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CLINICAL ARTICLE

Clinicopathological characteristics in patients presenting with acute onset of symptoms caused by Rathke's cleft cysts

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Abstract
Background Symptomatic Rathke's cleft cyst is usually accompanied by a long history of headache, visual disturbance, and hypopituitarism; however, rare cases present with acute onset and the clinical features in such cases remain uncertain. We report herein the clinical features of Rathke's cleft cyst with acute onset and discuss the clinical significance.
Method In this study, we defined acute onset as the clinical course with clinical symptoms within a 7-day history. From among 35 cases of symptomatic Rathke's cleft cyst that were pathologically diagnosed at Fukuoka University Hospital between 1990 and 2009, five cases presented with acute onset. The symptoms, endocrinological findings, MR image findings, and pathological findings of these cases were analyzed retrospectively.
Findings Mean age was 56.8 years. Initial symptoms included headache (n=3), general malaise (n=2), polyuria (n=2), and fever (n=1). MR imaging revealed an intrasellar cystic lesion with suprasellar extension in all cases and showed rim enhancement in three cases. All cases were treated by transsphenoidal surgery. Pathological findings included hemorrhage (n=2), hypophysitis (n=2), and abscess formation in the cyst (n=1). Postoperatively, all symptoms, except for hypopituitarism, improved in all cases.
Conclusions Rathke's cleft cysts sometimes present with acute onset, and the presentation is consistent with the features of pituitary apoplexy caused by pituitary adenoma. Although pituitary apoplexy due to hemorrhage, inflammation, or infection due to an underlying Rathke's cleft cyst is difficult to diagnose pre-operatively, Rathke's cleft cyst should be included in the differential diagnosis, and early surgical treatment is needed, as for pituitary apoplexy caused by pituitary adenoma.

Keywords Rathke's cleft cyst · Acute onset · Apoplexy · Hemorrhage · Hypophysitis · Abscess

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Introduction

Rathke's cleft cyst (RCC) is an epithelial cell-lined cystic lesion of the pituitary that is thought to be derived from the remnants of Rathke's pouch, a dorsal invagination of the stomodeal ectoderm, and most remains asymptomatic throughout an individual's life. Occasionally, however, the cysts grow and compress surrounding structures, becoming symptomatic. Symptomatic RCC is usually accompanied by a long history of headache, visual disturbance, and hypopituitarism [14, 15]. On the other hand, in rare cases, patients present with acute onset. Binning et al. reported a series of RCCs that mimicked pituitary apoplexy, and the cases consisted of hemorrhagic RCCs and non-hemorrhagic RCCs that presented with apoplexy-like symptoms without hemorrhage [3]. Although the characteristics of hemorrhagic RCCs are now being elucidated, the clinical features of non-hemorrhagic RCC cases remain obscure. We report herein RCC cases presenting with acute onset and describe the clinical features of these cases.

