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Amelioration of Acromegaly after Pituitary Infarction Due to Gastrointestinal Hemorrhage from Gastric Ulcer

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Abstract. We report a rare case of acromegaly in which pituitary infarction possibly developed in a GH-producing pituitary adenoma following gastrointestinal bleeding from peptic ulcer. In this case, pituitary infarction resulted in spontaneous remission of acromegaly associated with diabetes mellitus. In addition, detailed histological investigation revealed that clinically silent pituitary apoplexy was mainly an acute ischemic event which occurred recently in a GH-producing adenoma. This event led to massive coagulation necrosis of the tumor and endocrinological improvement.

Key words: Acromegaly, Pituitary infarction, Pituitary apoplexy, Gastrointestinal bleeding

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PITUITARY apoplexy, defined by intratumoral necrosis or hemorrhage in the pituitary occurs in 0.6–10.5% of pituitary adenomas, and may provoke the sudden onset of severe headache, visual disturbance, ophthalmoplegia, or meningial irritation [1, 2]. In addition, it has been reported that pituitary apoplexy can reduce circulating levels of hypersecreted hormones by destroying tumor tissue in part [1–5], but there is little information on detailed pathological findings in such cases. We recently treated a rare case of GH-producing pituitary adenoma in which detailed endocrinological and histological examination confirmed that pituitary infarction possibly induced by massive gastrointestinal bleeding, led to coagulation necrosis of the tumor and an associated endocrinological remission of acromegaly.

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Case Report

A 47-year-old male was initially referred to our gastrointestinal department for treatment of possible upper gastrointestinal tract bleeding. At the age of 40, the patient was first diagnosed as having diabetes mellitus and had been treated with insulin at another hospital since he was 44. Proliferative retinopathy developed and was treated with photocoagulation. His initial HbA1c level was 12.2%, which was gradually decreased to less than 7% by two or three daily injections of intermediate insulin at a dose of 50 U per day. The diabetes progressed further, especially during the last 6 months when HbA1c was increased from 6.7 to 8.5%. Other endocrine tests had not been performed prior to this admission. Neither anemia nor abdominal pain had been noted during his clinical course. The blood hemoglobin level was 14.1 g/dl. On June 19, he came to an emergency room because he had syncope when he woke up in the morning. Tarry stool was noticed by the patient since the day before admission. Blood

pressure and pulse rate were 100/70 and 84/min in the sitting position. He complained of dizziness when he was in the upright position, but his blood pressure at supine position was not determined. His skin was pale and he had the physical stigmata of acromegaly, including thickening and oiliness of the skin, enlarged hands and feet, excessive sweating and deep resonant voice. Physical examination of the abdomen was unremarkable. No focal signs were noted. Laboratory tests revealed anemia (Hb 10.4 g/d*l*) with an increase in blood urea nitrogen (51.2 mg/d*l*) and hyperglycemia (380 mg/d*l*) with high HbA1c of 8.7% (normal range, 4.0–5.8%). Since acute bleeding from the upper gastrointestinal tract was suspected, gastroscopy was performed and confirmed the presence of an actively bleeding giant acute gastric ulcer. The patient was treated with intravenous injection of an H2-blocker and a transfusion of 1200 m*l* of concentrated red blood cells and improved over the following few weeks. His diabetes was dramatically improved after admission. The total amount of sc. injection of insulin required per day was decreased form 50 U to 8 U. One month later, endocrine tests were performed, as acromegaly due to a GH-producing pituitary adenoma was highly suspected on the basis of his physical signs with a thickened heel pad of 33 mm, an enlarged sella on skull X-ray and a high level of basal GH of 5.1 μg/L and an IGF-1 level of 704 μg/L (normal range, 106–398) on admission. But repeat tests 1 month after his gastrointestinal bleeding showed a normal serum basal GH level (3.2 μg/L), IGF-1 level (232.5 μg/L), and IGFBP-3 level (2.42 μg/L) (Table 1). In addition, most GH levels in half-hourly samples obtained from 0800 to 1400 h were < 1 μg/L (Table 1). Although the patient exhibited normal GH response to L-DOPA (GH: from 0.6 to 10.0) and 100 g oral glucose administration (GH: suppressed to < 1 μg/L) (Table 1), GH paradoxically increased in response to TRH (from 2.5 to 5.1 after 90 min) and GnRH (from 2.3 to 9.6 after 90 min) administration (Table 1). Basal levels of pituitary, thyroid and adrenocortical hormones were normal, but the response of serum TSH and PRL to TRH was decreased, suggesting a disturbance of pituitary function. Visual fields were normal. Magnetic resonance imaging (MRI) revealed a 1.5 × 1.0-cm less enhancing mass lesion on the right side of the pituitary gland with suprasellar extension and stalk deviation to the left side (Fig. 1). There was no past-history indicating pituitary

