Changes in the epithelium of Rathke cleft cyst associated with inflammation

Selji Hama, M.D., Kazunori Arita, M.D., Takashi Nishisaka, M.D.,
Toshiyuki Fukuhara, M.D., Atsushi Tominaga, M.D., Kazuhiko Sugiyama, M.D.,
Hiroyuki Yoshioka, M.D., Kuniki Eguchi, M.D., Masayuki Sumida, M.D.,
Yui Heike, M.D., and Kaoru Kurisu, M.D.

Department of Neurosurgery, Hiroshima University School of Medicine; Department of Pathology and Laboratory Medicine, Hiroshima Prefectural Hospital, Hiroshima; and Division of Clinical Research, National Shikoku Cancer Center Hospital, Ehime, Japan

Object. Rathke cleft cysts (RCCs) are composed of tall, well-differentiated, ciliated columnar epithelia. Their structures are altered by hyperplasia or squamous metaplasia, but their cause remains unknown.

Methods. The authors studied pathological findings and anterior pituitary function in 20 patients harboring RCCs. They classified RCC epithelium as either single (a single ciliated columnar cell lining or a flattened cuboidal cell lining) or stratified (a stratified ciliated columnar cell lining, basal cell hyperplasia, columnar cell hyperplasia, or squamous metaplasia). Inflammation was classified as acute, subacute, chronic, or end stage.

The epithelial cell lining was observed in 13 specimens obtained during surgery (six specimens contained single and seven contained stratified epithelia). Inflammation had penetrated the cyst epithelium or subjacent stroma in 10 patients, and the stage of inflammation correlated well with the type of epithelia group: early stages of inflammation in the single epithelium group and chronic or end-stage inflammation in the stratified epithelia (p = 0.0027). The adenohypophysis was identified in 21 surgical specimens. Postoperatively, growth hormone (p = 0.019), cortisol (p = 0.027), and thyroid-stimulating hormone (p = 0.039) responses significantly worsened as the inflammation progressed. The presence of diabetes insipidus correlated well with advanced stages of neurohypophysitis (p = 0.025).

Conclusions. Epithelial stratification in the RCC is caused by inflammation that may extend into the adjacent adenohypophysis or neurohypophysis and overwhelm the hypophysis, resulting in panhypopituitarism. Transsphenoidal excision may represent the best choice for treatment, at least for cases of RCC in which there is partial impairment of hypophysial function.

Key Words • Rathke cleft cyst • inflammation • stratified epithelium • hyperplasia • metaplasia • hypophysitis

Rathke cleft cysts, which are considered to arise in the remnants of the Rathke pouch, an invagination of the stomodeum, are intrasellar or suprasellar cysts composed of tall, well-differentiated columnar epithelia with both ciliated and goblet cells. In some cysts, however, basal or reserve cells proliferate and undergo squamous metaplasia, resulting in a histological profile that is indistinguishable from that of craniopharyngiomas.

The various types of cuboidal and columnar epithelia undergo a similar change, such as basal cell hyperplasia or squamous metaplasia, resulting from persistent local irritation, chronic inflammation, or neoplasia. The variety of histological features of RCC epithelia may result from similar persistent stimulation. Reports show that RCCs are occasionally accompanied by a foreign-body type of inflammation around the cyst wall. One source of persistent RCC stimulation might be inflammation.

Inflammation is a characteristic response of mammalian tissue to injury. Tissue damaged by inflammation is usually replaced by a proliferation of parenchymal elements (regeneration) or by the nonspecialized elements of connective tissue or fibrosis (repair). In epithelial tissue, the regeneration process often results in complete restoration of the original tissue. Under various circumstances, however, proliferating cells in areas such as the lung and uterus are transformed into hyperplastic or squamous metaplastic epithelial cells.

In the present study we investigated whether persistent inflammation is reflected in more extensive histological changes in RCC epithelium. Patients with RCCs were classified according to duration of epithelial inflammation and epithelial changes, and other clinical features were compared.

Clinical Material and Methods

Patient Population

We studied 20 patients known to have RCCs based on findings of MR imaging and/or pathological studies. All
patients underwent surgery at the Department of Neu-rosurgery, Hiroshima University Hospital, between 1986 and 1998.