Table 1 Summary of RCCs complicated by hemorrhage, hypophysitis, or abscess

Case no./author year	Age/sex	Onset	Duration	Presentation	VD	AD	ND	RE	Neurological outcome	Endocrinological outcome (replacement therapy for)	Pathology
Case 1	46/M	A	4 days	H	−	−	−	+	Normal	Normal	Hem
Case 2	56/F	A	Sudden	H	−	−	−	−	Normal	Normal	Hem
Binning et al., 2008 [3]	24/F	A	Sudden	H	−	−	−	N.E.	Normal	Normal	Hem
	54/F	A	Sudden	H	−	−	−	N.E.	Normal	Normal	Hem
Rosales et al., 2004 [21]	34/M	C/+	4 months	H, D	+	−	−	−	Normal	AD & ND	Hem
Pawar et al., 2002 [19]	19/M	A	Sudden	H, V	+	−	−	N.E.	Normal	Normal	Hem
Nishioka et al., 1999 [16]	46/F	A	Sudden	H	+	−	−	−	Normal	Normal	Hem
Kurisaka et al., 1998 [11]	8/F	A	Sudden	H	−	−	−	+	Normal	Normal	Hem
Onesti et al., 1990 [18]	25/M	A	Sudden	H	−	−	−	N.E.	Normal	Normal	Hem
Case 3	72/M	A	2 days	M, P	−	+	+	+	Normal	AD & ND	Hyp
Case 4	44/M	A	3 days	M, P	−	+	+	+	Normal	AD & ND	Hyp
Murakami et al., 2008 [12]	57/M	C/−	6 months	M, P	−	+	+	−	Normal	AD & ND	Hyp
Schittenhelm et al., 2008 [22]	45/F	C/+	2 months	H, A	−	−	−	+	Normal	Normal	Hyp
Nishikawa et al., 2007 [13]	62/F	C/+	2 months	M, V, P	+	+	+	+	Normal	AD & ND	Hyp
Sonnet et al., 2006 [23]	29/F	C/+	6 months	H, V	+	+	+	−	Normal	AD & ND	Hyp
Daikokuya et al., 2000 [6]	61/F	C/–	1 year	V, P	+	+	+	+	Unknown	AD & ND	Hyp
Hama et al., 1999 [7]	48/F	C/+	6 months	P	−	−	+	−	Normal	ND	Hyp
Roncaroli et al., 1998 [20]	37/F	C/−	3 years	H, A	−	−	−	+	Unknown	AD & ND	Hyp
Wearne et al., 1995 [26]	19/F	C/−	9 months	H	−	−	−	N.E.	Unknown	Normal	Hyp
Albini et al., 1988 [1]	19/F	C/−	2 months	H, G	+	+	−	N.E.	Normal	AD	Hyp
Case 5 (Kimura et al., 1994 [10])	66/F	A	2 days	H, F, DR	+	−	−	N.E.	Normal	Normal	Abs
Celikoglu et al., 2006 [5]	48/F	C/−	3 years	V	+	−	−	+	Unknown	Unknown	Abs
	37/M	C/−	2 years	G, A, V	+	−	−	+	Unknown	Unknown	Abs
Israel et al., 2000 [8]	13/F	C/−	7 months	V	+	−	−	+	Normal	ND	Abs
Thomas et al., 1998 [25]	29/F	C/–	1 year	G, A	+	−	−	+	Unknown	Unknown	Abs
Bognar et al., 1992 [4]	33/F	C/−	11 years	P, A	+	+	+	+[a]	Dead	Dead	Abs
	53/F	C/−	2 years	P	−	+	+	+[a]	Unknown	AD & ND	Abs
Sonntag et al., 1983 [24]	39/M	C/−	4 months	H	+	−	−	+[a]	Normal	Normal	Abs
Obenchain et al., 1972 [17]	50/F	C/−	3 years	H, M	+	+	+	N.E.	Normal	AD & ND	Abs

M male, *F* female, *A* acute onset, *C* chronic onset (for chronic onset, episodes of acute onset presented during the history was are shown on the right, *H* headache, *D* diplopia, *V* visual disturbance, *M* general malaise, *P* polyuria, *G* galactorrhea, *A* amenorrhea, *F* fever, *DR* drowsiness, *VD* visual disturbance on neurological examination, *AD* adenohypophyseal dysfunction, *ND* neurohypophyseal dysfunction, *RE* rim enhancement, *N.E.* not examined, *Hem* hemorrhage, *Hyp* hypophysitis, *Abs* abscess

[a] Rim enhancement on CT

Materials and methods

Between 1990 and 2009, 35 cases of symptomatic Rathke's cleft cyst were surgically treated at Fukuoka University Hospital. The hospital charts for these cases were reviewed in order to determine whether the patients had developed any clinical symptoms with acute onset. In this study, we defined acute onset as the clinical course within a 7-day history. Five cases were identified as having acute onset, and we retrospectively analyzed the symptoms, endocrinological findings, MR image findings, and pathological findings in these cases.

Results

The five cases are summarized in Table 1. Mean age was 56.8 years (range, 44 to 72 years; male, n=3; female, n=2). Initial symptoms included headache (n=3), general malaise (n=2), polyuria (n=2), and fever (n=1). Neurologically, only one patient had bitemporal hemianopsia and oculomotor palsy as a visual disturbance. On endocrinological examination, two patients exhibited panhypopituitarism (growth hormone deficiency, hypogonadism, hypocortisolism, and hypothyroidism) and diabetes insipidus. On MR imaging, three of four patients who were given gadolinium showed rim enhancement along the cyst wall. Enhancement of the infundibulum was seen in four patients, one of whom showed a thickened infundibulum. In contrast, the infundibulum in the other patients was compressed by the cyst. All patients were treated by transsphenoidal surgery and underwent simple drainage of the cyst contents with biopsy of the cyst wall. On pathology, two cases had hemorrhage, two cases had hypophysitis, and one case had abscess formation in the cyst. No evidence of squamous metaplasia or atypia was observed in all cases. Systemic diseases were ruled out in the two hypophysitis cases to differentiate them from autoimmune hypophysitis. Postoperatively, all symptoms, except for hypopituitarism, improved in all cases.

