

CASE REPORT

Granulomatous hypophysitis caused by Rathke's cleft cyst mimicking a growth hormone-secreting pituitary adenoma

Masato Hojo, Ryota Ishibashi, Hiroshi Arai¹, Susumu Miyamoto

Departments of Neurosurgery and ¹Medicine and Clinical Science, Kyoto University Graduate School of Medicine, Kyoto 606-8507, Japan

ABSTRACT

We report a case of granulomatous hypophysitis caused by Rathke's cleft cyst (RCC) mimicking a growth hormone (GH)-secreting pituitary adenoma. Neuroradiological and endocrinological evaluations showed abnormal findings consistent with acromegaly: Magnetic resonance imaging demonstrated a pituitary mass lesion, and GH and insulin-like growth factor I levels were markedly elevated, and GH levels were not suppressed in oral glucose tolerance test. Transsphenoidal surgery was performed, but no adenomatous tissue could be detected. Histological examination revealed RCC and concurrent granulomatous giant cell inflammatory reaction of the anterior hypophysis. To the authors' knowledge, this is the first documented case of granulomatous hypophysitis caused by RCC mimicking a GH-secreting pituitary adenoma.

Key words: Acromegaly, granulomatous hypophysitis, growth hormone, insulin-like growth factor I, Rathke's cleft cyst

Introduction

Granulomatous hypophysitis is a rare inflammatory disorder of the pituitary gland; it is pathologically characterized by granulomatous reaction with epithelioid histiocytes, lymphocytes, plasma cells, and multinucleated giant cells.^[1-5] This pituitary lesion is distinct from systemic granulomatous disorders such as sarcoidosis, tuberculosis, and syphilis, and has two possible different etiologies: Autoimmune disorder and secondary inflammation.^[1,3,4] Although Rathke's cleft cyst (RCC) is one of the causes of pituitary inflammation, granulomatous hypophysitis caused by RCC is a very rare pituitary disorder.^[4,6-8] Moreover, the predominant endocrinological feature of granulomatous hypophysitis is hypopituitarism, and no case with growth hormone (GH) hypersecretion has been previously reported. Here,

we report an extremely rare case of granulomatous hypophysitis caused by RCC, which endocrinologically and neuroradiologically mimicked a GH-secreting pituitary adenoma.

Case Report

A 22-year-old man presented with a 2-month history of gradual onset of headache, excessive sweating, fatigue, and gonadal dysfunction. The characteristic facial features of acromegaly were not apparent. Magnetic resonance imaging (MRI) demonstrated a pituitary mass lesion with suprasellar extension [Figure 1]. The high signal of the posterior lobe was not detected in T1-weighted images. Contrast-enhanced T1-weighted image showed the intense rim enhancement of the lesion, suggesting cystic change. The hypothalamus was not affected. The stalk appeared to be normal in sagittal T1-weighted images (sagittal contrast-enhanced images had not been obtained). Neuro-ophthalmological examination revealed bitemporal upper quadrant hemianopsia. Endocrinological

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

Access this article online	
Quick Response Code: 	Website: www.asianjns.org
	DOI: 10.4103/1793-5482.146390

Address for correspondence:

Dr. Masato Hojo, Department of Neurosurgery, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan.
 E-mail: mhojo@kuhp.kyoto-u.ac.jp

How to cite this article: Hojo M, Ishibashi R, Arai H, Miyamoto S. Granulomatous hypophysitis caused by Rathke's cleft cyst mimicking a growth hormone-secreting pituitary adenoma. *Asian J Neurosurg* 2017;12:283-6.

evaluations showed that the GH level was increased: 5.42 µg/L (normal value, 0.04-0.34 µg/L), and the insulin-like growth factor I (IGF-I) level was also elevated: 134.9 nmol/L (normal value, 13.9-52.1 nmol/L). In oral glucose tolerance test (OGTT), GH levels were not suppressed [Table 1]. These findings were consistent with acromegaly. Mild adrenal dysfunction and diabetes insipidus were proved, and replacement therapy was started.

Two months after the first visit, transsphenoidal surgery was performed. The operation was performed via a sublabial transsphenoidal approach. After dural opening, the anterior pituitary gland was encountered. When this anterior gland was incised, white creamy content poured out [Figure 2a]. The cyst wall and the anterior lobe were incised and sent for histological examination. The biopsy specimens (3 mm in size) were obtained in different three sites. Although we inspected the lesion meticulously and carefully, we could not detect any adenomatous tissue.