Magnetic Resonance Imaging

Magnetic resonance imaging was performed at a low magnetic field strength (0.1 tesla) in two patients, an inter-

medate magnetic field strength (0.5 tesla) in two, and a high magnetic field strength (1.5 tesla) in 16, as previously
described.\textsuperscript{15}

In patients harboring RCCs without an epithelial lining,
diagnosis was based on findings of a single, uniloculated,
sharply demarcated, noncalcified, homogeneous intrasellar
and/or suprasellar mass on MR images.

The volume of the RCC was calculated according to
the formula\textsuperscript{29} for an ellipsoid: \( \text{volume} = \frac{\text{height} \times \text{width} \times \text{length}}{2} \times 0.5 \text{ mm}^3 \).

Endocrinological Studies

All endocrinological tests were performed with the
patients at rest after an overnight fast. Anterior pituitary func-
tion was tested by checking insulin tolerance and by admin-
istering both TSH-releasing hormone (500 \( \mu \)g) to measure
levels of TSH and prolactin, and LH-releasing hormone
(100 \( \mu \)g) to measure levels of LH and FSH. Concentrations
of serum GH, cortisol, TSH, prolactin, LH, and FSH were
determined using a radioimmunoassay, which was de-
scribed in an earlier study\textsuperscript{18} in which the normal basal val-
ues and normal responses to stimuli used in this study were
also described.

Surgical Procedures

Patients underwent transsphenoidal and/or tran-
cranial surgery. Informed consent was obtained from all partici-
pants for partial removal of the cyst wall.
Rathke cleft cyst and epithelial change

### Histological Studies

Surgical specimens were routinely fixed in 10% buffered formalin, embedded in paraffin, and stained with hematoxylin and eosin. The paraffin sections were immunohistochemically stained with avidin–biotin complex and monoclonal antibodies. The monoclonal antibodies used in the immunohistochemical studies included the following: anti–human leukocyte common antigen; anti-CD45R0 (clone UCHL1, T cell) and anti-CD20cy (clone L26, B cell) (Dako Corp., Carpinteria, CA); and antivinvolinucrin antibody (Novocastra Laboratories Ltd., Newcastle, UK).

### Classification of Epithelial Cell Lining

A pathologist (T.N.) blinded to the rest of the histological and clinical findings conducted the classification of epithelial cell lining.

We considered RCC epithelium to be typical when either ciliated columnar or cuboidal cells were present in a single row; we considered the epithelium to be changed if its appearance was anything other than typical. Initially, we classified RCC epithelium according to the number of rows of epithelial cells: a single row (single epithelium group) or multiple rows (stratified epithelium group).

The single epithelium group was divided into two subgroups according to the structure of the constituent cells: single ciliated columnar cell lining, composed of well-differentiated columnar epithelium with both ciliated and goblet cells (Fig. 1a), and flattened cuboidal cell lining, some of which was compressed and poorly preserved.

The RCC stratified epithelium group without hyperplasia or metaplasia was described as stratified ciliated columnar cell lining, consisting of a basal layer and a layer of columnar ciliated epithelium. The RCC stratified epithelium group with hyperplasia or metaplasia was divided into three subgroups according to the structure of the constituent cells: basal cell hyperplasia (Fig. 1b), columnar cell hyperplasia (Fig. 1c), and squamous metaplasia (Fig. 1d). Squamous metaplasia was confirmed by immunohistochemical staining with antivinvolinucrin antibody (Fig. 1e).

Several different lesions were often identified in the same tissue section. Such multiple lesions were evaluated as a percentage of the entire epithelium in each section.

### Classification of Inflammation in the RCC Epithelium and the Hypophysis

A pathologist (T.F.) blinded to the rest of the histological and clinical findings classified the progress of epithelial cell lining.

According to its progression, inflammation was classified as acute, a stage characterized by the migration of neutrophilic leukocytes; subacute, a transitional stage between acute and chronic inflammation, during which there is migration of both neutrophils and lymphocytic leukocytes; chronic, during which the infiltration is predominated by lymphocytes, fibroblasts, granulocytes, macrophages, epithelioid cells, and giant cells; and end stage, in which the main contribution to the inflammation is composed of nonspecialized elements of connective tissue and fibrosis accompanied by capillary proliferation.

### Statistical Analysis

We used the Fisher exact test to compare categorical variables and the Mann–Whitney U-test to compare continuous variables. All probability values are based on two-tailed tests.