Illustrative cases

Case 1

A 46-year-old man began experiencing severe pulsating headache in the right frontal region 4 days previously. His visual acuity and visual field test were normal. Endocrinological findings indicated normal function. MR imaging revealed an intrasellar cystic mass with suprasellar extension, which appeared isointense on T1-weighted images, of mixed intensity on T2-weighted images, and displayed rim enhancement following gadolinium injection (Fig. 1).

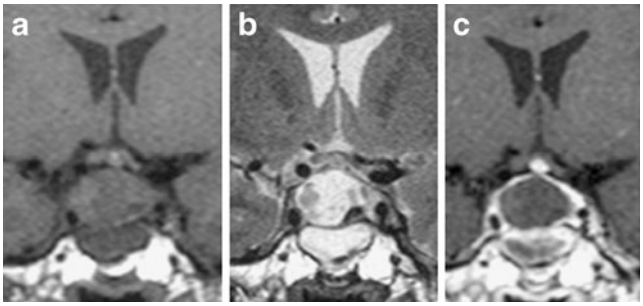

Fig. 1 Coronal MR imaging of case 1 showing an intrasellar cystic mass with suprasellar extension, which appears isointense on T1-weighted images (**a**), and of mixed intensity on T2-weighted images (**b**), and it displays rim enhancement along the cyst wall following gadolinium injection (**c**)

Transsphenoidal surgery was performed, and the cyst was found to be filled with hematoma. Pathologic examination revealed RCC consisting of ciliated columnar epithelium. Final diagnosis was RCC with hemorrhage (Fig. 2). Postoperatively, his severe headache disappeared.

Case 3

A 77-year-old male developed general malaise and polyuria after working in a field. Because his condition deteriorated severely after 2 days, he was admitted to our hospital as an emergent case. Visual acuity and visual field test were normal. Endocrinological findings indicated panhypopituitarism and diabetes insipidus: adrenocorticotrophic hormone 5.0 pg/ml (normal, 9–40 pg/ml), cortisol 2.4 μg/dl (3.0–15.2 μg/dl), thyroid-stimulating hormone 0.110 μIU/ml (0.2–5.0 μIU/ml), free T3 1.54 pg/ml (2.0–6.0 pg/ml), free T4 0.44 μg/ml (0.7–2.1 μg/ml), growth hormone 0.05 ng/ml (<0.42 ng/ml), prolactin 8.7 ng/ml (2.0–30 ng/ml), luteinizing hormone 0.2 mIU/ml (1.1–8.8 mIU/ml), follicle-stimulating hormone 1.8 mIU/ml (1.8–13.6 mIU/ml), and urine volume 3,000–6,000 ml/day (specific gravity, ~1.005). MR imaging revealed an intrasellar cyst, which appeared isointense on T1-weighted images and displayed rim enhancement following gadolinium injection (Fig. 3). Trans-

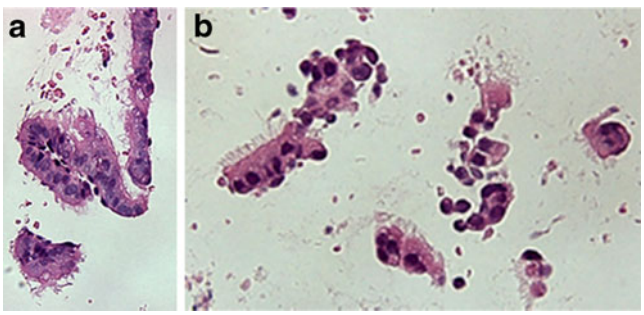

Fig. 2 Hematoxylin and eosin (H&E)-stained section of case 1 showing RCC consisting of ciliated columnar epithelium (original magnification: **a** ×200, **b** ×400)

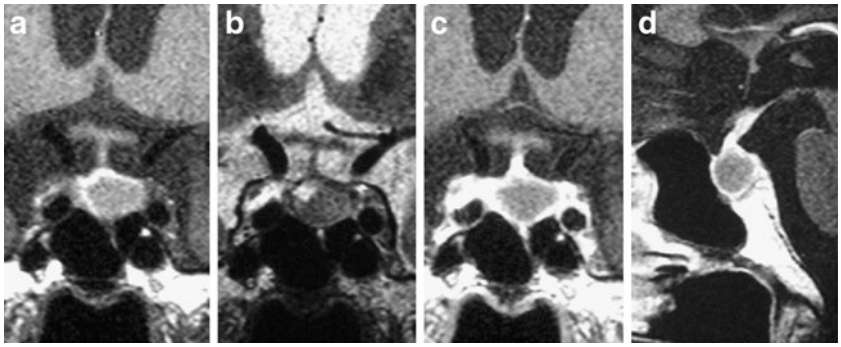

Fig. 3 Coronal and sagittal MR imaging of case 3 showing an intrasellar cyst, which appears isointense on T1-weighted images (**a**) and of mixed intensity on T2-weighted images (**b**), and it displays rim enhancement along the cyst wall following gadolinium injection (**c** coronal view, **d** sagittal view). The infundibulum is thickened and shows enhancement

