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Original Article

Clinical significance of thickened sphenoid sinus mucosa in Rathke's cleft cyst

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Abstract

Background: To determine the clinical significance of thickening of the sphenoid sinus mucosa (TSSM) in Rathke's cleft cyst (RCC).

Methods: We retrospectively reviewed patients with pituitary lesions. A total of 99 patients, who underwent surgery of pituitary lesions between 2008 and 2015, were analyzed to evaluate the clinical significance of TSSM using magnetic resonance imaging. The patients with TSSM were evaluated for their characteristics.

Results: Of the 99 operations, 15 patients with paranasal sinusitis, direct invasion to the sellar floor, and/or a history of transsphenoidal surgery were excluded. There were 51 pituitary adenomas (PAs), 18 RCCs, and 15 other tumors. TSSM was observed in 6 patients (7.1%). Pathologies included 3 RCCs (16.7%), 1 PA (2.0%), and 2 other lesions. Three RCCs were especially analyzed. The pituitary dysfunction was found in all 3 patients with TSSM, whereas that was noted in 2 of 15 patients (13.3%) without TSSM. The sensitivity was 60%, specificity was 86.7%, and the positive predictive value was 100%. There was no significant difference in the age, thickness of TSSM, symptoms, and squamous metaplasia between patients with and without TSSM.

Conclusions: TSSM occurs more frequently in RCCs than in PAs. TSSM can potentially suggest hypopituitarism in RCCs. The surgical and/or endocrinological interventions are required for preventing further endocrine deterioration.

Key Words: Hypophysitis, hypopituitarism, mucosal thickening, Rathke's cleft cyst sphenoid sinus

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INTRODUCTION

Rathke's cleft cyst (RCC) is a nonneoplastic lesion, which is considered to arise from the remnants of Rathke's pouch, an invagination of the stomodeum. This lesion is often clinically silent all through the person's lifetime. If an RCC enlarges to affect surrounding structures such as the pituitary gland and/or the optic chiasm, headache, visual disturbance, and endocrine insufficiency are common presenting features. However, a point of

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controversy remains regarding the natural history, surgical indication, and recurrence; and it is difficult to determine the therapeutic intervention. Hormonal dysfunction is not uncommon but subclinical in many cases, which may lead to delayed diagnosis.[5,12] On the other hand, pituitary apoplexy is defined as acute hemorrhage or infarction of pituitary adenoma (PA). Sudden onset of this event results in several symptoms including severe headache, nausea, visual impairment, opthalmoplegia, and hypopituitarism.[13] Arita *et al.*[2] first reported thickening of the sphenoid sinus mucosa (TSSM) during the acute stage within a week of pituitary apoplexy. We experienced a patient with RCC accompanied with TSSM that was not observed on the previous magnetic resonance imaging (MRI). To our knowledge, there is no comprehensive analysis of TSSM in RCCs. In the present study, we retrospectively review patients with TSSM in pituitary lesions, including RCC, to identify the clinical characteristics.