### Results

#### Clinical Presentation

The ages of the 20 patients (nine men and 11 women) in this study ranged from 22 to 74 years (mean 54.9 years).

The presenting signs and symptoms in the patient population were visual and endocrinological. Visual changes involving decreased acuity or field deficits were found in 11 patients (55%). Polyuria and polydipsia were present in five patients (25%). Anterior pituitary dysfunction is described later.

#### Findings on MR Images

Both T₁- and T₂-weighted images were obtained in all patients (Table 1). On T₁-weighted images the lesions displayed high (six patients), iso- (three patients), low (nine patients), or mixed-signal intensity (two patients). On T₂-weighted images the signals were high (15 patients), iso- (one patient), low (two patients), or mixed intensity (two patients).

The volume of each RCC was calculated based on the relevant MR image. Twenty patients underwent MR examinations before their first operations, and three before their second operations. The volumes of the lesions ranged from 120 to 9488 mm³ (mean ± standard deviation 2711 ± 1904 mm³).

#### Surgical Findings

Initially, 17 patients underwent transsphenoidal surgery and three patients underwent transcranial surgery. In three cases, a second operation was required and the transcranial approach was used for those surgeries. In the three patients in whom the transcranial approach was used during the first operation, the preoperative diagnosis had been craniopharyngioma. All patients underwent aspiration of cyst contents, with partial resection of the cyst wall.

During the operations, the cyst contents were found to be yellowish (six patients), whitish (eight patients), whitish yellow (four patients), or clear (two patients; Table 1). The coefficient of viscosity was high in 18 patients and zero in two.

#### Classification of RCC Epithelium

Microscopic examination of surgical specimens that had been stained with hematoxylin and eosin detected epithelial cell lining in 13 surgical specimens. Six of these specimens belonged to the single epithelium group (four were composed of single ciliated columnar cells and two were composed of flattened cuboidal cells), and the other seven specimens belonged to the stratified epithelium group (Table 1). Of the latter seven specimens, five displayed basal cell hyperplasia, one columnar cell hypoplasia, and two squamous metaplasia components.

We investigated whether there was a correlation between epithelial cell classification and findings on MR images or cyst contents; no correlation could be found (p > 0.05).
### TABLE 1

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Stage of Epithelial Inflammation</th>
<th>Composition of Epithelium (%)</th>
<th>MR Imaging Signal</th>
<th>Cyst Contents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>SCCC Lining</td>
<td>FCC Lining</td>
<td>SCCL</td>
</tr>
<tr>
<td>Group 1: single epithelium†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>67, F</td>
<td>none</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>37, M</td>
<td>none</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>60, F</td>
<td>none</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>53, F</td>
<td>acute</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>70, F</td>
<td>acute</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>70, F</td>
<td>subacute</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Group 2: stratified epithelia†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>58, F</td>
<td>chronic</td>
<td>0</td>
<td>0</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>48, F</td>
<td>chronic</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>48, M</td>
<td>chronic</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>48, F</td>
<td>chronic</td>
<td>0</td>
<td>0</td>
<td>80</td>
</tr>
<tr>
<td>11</td>
<td>54, F</td>
<td>chronic</td>
<td>0</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>12</td>
<td>70, M</td>
<td>chronic</td>
<td>0</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>13</td>
<td>63, M</td>
<td>end stage</td>
<td>15</td>
<td>0</td>
<td>65</td>
</tr>
</tbody>
</table>

* BCH = basal cell hyperplasia; CCH = columnar cell hyperplasia; CV = coefficient of viscosity; FCC = flattened cuboidal cell; H = high intensity; I = isointense; L = low intensity; M = mixed intensity; SCCC = single ciliated columnar cell; SCCL = stratified ciliated columnar layer; SM = squamous metaplasia; T1 = T1-weighted image; T2 = T2-weighted image; W = whitish; Y = yellowish; + = present; − = absent.

† p = 0.0027 for comparison with stage of epithelial inflammation.