sphenoidal surgery was performed in order to clarify the diagnosis. The cyst was filled with yellowish tenacious content, but culture was negative. Pathologic examination revealed RCC with lymphocytic infiltration (Fig. 4). Findings indicated secondary lymphatic hypophysitis caused by the cyst contents. Postoperatively, no improvement in endocrinological findings was observed.

Case 5

A 66-year-old female experienced headache and fever, and after 2 days, became drowsy and was admitted to our hospital as an emergent case. Neurological examination revealed nuchal rigidity, bitemporal hemianopsia, and right oculomotor palsy. White blood cell count and CRP were elevated. Endocrine tests were normal. MR imaging on admission revealed an intrasellar cystic mass with suprasellar and right cavernous extension, which appeared almost isointense on T1-weighted images (Fig. 5). Gadolinium enhancement was not examined. CSF from a lumbar tap indicated purulent meningitis. Transsphenoidal surgery was performed, and the cyst was found to be filled with abscess. Culture of the cyst contents revealed β-hemolytic streptococcus. Pathologic examination revealed RCC consisting of

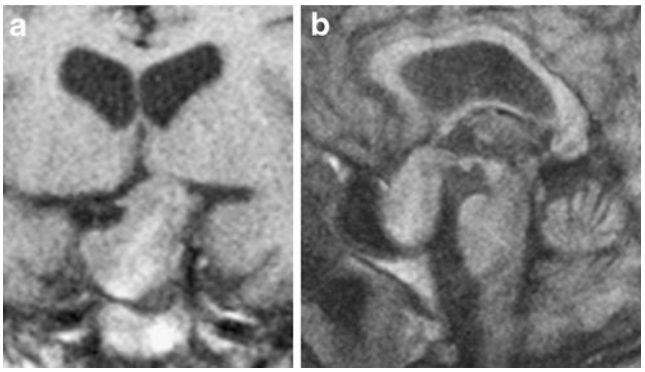

Fig. 5 T1-weighted MR imaging of case 5 (**a** coronal view, **b** sagittal view) showing a large intrasellar cystic mass with suprasellar and right cavernous extension

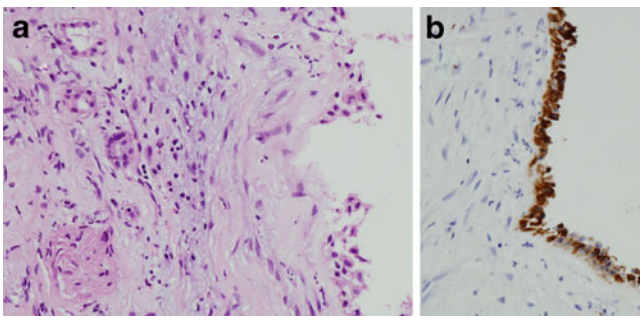

Fig. 4 Histology of the surgical specimen (H&E) of case 3 showing ciliated columnar epithelium and diffuse lymphocytic infiltration (**a** original magnification ×200). Immunohistological staining is positive for cytokeratin AE1/AE3, which is a marker for epithelium, on the cyst wall (**b** original magnification ×200)

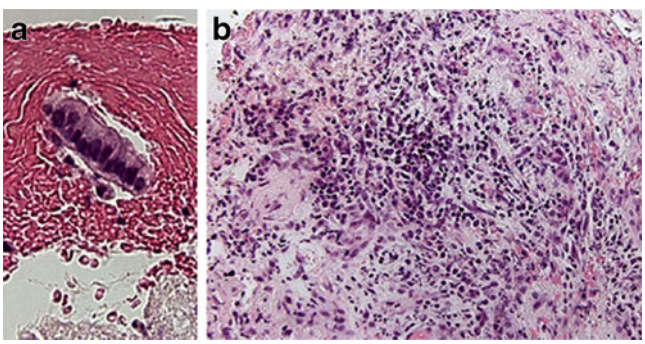

Fig. 6 Histological examination of case 5 showing ciliated columnar epithelium (**a** H&E, ×400) and a considerable degree of inflammatory cell infiltration (**b** H&E, ×200)

ciliated columnar epithelium. Infiltration of inflammatory cells in the cyst wall was observed. Final diagnosis was RCC with abscess (Fig. 6). Postoperatively, all symptoms improved.