Histological examination revealed an epithelial cyst wall consistent with RCC [Figure 2b]. No neoplasm could be detected. The pituitary tissue was infiltrated by mature lymphocytes, plasma cells, and neutrophils. The surrounding tissue was infiltrated by plasma cells, neutrophils, and multinucleated giant cells consistent with granulomatous giant cell inflammatory reaction of the anterior pituitary gland [Figure 2c]. Immunohistochemistry showed that GH-positive cells were increased in limited areas, and that positive staining for GH was also observed in the extracellular space [Figure 2d]. This finding suggested the possibility that somatotrophs might be stimulated and destructed due to inflammation and that GH might be released resulting in hypersecretion. In immunohistochemical studies, the cyst wall did not contain endocrine cells scattered between ciliated and mucin-producing cells. We concluded, therefore, that this

pituitary lesion was granulomatous hypophysitis caused by RCC, but not pituitary adenoma, and GH hypersecretion was induced by pituitary inflammation.

The postoperative course was uneventful. On the next day after surgery, the IGF-I level had already improved: 37.6 nmol/L [Table 2]. Eight days after surgery, GH levels were suppressed to <2.0 µg/L in OGTT [Tables 1 and 2]. The visual field defect was resolved completely. Postoperative MRI revealed that the cyst was evacuated, but the pituitary stalk was thickened and heavily enhanced [Figure 3a]. Fifty days after surgery, GH levels were suppressed to <1.0 µg/L in OGTT [Tables 1 and 2]. 1-year after surgery, MRI demonstrated that the thickened and enhanced pituitary stalk was normalized [Figure 3b]. GH and IGF-I levels were also normal: 0.75 µg/L and 19.8 nmol/L, respectively. Hypopituitarism was gradually resolved except for diabetes insipidus. The patient is doing well on replacement therapy with only nasal vasopressin 6 years after surgery, and GH and IGF-I levels remain normal for these 6 years.

Table 1: GH levels in oral glucose tolerance test

Time (min)	Preoperative		Postoperative day 8		Postoperative day 50	
	Glucose (mmol/L)	GH (µg/L)	Glucose (mmol/L)	GH (µg/L)	Glucose (mmol/L)	GH (µg/L)
0	4.72	8.47	3.77	4.26	4.66	2.17
30	6.72	7.29	5.61	3.24	4.83	0.77
60	5.16	6.14	6.38	2.81	5.11	0.47
90	4.55	4.11	5.94	1.99	6.99	0.32
120	5.99	3.14	4.77	2.00	7.10	0.52

GH – Growth hormone. Nadir GH levels are indicated by boldface

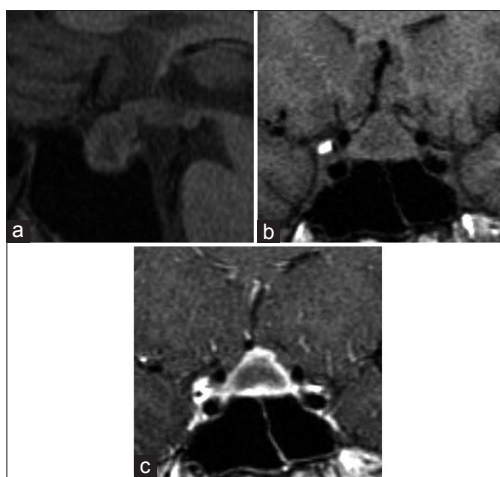


Figure 1: Preoperative magnetic resonance imaging. Sagittal (a) and coronal (b) T1-weighted images demonstrate a pituitary mass lesion with suprasellar extension. The high signal of the posterior lobe was not detected (c) coronal contrast-enhanced T1-weighted image shows the intense rim enhancement of the lesion, suggesting cystic change. The hypothalamus was not affected

