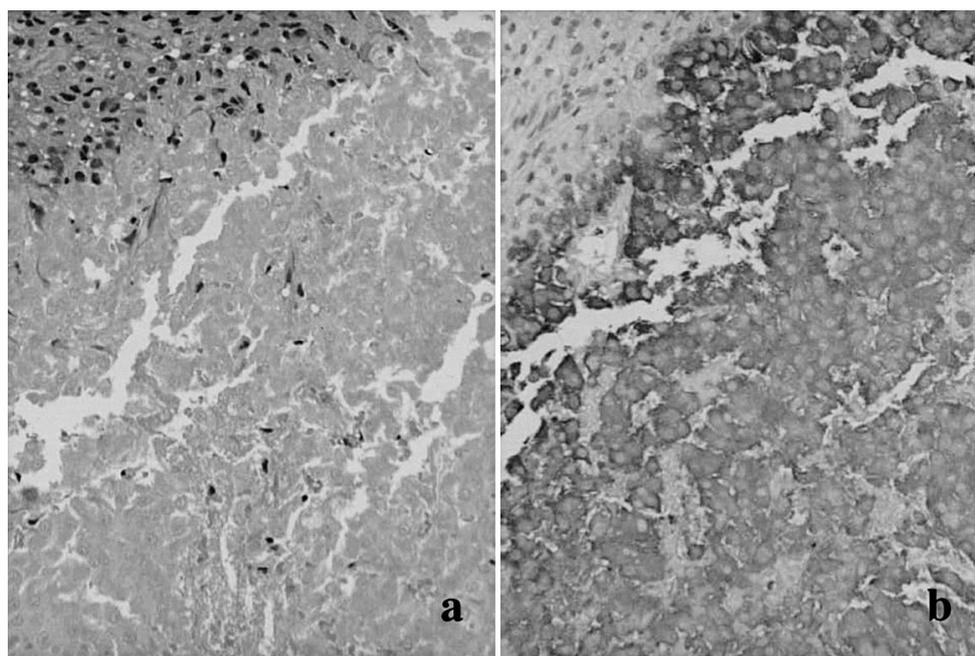


Fig. 2. The histology of the tumor showed a necrotic adenoma surrounded by granulation tissue and inflammatory cell infiltration (a; hematoxylin-eosin stain). Most of the necrotic cells were immunopositive for GH (b; immunohistochemistry).