Table 1. Endocrinological data before and after surgery

		Before surgery					After surgery				
	fT3 (pg/m*l*)	2.95					2.60				
	fT4 (ng/m*l*)	0.92					1.30				
	ACTH (pg/m*l*)	73.5					80.3				
	Cortisol (mg/d*l*)	15.0					17.7				
	IGF-1 (mg/L)	232.5					273.0				
	IBFBP-3 (mg/L)	2.42									
		0	30	60	90	120 (min)	0	30	60	90	120 (min)
100g OGTT	Plasma glucose (mg/d*l*)	150	224	277	300	267	127	184	248	306	317
	GH (mg/L)	3.3	2.2	0.8	0.8	0.7	6.67	1.71	0.83	0.89	1.50
TRH Test	TSH (U/L)	0.50	2.67	2.53	2.30	1.87	0.20	1.94	1.78	1.45	1.07
	PRL (mg/L)	2.2	6.8	5.0	3.9	3.1	2.8	8.2	5.4	4.5	3.1
	GH (mg/L)	2.5	3.2	4.3	5.1	3.2	2.1	1.4	1.5	1.9	0.8
GnRH Test	LH (IU/L)	2.9	14.2	16.6	15.3	13.5	6.2	16.5	17.1	16.4	14.3
	FSH (IU/L)	8.97	11.6	14.2	13.6	13.0	9.3	12.6	13.7	15.1	13.1
	GH (mg/L)	2.3	3.6	5.9	9.6	4.6	2.1	1.4	1.5	1.9	0.8
L-DOPA Test	GH (mg/L)	0.6	0.5	1.4	7.0	10.0					

Daily profile	Time	0700	0730	0800	0830	0900	0930	1000	1030	1100	1130	1200	1230	1300	1330	1400 h
before surgery	GH (mg/L)	0.6	1.5	2.7	0.9	0.5	0.4	0.7	0.8	0.8	1.1	3.3	1.0	0.6	0.4	0.4

apoplexy, including severe headache, visual disturbance or ocular palsy.

Overall the endocrinological data of this patient met the definition of "cure", including a normal serum IGF-1 level and a reduction of the GH level to less than 1 $\mu g/L$ as measured by IRMA after ingestion of 100 g glucose [6]. Endocrine activity before the acute gastrointestinal tract bleeding, however, was verified only by one-point serum GH and IGF-1 determinations, which supported hypersecretion of GH. As a result of sudden compromise of the vascular supply during that event, clinically silent pituitary apoplexy or infarction occurred, and then acromegaly was thought to be resolved spontaneously. The patient underwent transsphenoidal surgery for the following reasons: Paradoxical increase in GH after TRH and LHRH may indicate residual GH producing tumor cells. MRI clearly showed the presence of a macroadenoma with suprasellar extension. Informed consent including these points was obtained. Intraoperatively, a yellow, elastic soft mass was identified in the right of the sella, surrounded by a thick fibrous capsule. This lesion was totally excised with preservation of a normal pituitary gland.

Histopathological examination of the removed tissue revealed no intact adenomatous area but instead coagulation necrosis with surrounding granulation tissue which contained lymphocytes, plasma cells and histiocytes with hemosiderin pigments (Fig. 2a). By means of immunohistochemistry, GH immunoreactivity was observed in most of the necrotic cells (Fig. 2b). Immunostains for PRL, corticotropin, beta-FSH, beta-LH and the alpha-subunit were negative in these cells. These findings suggest that the coagulation necrotic area was consistent with GH-producing adenoma.