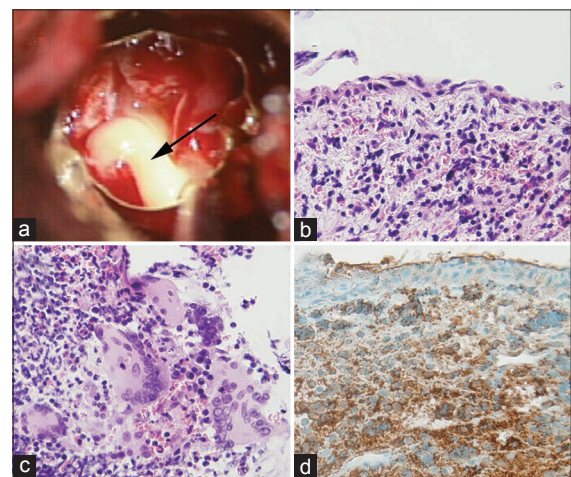


Figure 2: Intraoperative microscopic image and photomicrographs of surgical specimen. (a) Intraoperative photograph showing cyst content. Insipitated cyst content was evacuated through a transsphenoidal surgery (arrow) photomicrographs of surgical specimen (H and E, original magnification x400). The cyst wall is lined by epithelium (b). The surrounding tissue is infiltrated by multinucleated giant cells and lymphocytes (c and d) immunostaining for growth hormone (GH) (original magnification, x400). GH-positive cells are increased in limited areas, and positive staining for GH is also observed in the extracellular space

Discussion

It has been previously reported that RCC can be one of the causes of inflammatory reaction of the pituitary gland.^[9-14] But granulomatous hypophysitis caused by RCC is a rare pituitary inflammatory disorder, and only four cases have been previously reported.^[4,6-8] However, all four cases presented with hypopituitarism and were not associated with GH hypersecretion.^[4,6-8] In contrast, our case is associated with GH hypersecretion and mimicked a GH-secreting pituitary adenoma. Since GH exhibits a prominent pulsatile secretion pattern, randomly drawn blood samples are not appropriate for the evaluation of GH-secretion pattern and measurement of IGF-I is necessary for the evaluation of GH hypersecretion.^[15] Previously, only one case of lymphocytic hypophysitis with slightly elevated IGF-I level was reported.^[16] In this case, the IGF-I level was slightly elevated: 62.5 nmol/L (normal value, 16.1-60.7 nmol/L).^[16] In contrast, in our case, the IGF-I level was markedly elevated: 134.9 nmol/L (normal value, 13.9-52.1 nmol/L). To our knowledge, our case is the first report of granulomatous hypophysitis caused by RCC associated with severe GH hypersecretion.

In the present case, the elevated IGF-I level had already been normalized by the next day after surgery [Table 2]. Since it usually takes several months for the IGF-I level to be normalized after normalization of GH-secretion, it is unlikely that the

IGF-I level was normalized by the direct effect of the surgery. According to this reason, it is highly unlikely that hidden GH producing pituitary adenoma had induced GH hypersecretion. Therefore, in the present case, it is considered highly likely that GH hypersecretion was induced by inflammation of the pituitary gland and normalization of GH-secretion was due to improvement of pituitary inflammation. We propose two possible mechanisms for GH hypersecretion in the present case. One possible mechanism is that destruction of somatotrophs by the inflammatory process may result in escape of hormone into the circulation. In the present case, immunohistochemical staining for GH demonstrated that positive staining for GH was observed in the extracellular space, suggesting the validity of our estimation. The other possible mechanism of GH hypersecretion is that cytokines secreted from lymphocytes may stimulate somatotrophs to overproduce GH. *In vitro* studies have shown that cytokines such as interleukin (IL)-6 and IL-1 β promote GH-secretion.^[17,18] These *in vitro* data support our speculation on the mechanism of excessive GH production.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