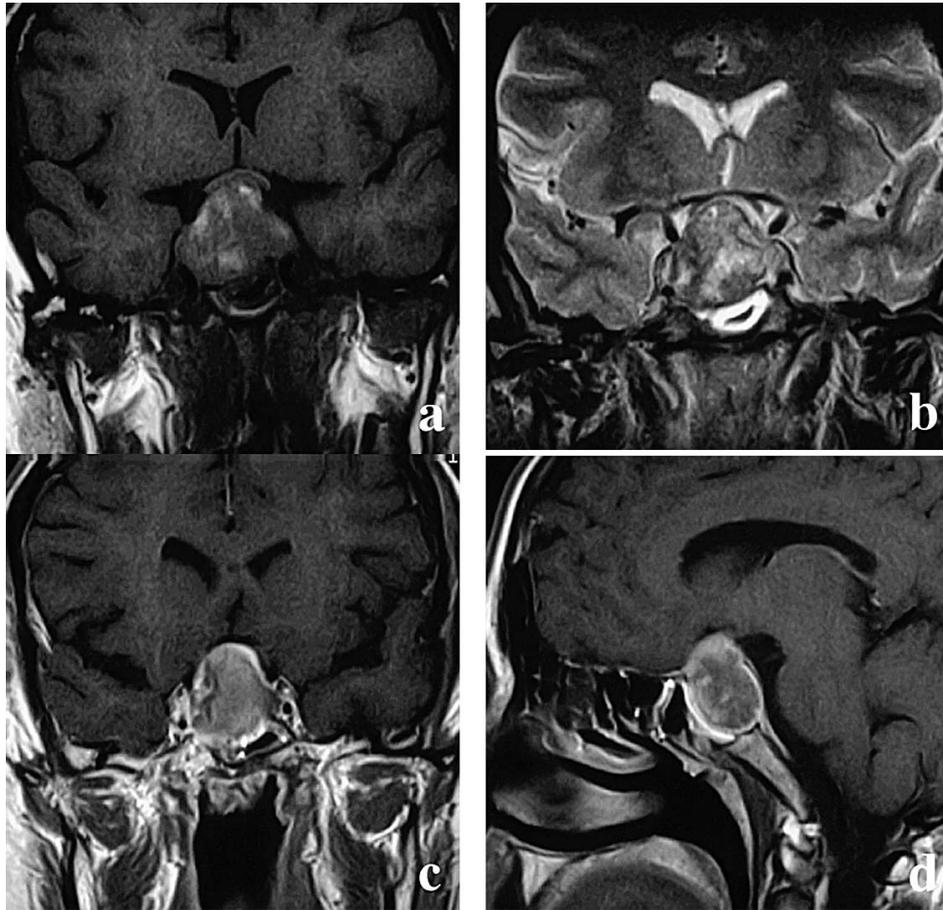


Fig. 3. MR imaging obtained 5 days after apoplexy. The tumor, compressing the chiasma, was low and slightly high mixed-intensity (a) and high and iso mixed-intensity (b) on T1- and T2-weighted images, respectively. The tumor showed ring enhancement (c, d).

Table 2. Chronological changes in pituitary and target organ hormone levels in case 2

Time after onset of apoplexy	3 days (before surgery)	35 days (after surgery)	38 months (at recurrence)	normal range
GH (ng/ml)	2.07 (7.12)	0.64 (16.8)	N.E.	0.66–3.68
IGF-1 (ng/ml)	200	N.E.	N.E.	121–436
Prolactin (ng/ml)	28.0 (40.9)	9.6 (19.0)	46.2	1.4–14.6
ACTH (pg/ml)	12.0 (45.6)	22.0 (58.0)	N.E.	9–52
Cortisol (μg/dl)	3.4 (10.2)	7.1 (15.9)	N.E.	3.8–18.4
TSH (U/L)	1.15 (12.5)	1.40 (11.0)	N.E.	0.35–4.94
Free T3 (pg/ml)	2.35	N.E.	N.E.	1.71–3.71
Free T4 (ng/ml)	1.08	N.E.	N.E.	0.70–1.48
LH (IU/L)	1.2 (3.6)	5.1 (34.2)	N.E.	8.7–38.0
FSH (IU/L)	4.8 (6.9)	11.0 (18.0)	N.E.	26.2–113.3

N.E.: not examined; (): peak level after provocation test

LH-RH was decreased. At 16 days after onset, she underwent transsphenoidal surgery. The tumor was a yellow, soft mass and no hematoma was found. The tumor was subtotally removed with preservation of the surrounding normal pituitary gland.

Histological examination revealed an adenoma with coagulation necrosis and no massive hemorrhage (Fig. 4a). Few non-necrotic adenoma cells were present on the periphery of the tumor. On immunohistochemistry, most of the necrotic cells showed dif-

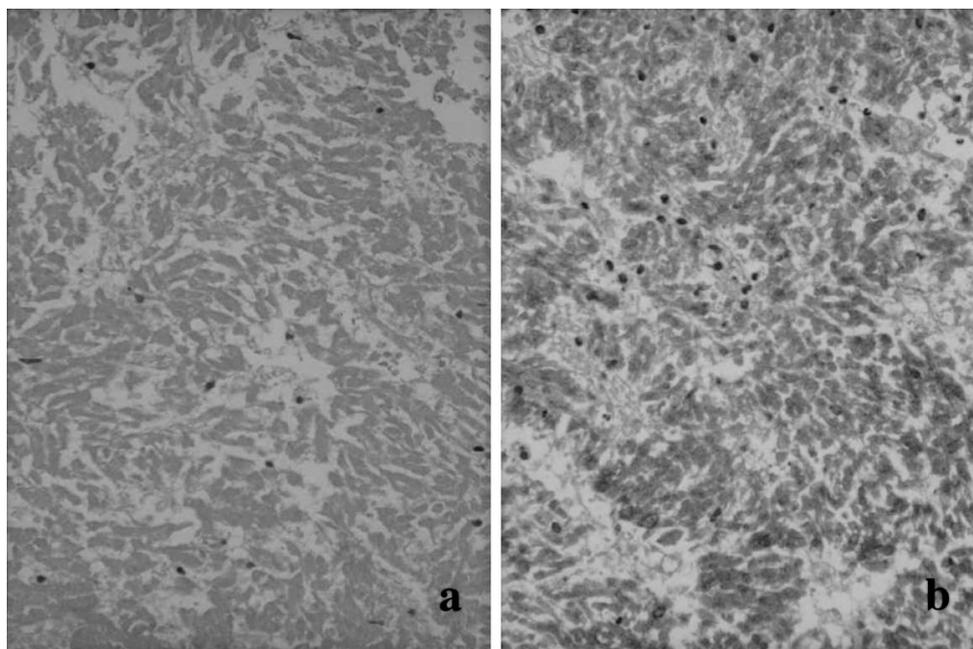


Fig. 4. The histology of the tumor showed a necrotic adenoma (a; hematoxylin-eosin stain). Most of the necrotic cells were immunopositive for prolactin (b; immunohistochemistry).

fuse reactivity for prolactin (Fig. 4b). GH, ACTH, alpha-subunit, FSH-beta, LH-beta, and TSH-beta were negative. These findings yielded a diagnosis of bland infarction of a prolactinoma.