The post-operative course was uneventful. Basal pituitary hormones were normal and no pituitary insufficiency was observed, although the response of TSH and PRL to TRH was still decreased (Table 1). Paradoxical response of GH to TRH and GnRH disappeared postoperatively (Table 1). Diabetes spontaneously improved, and insulin is now no longer necessary to control his blood glucose level (Table 1).

Discussion

Prior to his first admission, this patient had active acromegaly due to GH hypersecretion from a pituitary adenoma, in light of his physical findings, supranormal GH and IGF-1 levels and MRI findings on admission. Nevertheless, the detailed endocrine data obtained one month later demonstrated the apparent endocrinological cure of acromegaly. The clinical findings of pituitary apoplexy vary greatly but severe headache, visual disturbance, ocular palsy and/or meningeal irritation are present in most patients [1]. Although he did not exhibit

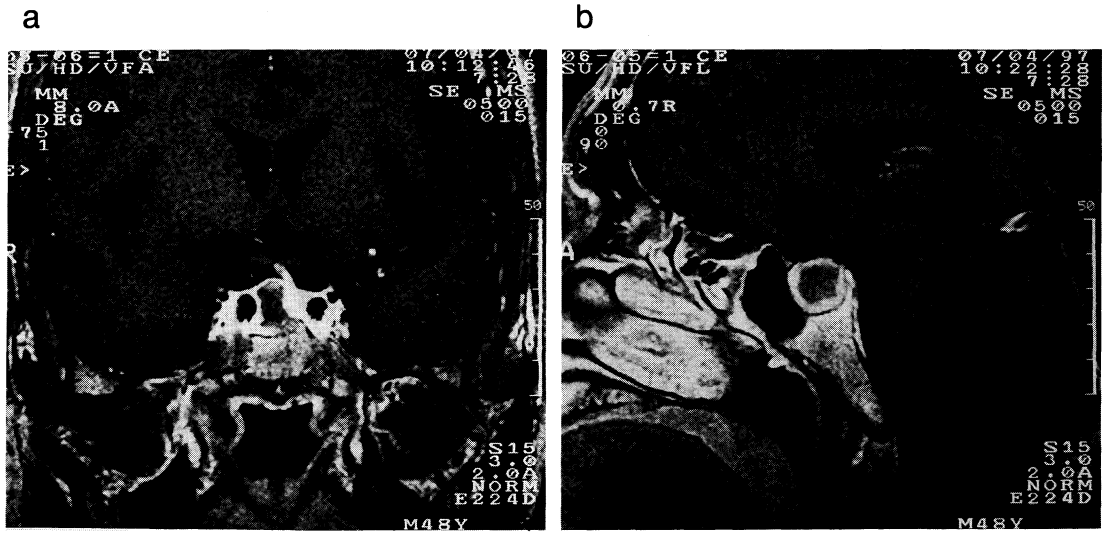

Fig. 1. (a) Coronal and (b) sagittal section of T-1 weighed MRI scan demonstrating a pituitary adenoma in the right lateral wing of the sella with extension superiorly and deviation of the pituitary stalk.