MATERIALS AND METHODS

An exhaustive retrospective analysis was performed among 99 patients in whom pituitary and sellar lesions were diagnosed at our institution between 2008 and 2015. The presence of TSSM was determined with MRI. The thickness of the sphenoid sinus mucosa adjacent to the sellar floor was measured on T1- or Gadolinium T1- and T2-weighted images. A mucosal thickness of more than 1 mm was considered abnormal, as previously described.[4,5] Cases that even had slight thickening of mucosa in the other paranasal sinuses were excluded. Cases with direct invasion to the sellar floor and/or a history of transsphenoidal surgery were also excluded. Visual function was evaluated by visual acuity and Goldman perimetry before and after surgery. The endocrinological evaluation included measurement of baseline serum levels of PRL, GH, insulin-like growth factors-1 (IGF-1), TSH, free T3, free T4, LH, FSH, estradiol (women) or testosterone (men), ACTH, cortisol, and antidiuretic hormone. If indicated by a low baseline serum level or clinical symptoms related to endocrine insufficiency, a simultaneous three-hormone loading test [TRH 200 μg LHRH (luteinizing hormone-releasing hormone) 100 μg CRH 100 μg] and/or growth hormone-releasing peptide-2 (GHRP-2) loading test (GHRP 100 μg) were performed. Pituitary insufficiency was defined as low serum level of baseline hormone below the reference value or the low level of IGF-1 and no response to the loading test or the low serum level of baseline hormone with clinical symptom. A peak GH level of 9 ng/ml or less was used as a threshold to diagnose the GH deficiency. Diabetes insipidus (DI) was diagnosed on the basis of urine-specific gravity <1.005 and urine volume >200 ml/h. In particular, the diagnosis of RCC was based on not only clinical and neuroimaging findings but also on surgical specimens. Surgical indications for RCC include headache, visual disturbance, pituitary endocrinopathy, and cranial nerve palsy related to the cavernous sinus.

Statistical analysis

The distributed data are shown as the means. Mann–Whitney U test was used to analyze correlations between two groups. A P value of <0.05 was considered to indicate statistical significance. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the relative factor of TSSM.

RESULTS

Between 2008 and 2015, we operated on 99 patients with pituitary lesions. Fifteen patients had paranasal sinusitis, direct invasion, and/or a history of transsphenoidal surgery. Among the remaining 84 patients, there were 36 men and 48 women whose mean age was 46.5 years (range 12–82 years). There were 51 PAs, the most common pathology identified, followed by 18 RCCs, and 15 other tumors (10 craniopharyngiomas, 2 germinomas, 2 xanthogranulomas, and 1 arachnoid cyst). TSSM was observed in 6 patients (7.1%) on MRI. The pathologies included 3 RCCs, 1 PA, and 2 other tumors. The patients' mean age was 40.8 years, and the mean thickness of the mucosa adjacent to the sellar floor was 3.1 mm. Transsphenoidal surgery was performed and histological findings of the sphenoid sinus mucosa were examined in all 6 cases. The frequency of TSSM without tumor invasion proven by histological examination was 6 of 84 cases (7.1%). We compared the PAs and RCCs; and TSSM was observed in 2.0% (1 of 51) of PAs (Case 1) [Figure 1] and 16.7% (3 of 18) of RCCs (Cases 2–4) [Figure 1]. The mean age was 44.3 years, and the mean thickness of mucosa was 2.9 mm. Three of 4 cases had headache, and all 4 cases had 3 or 4 insufficient hormone axes [Table 1]. A case of PA had sudden onset of severe headache and oculomotor nerve palsy suggesting pituitary apoplexy. The pituitary dysfunction was observed in each case with TSSM, and 14 of 50 (28.0%) PAs and 2 of 15 (13.3%) RCCs without TSSM [Table 2]. In the presence of TSSM for pituitary dysfunction, the sensitivity was 60%, the specificity was 86.7%, and the PPV was 100%. However, with the presence of pituitary dysfunction for TSSM, PPV was 6.7% and 60%, the NPV was 100% in both PAs and RCCs. Furthermore, regarding the RCCs, 3 patients with and 15 patients without TSSM are compared in Table 3. All 3 patients with TSSM had hypopituitarism, whereas 13.3% (2 of 15 patients) were without TSSM. These 3 patients required hormone replacement therapy. Statistical significance was only observed in endocrine insufficiency.