The patient did well postoperatively. No pituitary deficiency developed (Table 2) and her menstruation recovered. Her abducens nerve palsy fully improved 2 months after the surgery. Three years after the surgery, however, mild dysmenorrhea developed again. The basal prolactin level was elevated to 46.2 ng/ml but MRI failed to demonstrate recurrent prolactinoma. One year after the commencement of dopamine agonist drug therapy, she became pregnant.

Discussion

Spontaneous remission of acromegaly following apoplexy has been reported in more than 20 cases [5–12]. Most of them were reported in the pre-MRI era, were associated with hypopituitarism, and were treated conservatively. A review of the literature demonstrated that pituitary deficiencies usually develop in cases after hemorrhagic apoplexy [6, 12, 16], whereas pituitary function was preserved in two cases, including case 1, following apoplexy with non-hemorrhagic infarct [5].

Another case of pituitary infarct in acromegaly reported by Imaki *et al.* [5] showed clinically silent apoplexy. By following a large number of untreated acromegalic patients, Bjerre *et al.* [16] suggested that a few GH adenomas might show complete or partial disappearance, probably as a result of the infarction.

In prolactinomas, particularly in large tumors, degenerative features such as fibrosis, calcification, cyst formation, necrosis, and hemorrhage are common. These changes result in decreased prolactin production [17]. In contrast to acromegaly, however, apoplectic cases leading to remission of amenorrhea in prolactinomas have been rarely reported [13]. This may be due to secondary hypopituitarism that is often accompanied with apoplexy, particularly with hemorrhagic apoplexy. Indeed, an apoplexy that led to spontaneous remission of amenorrhea and galactorrhea was a silent infarction of a microprolactinoma in a case reported by Corkill *et al.* [13].

Despite no cavernous sinus invasion of the tumor, double vision was observed transiently for short period after the apoplexy in both cases. The apoplexy seems to concern mainly the adenoma and not the pituitary [12]. Necrotic adenoma was sharply demarcated from adjacent pituitary gland by granulation tissue in case 1. We suggest that selective infarction of an adenoma had

led to remission of endocrinopathy, acute expansion of the macroadenoma, but small damage in the surrounding pituitary gland. This may be quite different from hemorrhagic apoplexy that affects not only adenoma but may also destruct the surrounding adenohypophysis, frequently resulting in hypopituitarism.

The utility of immunohistochemistry for detection of subtype in apoplectic adenoma has been reported. In a pathological study of apoplectic adenomas by Kleinschmidt-DeMasters [4], immunohistochemistry was informative in 13 of 15 adenomas, most of which were endocrine inactive null cell adenomas and weak gonadotroph cell adenomas. Distinct GH immunoreactivity was demonstrated in the necrotic adenoma cells in the present case and a case reported by Imaki *et al.* [5]. The immunohistochemistry for GH was definitive and diagnostic in case 1. Diffuse cytoplasmic immunoreactivity for prolactin observed in case 2 was quite different from the Golgi pattern reactivity that is commonly observed in prolactinomas, probably due to intracellular degeneration. Despite the patchy nature of the necrosis, immunohistochemistry is informative and should be performed in apoplectic adenomas for definitive diagnosis [4].

The indications and timing of surgery for patients

with pituitary apoplexy remain controversial [1]. Many authors have advocated surgical decompression in patients with prominent visual disturbance or neurologic deficits. Surgery may also improve pituitary function [18]. Recently, however, many cases showing spontaneous recovery with satisfactory results after conservative treatment have been reported [7, 9, 19]. In case of functioning adenomas with complete remission of endocrinopathy following apoplexy, surgical intervention may be unnecessary when definitive diagnosis could be obtained without histological verification. Surgery was performed in case 1 since diagnosis was not achieved before surgery. Her denial of physical changes of acromegaly, atypical MRI findings (non-hemorrhagic "cystic" lesion), and the negative endocrine data at our hospital confused our preoperative diagnosis. On the other hand, presurgical diagnosis had been obtained in case 2, but surgery was performed to achieve endocrinological cure. More aggressive removal of the tumor was necessary to prevent the recurrence in this case. Accordingly, we consider that transsphenoidal surgery may be indicated for patients with questionable pathology and/or with incomplete endocrinological remission that suggests residual tumor [5].

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