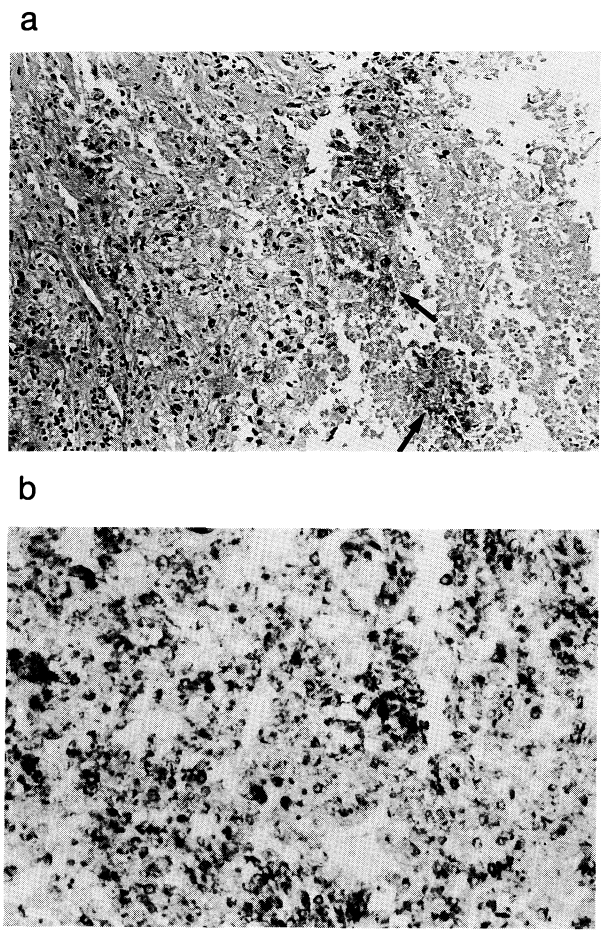

Fig. 2. (a) Histology of the resected tumor (hematoxylin-eosin). The right portion of the specimen is composed of necrotic tissue. Some hemosiderin deposition is seen (arrow heads), consistent with past bleeding. (b) Immunostaining of the resected tumor with anti-GH antibody. Much of the tissue specimen is positively stained with anti-GH antibody.

clinical symptoms or signs indicating pituitary apoplexy, histological examination of the removed tissue revealed coagulation necrosis with hemosiderin deposits. In contrast to hemorrhage, the necrosis often involves only small areas of the gland and remains unrecognized clinically [7]. In this patient, the primary condition, ischemia associated with hemorrhagic necrosis, was located within adenomatous tissue. Selective infarction of the tumor probably makes this patient's event clinically silent. Although asymptomatic pituitary apoplexy is sometimes referred to in the literature as silent [8], the term silent pituitary infarction would be more accurate in this case.

Pituitary apoplexy usually occurs spontaneously since the blood supply to a tumor is precarious, but it has been described in association with a great variety of events, including minor head trauma [3], medications [1], and dynamic pituitary function test [9, 10], although the mechanism leading to apoplexy is obscure in most of these events. This patient presumably had massive bleeding from an acute gastric ulcer. Hemoglobin less than 11 g/d*l* and a BUN greater than 40 mg/d*l* suggest loss of at least a liter of blood [11]. Pituitary infarction can be seen with various conditions associated with vascular occlusion or simply hypoperfusion, leading to ischemia and cell death [12]. The complication of pituitary infarction is well known in the setting of massive obstetrical hemorrhage during delivery [13]. In this patient, like Sheehan syndrome, pituitary infarction occurred after systemic hypotension by acute massive gastrointestinal bleeding. Moreover, diabetes mellitus has been implicated in the infarction of the normal pituitary gland because of degenerative changes in the microvasculature in the pituitary [14]. This patient had diabetes mellitus for at least 5 years and severe proliferative diabetic retinopathy as a complication. Diabetic micro- and/or macroangiopathy may therefore be another factor contributing to the development of pituitary infarction in this case. Although pituitary apoplexy caused by gastrointestinal bleeding has been described [15], it is an extremely rare condition.

Various degrees of hypopituitarism and/or decreases in blood levels of hypersecreted pituitary hormone possibly resulting from pituitary apoplexy have been reported [8, 16]. Pituitary function may range from being normal to complete absent [16]. The effect of pituitary apoplexy on the secretary activity of the pituitary adenomas has been best documented in patients with acromegaly. Substantial lowering of the serum GH concentration after pituitary apoplexy has been described [4, 5]. Spontaneous remission of acromegaly after pituitary apoplexy has also been reported [17, 18]. Although pathological findings were described in a number of cases of pituitary apoplexy [2, 12, 19–22], no detailed analysis, including immunohistochemistry, in a case showing remission of a functioning pituitary tumor after infarction has been reported. To our knowledge, this is the first report of pathological findings of no intact tumor cells, but massive coagulation necrosis revealing GH

immunopositivity, surrounding granulation tissue with inflammatory cell infiltration and hemosiderin deposit, clearly showing a pituitary infarction as a mainly acute ischemic event which occurred recently in a GH-producing adenoma. This event led the tumor to massive coagulation necrosis of the tumor and endocrinological cure of acromegaly. Selective infarction of the tumor may preserve normal pituitary function, except for decreased response of TSH and PRL to TRH and make the event clinically silent.

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