- Caturegli P, Newschaffer C, Olivi A, Pomper MG, Burger PC, Rose NR. Autoimmune hypophysitis. *Endocr Rev* 2005;26:599-614.
- Flanagan DE, Ibrahim AE, Ellison DW, Armitage M, Gawne-Cain M, Lees PD. Inflammatory hypophysitis-The spectrum of disease. *Acta Neurochir (Wien)* 2002;144:47-56.
- Honegger J, Fahlbusch R, Bornemann A, Hensen J, Buchfelder M, Müller M, et al. Lymphocytic and granulomatous hypophysitis: Experience with nine cases. *Neurosurgery* 1997;40:713-22.
- Roncaroli F, Bacci A, Frank G, Calbucci F. Granulomatous hypophysitis caused by a ruptured intrasellar Rathke's cleft cyst: Report of a case and review of the literature. *Neurosurgery* 1998;43:146-9.
- Vasile M, Marsot-Dupuch K, Kujas M, Brunereau L, Bouchard P, Comoy J, et al. Idiopathic granulomatous hypophysitis: Clinical and imaging features. *Neuroradiology* 1997;39:7-11.
- Albini CH, MacGillivray MH, Fisher JE, Voorhess ML, Klein DM. Triad of hypopituitarism, granulomatous hypophysitis, and ruptured Rathke's cleft cyst. *Neurosurgery* 1988;22:133-6.
- Cannavò S, Romano C, Buffà R, Faglia G. Granulomatous sarcoidotic lesion of hypothalamic-pituitary region associated with Rathke's cleft cyst. *J Endocrinol Invest* 1997;20:77-81.
- Wearne MJ, Barber PC, Johnson AP. Symptomatic Rathke's cleft cyst with hypophysitis. *Br J Neurosurg* 1995;9:799-803.
- Benveniste RJ, King WA, Walsh J, Lee JS, Naidich TP, Post KD. Surgery for Rathke cleft cysts: Technical considerations and outcomes. *J Neurosurg* 2004;101:577-84.
- Daikokuya H, Inoue Y, Nemoto Y, Tashiro T, Shakudo M, Ohata K. Rathke's cleft cyst associated with hypophysitis: MRI. *Neuroradiology* 2000;42:532-4.
- Hama S, Arita K, Nishisaka T, Fukuhara T, Tominaga A, Sugiyama K, et al. Changes in the epithelium of Rathke cleft cyst associated with inflammation. *J Neurosurg* 2002;96:209-16.
- Hama S, Arita K, Tominaga A, Yoshikawa M, Eguchi K, Sumida M, et al. Symptomatic Rathke's cleft cyst coexisting with central diabetes insipidus and hypophysitis: Case report. *Endocr J* 1999;46:187-92.

Table 2: Clinical course, and changes of nadir GH levels in OGTT and IGF-I levels

	Nadir GH* ($\mu\text{g/L}$) ($<1.00\mu\text{g/L}$)	IGF-I (nmol/L) (13.9-52.1 nmol/L)
Postoperative day (days)		
-50	3.14	134.9
-14	not performed	68.4
0 (transsphenoidal surgery)		
1	not performed	37.6
8	1.99	32.8
50	0.32	35.8

*Nadir GH levels in OGTT. GH – Growth hormone; IGF-I – Insulin-like growth factor I; OGTT – Oral glucose tolerance test. Normal values are given in brackets

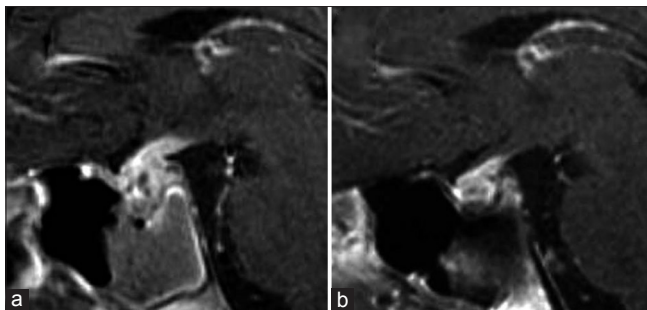


Figure 3: Postoperative magnetic resonance imaging (MRI). (a) Postoperative MRI performed 1-week after surgery. Sagittal contrast-enhanced T1-weighted image shows thickened and heavily enhanced pituitary stalk and gland (b), 1-year after surgery, the abnormal enhancement of the pituitary stalk was resolved

13. Nishikawa T, Takahashi JA, Shimatsu A, Hashimoto N. Hypophysitis caused by Rathke's cleft cyst. Case report. *Neurol Med Chir (Tokyo)* 2007;47:136-9.
14. Sade B, Albrecht S, Assimakopoulos P, Vézina JL, Mohr G. Management of Rathke's cleft cysts. *Surg Neurol* 2005;63:459-66.
15. Barkan AL. Biochemical markers of acromegaly: GH vs. IGF-I. *Growth Horm IGF Res* 2004;14 Suppl A: S97-100.
16. Hughes JM, Ellsworth CA, Harris BS. Clinical case seminar: A 33-year-old woman with a pituitary mass and panhypopituitarism. *J Clin Endocrinol Metab* 1995;80:1521-5.
17. Gong FY, Deng JY, Shi YF. Stimulatory effect of interleukin-1beta on growth hormone gene expression and growth hormone release from rat GH3 cells. *Neuroendocrinology* 2005;81:217-28.
18. Gong FY, Shi YF, Deng JY. The regulatory mechanism by which interleukin-6 stimulates GH-gene expression in rat GH3 cells. *J Endocrinol* 2006;190:397-406.