Discussion

According to previous reports, the incidence of the acute presentations of RCC (including headache and aseptic meningitis) ranged from 11.3% to 13% [2, 9]. In the present series, RCCs presenting with acute onset tended to be complicated by hemorrhage, hypophysitis, or abscess. We also reviewed the literature related to pathogenesis (Table 1). To date, few cases of RCC apoplexy caused by intracystic hemorrhage have been reported in the literature, and their clinical features were similar to those of apoplexy caused by pituitary adenoma in terms of sudden onset of symptoms [11, 16, 18, 19, 21]. Hemorrhagic RCCs presented with acute onset at high frequency, and most of the cases were sudden onset; although they often showed visual disturbance, complicating hypophyseal dysfunction was rare. Early surgical decompression improved visual symptoms at a high rate [11, 16, 18, 19, 21]. This may be attributed to rapid increases in cystic volume by intracystic hemorrhage and compression of surrounding structures, rather than the direct damage to the hypophyseal tissue. Nishioka et al. described a case of hemorrhagic RCC upon which pathological examination showed that the wall of the cyst contained many thin blood vessels in granulation tissue with layers of hematoma, and they hypothesized that the cause of hemorrhage was disruption of these small vessels [16].

On the other hand, two cases of RCC with hypophysitis showed acute onset. RCC is thought to occasionally induce secondary hypophysitis triggered by rupture of cyst content containing mucous material [14, 20, 22, 23]. In the reported RCCs with hypophysitis, they were often complicated by adeno- and neurohypophyseal dysfunction, but they less often showed visual disturbance than hemorrhagic RCCs [1, 6, 7, 12, 13, 20, 22, 23, 26]. Presumably, this means that the symptoms of RCC with hypophysitis stem from chemical reactions to hypophyseal tissue following the rupture of the cyst contents rather than the compression of the parasellar structure. Although the many RCCs with hypophysitis deteriorate over a period of several months, our cases represented acute onset with severe endocrinological deficits with panhypopituitarism and diabetes insipidus. Because of the drastic change in endocrinological function, acute cases exhibiting high severity were managed as emergency cases. In these cases, early diagnosis and hormonal replacement therapy were particularly important.

Furthermore, according to our review of the literature, approximately half of the RCC cases with hypophysitis cases that presented with long history exhibited acute headache or acute endocrinological symptoms during the history [7, 13, 22, 23]. This can be explained by the inflammation caused by minor rupture of the cyst, after which the contents would lead to acute symptoms, and repeated rupture would gradually result in irreversible pituitary damage. Even when patients having RCC with hypophysitis causing hypopituitarism undergo surgical treatment, recovery from hypopituitarism is difficult after hormonal function has been disrupted [1, 6, 7, 12, 13, 23]. However, early surgical treatment for RCC with hypophysitis may prevent further progression of hypopituitarism.

Most RCCs with abscess formation present with more than several months of history [4, 5, 8, 17, 24, 25], and only one case presented as acute onset, which is thought to be extremely rare [10]. In addition, no cases have ever been reported to show acute symptoms during a long history, such as RCC with hypophysitis. RCC with abscess thus appears to represent a slow progressive visual disturbance with a long history, frequently showing rim enhancement on MR imaging.

In conclusion, RCC sometimes presents with acute onset, and the presentation is quite consistent with the features of pituitary apoplexy caused by pituitary adenoma. Although pituitary apoplexy due to hemorrhage, inflammation, or infection due to underlying RCC is difficult to diagnose pre-operatively, RCC should be included in the differential diagnosis, and early surgical treatment, as for pituitary apoplexy caused by pituitary adenoma, is needed.

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Comment

In this report, in the 10-year series of 35 Rathke's cleft cysts treated at Fukuoka University, five cases that presented with pituitary apoplexy are presented. The finding is that a lot of individuals carry Rathke's cleft cysts; some of these cysts became symptomatic due to their mass effect. Only a few of these cysts present with pituitary apoplexy. In these cases, hemorrhage, hypophysitis, or abscess is the cause of the sudden onset. For clinical symptoms and treatment, the Rathke's cleft cyst becomes the secondary pathology.

For these rare pathologies with even more uncommon presentation, the retrospective analysis still remains our only source of information. So, it is important to publish series of this kind.

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