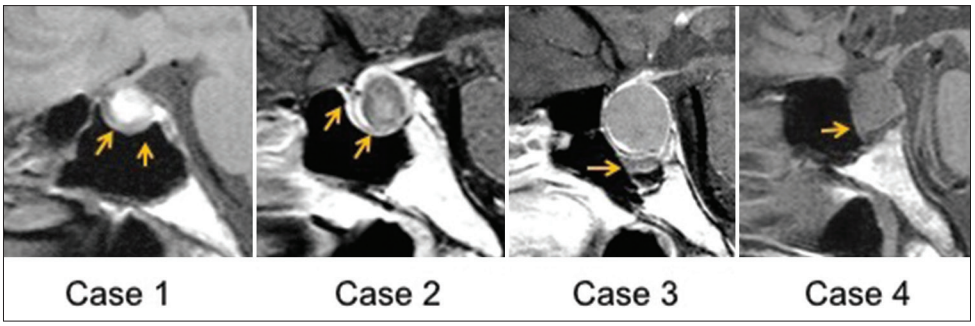

Figure 1: Thickening of sphenoid sinus mucosa (TSSM) is seen on magnetic resonance image (MRI) in patients with pituitary adenomas or Rathke's cleft cysts. Sagittal planes of MRIs show the thickened sphenoid sinus mucosa adjacent to the sellar floor (arrows). Case numbers correspond to those in Table 1

Table 1: Summary of characteristics in PAs and RCCs with TSSM

Case no.	Age (yrs)	Sex	Pathology	Size (mm)	TSSM (mm)	HA	VI	EI	APHI (axes)	Cranial neuropathy	Onset to Dx
1	53	F	PA	15	2.5	Yes	-	Yes	3	Yes	8 days
2	30	M	RCC	15	2.2	Yes	-	Yes	3	-	4 days
3	29	M	RCC	20	4.8	Yes	-	Yes	4	-	12 months
4	65	M	RCC	19	2.2	-	-	Yes	4	-	2 months
Ave.	44.3			17.3	2.9						

TSSM: Thickening of sphenoid sinus mucosa, HA: Headache, VI: Visual impairment, EI: Endocrine insufficiency, PA: Pituitary adenoma, RCC: Rathke's cleft cyst, APHI: Anterior pituitary hormone insufficiency, Dx: Diagnosis (Onset to Dx; Period from onset of symptom to radiological diagnosis)

Table 2: Incidence of TSSM and EI in PAs and RCCs

	Endocrine function	
TSSM	**Disturbed**	**Normal**
PA		
+	1	0
–	14	36
RCC		
+	3	0
–	2	13

TSSM: Thickening of sphenoid sinus mucosa, EI: Endocrine insufficiency, PA: Pituitary adenoma, RCC: Rathke's cleft cyst

Table 3: Clinical characteristics of RCCs with and without TSSM

	TSSM		
	With ($n=3$)	**Without ($n=15$)**	***P***
Age (yrs)	41.3	41.4	0.859
Size (mm)	19.3	17.1	0.441
Headache	2 (67%)	5 (33%)	0.889
Visual impairment	0	7 (47%)	0.214
Endocrine insufficiency	3 (100%)	2 (13%)	0.021
APHI (axes)	3.7	2.0	0.149
Squamous metaplasia	1 (33%)	4 (27%)	0.859

Illustrative case (Case 3)

A 28-year-old man had severe headache especially retro-orbital pain. MRI revealed a 16-mm cyst in the intra- and suprasellar region. This cyst appeared as a slightly high intensity on T1-weighted image, high intensity on T2-weighted image, and without enhancement on gadolinium-enhanced T1-weighted image. An intracystic nodule can be seen which was most likely an RCC [Figure 2a]. There was no abnormality on the hormonal examination. Follow-up MRI taken after a year showed enlargement of the cyst up to 20 mm without the intracystic nodule [Figure 2b]. TSSM was newly developed, although no lesions in the sphenoid sinus were seen on the initial MRI. Hormonal examination including the simultaneous three-hormone loading test and GHRP-2 loading test revealed the total anterior hypopituitarism. Hormone replacement therapy was started with hydrocortisone and levothyroxine sodium hydrate. An endoscopic endonasal transsphenoidal surgery was performed to drain the cystic contents and for histological confirmation of the cyst wall. There was no infectious sinusitis such as purulent fluid contents in the sphenoid sinus. Edematous mucosal thickening of the sphenoid sinus was also observed [Figure 2c]. The bony structure of the sellar floor was kept normal. A jelly-like content was discharged when the cyst wall was opened [Figure 2d]. Craniopharyngioma could not be denied in the intraoperative histological examination. Complete removal of the cyst wall was performed because the patient's hormonal function had been total anterior hypopituitarism before the operation. This cavity was irrigated with copious amounts of normal saline. The sphenoid sinus mucosa suffered from inflammatory cells such as lymphocyte and plasma cells in the edematous stroma in the postoperative histological examination [Figure 2e]. The extracted cyst wall had

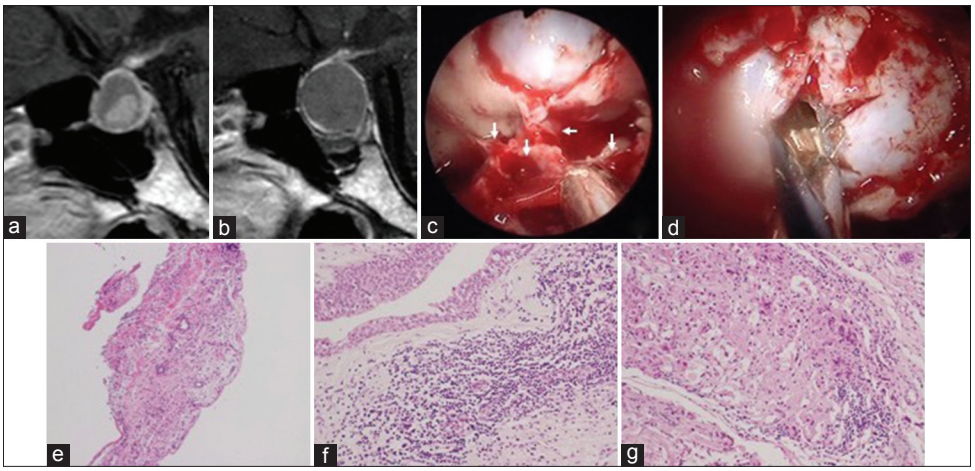

Figure 2: An MRI 1 year before (a) and just before the operation showing the TSSM (b). The endoscopic view revealed a thickening of the mucosa over the sellar floor (white arrows) (c), and yellowish jelly-like fluid in the cyst (d). Hematoxylin and eosin staining of the sphenoid sinus mucosa shows inflammatory cells (e). The columnar epithelium with cilia and stratified squamous epithelium, infiltration of inflammatory cells adjacent to the cyst wall were noted in the extracted cyst wall (f). Chronic inflammatory cells are found in the pituitary gland (g)

ciliated epithelium and inflammatory change in the anterior pituitary gland [Figure 2f and g]. He suffered DI with thirst and hypotonic polyuria immediate after the operation, which was effectively controlled with desmopressin. Methyltestosterone and somatropin were also administered after the operation. No postoperative recurrence was seen for 3 years.

DISCUSSION

TSSM has been reported during the acute stage of pituitary apoplexy. TSSM was observed in 82%[2] and in 79%[11] cases of PA within 7 days after onset of pituitary apoplexy. Agrawal *et al*.[1] also reported 2 cases of TSSM in pituitary apoplexy. TSSM was found in 15 among 100 PAs without apoplexy, and 5 patients had pansinusitis.[2] TSSM consists of subepithelial swelling on histological examination. The mechanism of thickening of the parasellar dura mater and sphenoid sinus mucosa have been considered to be caused by congestion of dural blood flow because of increased cavernous and circular sinus pressure due to a sudden increase in intrasellar pressure. TSSM during the acute stage of a pituitary apoplexy may also be associated with worsening of the endocrinological and neurological outcome. Patients with TSSM had a higher rate of hypopituitarism and subsequent hormone replacement therapy than those without TSSM. Early surgical decompression can help prevent ischemic necrosis of the anterior pituitary gland and subsequent hypopituitarism.

In some reports, MRI in patients with noninfectious granulomatous hypophysitis showed swelling of the mucosa in the sphenoid sinus.[4,6,9] The mechanism of these mucosal swellings was suggested by spreading of inflammation from the pituitary fossa into the sphenoid sinus and other adjacent structures. Honneger *et al*.[9] reported 9 cases of lymphocytic and granulomatous hypophysitis. TSSM was observed in 4 cases (2 lymphocytic and 2 granulomatous), and the infiltration of inflammation into the sphenoid sinus resembled the intrasellar pathologies in 2 cases. There were 5 cases each of partial anterior hypopituitarism and DI, and only 1 case presented with normal pituitary function.

Hypophysitis can be classified as primary or secondary. Primary hypophysitis is very rare, and the incidence among pituitary pathologies is between 0.2% and 6.5%.[3,8,10] Lymphocytic, granulomatous, and xanthomatous, three types of hypophysitis, are easily distinguished. Secondary hypophysitis is caused by local lesions, such as RCCs, craniopharyngiomas, and PAs, or systemic diseases, such as sarcoidosis, granulomatosis with polyangiitis, formerly known as Wegener's granulomatosis, and Langerhans cell histiocytosis.

In the present study, histological investigation showed inflammatory cells such as plasmacytes and lymphocytes in the pituitary gland around the RCCs. Infiltrations of inflammatory cells were also observed in the mucosa of the sphenoid sinus adjacent to the sellar floor in the surgical specimens in the present study. This inflammatory change suggested that the secondary inflammation caused by the RCC was extended over the sphenoid sinus mucosa. Among 3 RCCs with TSSM, the period from the development of symptoms to diagnosis was shorter than 2 months in 2 cases (Cases 2 and 4) and the other was in 12 months (Case 3). These two kinds of onset patterns suggested the possibility of two kinds of mechanisms. Hama *et al*. described that secondary inflammation due to the RCC causes epithelium to stratify and the inflammation spreads into the

subjacent and overwhelm the hypophysis, resulting in hypopituitarism.[7] Furthermore, the stage of epithelial inflammation correlated with the single epithelium in the acute phase of inflammation and stratified epithelium in the chronic phase. Squamous metaplasia was noted only in 1 patient (Case 3) in whom it took 1 year from the initial symptoms to the diagnosis. Therefore, we considered TSSM had two different phases of acute and chronic inflammation, the hypopituitarism was caused by hypophysitis.

Transsphenoidal surgery typically remains the preferred option for patients with symptomatic RCC and offers excellent outcomes with regard to symptomatic improvement, preservation of normal pituitary function, and minimization of complications. In 18 cases in the present study, worsening of the pituitary function, except for case 3, was not seen after the surgery. The existence of TSSM suggests clinical or subclinical hypopituitarism, endocrine insufficiency does not cause TSSM because of high NPV. Therefore, coexistence of TSSM and hypopituitarism is helpful for diagnosing RCC with pituitary inflammation. Surgical treatment is advisable to prevent further functional degradation. Endocrinological intervention is also required as soon as possible for hormonal evaluation and subsequent replacement therapy.

CONCLUSIONS

Retrospective analysis of MR images in patients with a pituitary lesion demonstrated that TSSM was observed in 16.7% of RCCs. Pituitary lesions with TSSM, especially with an RCC, are likely to already have exhibited pituitary dysfunction. TSSM may suggest hypopituitarism in RCCs. Transsphenoidal surgical intervention should be considered to prevent further endocrine deterioration, and hormone replacement therapy is also recommended as soon as possible.

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Conflicts of interest
There are no conflicts of interest.

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