---

**Fig. 2.** Photomicrographs of lesions in which the adenohypophysis has been infiltrated by various inflammatory processes. a: Case 9 (first operation). Anterior pituitary cells have been infiltrated by inflammatory cells, although they remain relatively well preserved. b: Case 9 (first operation). Adenohypophysis has been infiltrated by neutrophilic leukocytes (acute stage of inflammation). c: Case 8 (first operation). Anterior pituitary cells have been infiltrated by inflammatory cells, although they remain relatively well preserved. d: Case 8 (first operation). Adenohypophysis has been infiltrated by both neutrophils and lymphocytic leukocytes (subacute stage of inflammation). e: Case 11. Anterior pituitary cells have been destroyed by inflammatory infiltration. f: Case 11. Adenohypophysis has been infiltrated predominantly by lymphocytes, fibroblasts, granulocytes, and macrophages (chronic stage of inflammation). g: Case 8 (second operation). Section demonstrating a few remaining pituitary cells embedded in connective tissue, and fibrosis accompanied by capillary proliferation (end-stage inflammation). H & E, original magnifications × 513 (a, c, and e), × 1416 (b), × 1026 (d and f), and × 484 (g).
Rathke cleft cyst and epithelial change

Evaluation of Inflammation in RCC Epithelium

The number and variety of inflammatory cells infiltrating the cyst epithelium or subjacent stroma (epithelial inflammation) were evaluated during an immunohistochemical study by using anti–leukocyte common antigen, anti–UCHL1, and anti–L26 antibodies. Three patients were free of inflammation, whereas two had acute, one subacute, six chronic, and one end-stage epithelial inflammation. Most infiltrating lymphocytes were stained with both UCHL1 and L26 antibodies.

Among the six patients whose cysts were in the single epithelium group, three displayed none, two acute, and one subacute epithelial inflammation. Of the seven patients whose cysts were in the stratified epithelium group, however, six displayed chronic and one end-stage epithelial inflammation.

The stage of epithelial inflammation correlated well with the type of epithelium group: early stages of inflammation in the single epithelium group and chronic or end-stage inflammation in the stratified epithelium group (p = 0.0027).

We examined the correlation between epithelial inflammation and MR imaging findings or cyst contents; however, these factors did not correlate with epithelial inflammation stage (p < 0.05).

Evaluation of Inflammation in the Adenohypophysis

The adenohypophysis was identified by applying hematoxylin and eosin to 18 surgical specimens obtained during the first operation. The extent and variety of inflammatory cells infiltrating the adenohypophysis were examined in the same manner as epithelial inflammation (Fig. 2). We found inflammation in 10 specimens: acute in four, subacute in two, chronic in three, and end-stage inflammation in one specimen.

Three patients underwent surgery for recurrent RCC. The inflammatory cells had infiltrated the adenohypophysis of all of these patients, and the extent of inflammation had markedly increased by the time of the second operation (in Case 3 from none to the chronic stage, in Case 9 from the acute to the chronic stage, and Case 8 from the subacute to the end stage).

The adenohypophysis was therefore histologically inspected in a total of 21 specimens (18 at the first operation and three at the second operation). Thirteen of these specimens were determined to be at some stage of the inflammatory process (acute in four, subacute in two, chronic in five, and end stage in two specimens).

Endocrinological Findings in the Anterior Pituitary Gland

A total of 23 endocrinological analyses were performed in this study (20 at the first operation and three at the second). After excluding the endocrinological data of three patients (that of one patient who did not undergo postoperative endocrinological study and that of two patients in whom the adenohypophysis was not histologically identified), the results of the remaining 20 endocrinological studies (17 obtained at the first operation and three at the second) were included in the subsequent analysis (Tables 2–4).

The volume of the RCC, type of surgical procedure, preoperative response of anterior pituitary hormones, and postoperative responses of prolactin, LH, and FSH did not correlate with the progression of adenohypophysitis (p > 0.05). In contrast, postoperative GH (p = 0.019), cortisol (p = 0.027), and TSH (p = 0.039) responses significantly deteriorated as inflammation progressed.

Evaluation of Inflammation in the Neurohypophysis

The neurohypophysis was demonstrated in eight surgical specimens by applying hematoxylin and eosin. One specimen was obtained during the second operation. Inflammation was detected in seven of the eight specimens (subacute in two, chronic in one, and end-stage inflammation in four specimens; Fig. 3 and Table 5).

One patient with chronic and four patients with end-

---

TABLE 2

<table>
<thead>
<tr>
<th>No. of Patients With Disturbance of APH (%)</th>
<th>GH†</th>
<th>Cortisol</th>
<th>TSH‡</th>
<th>PRL§</th>
<th>LH¶</th>
<th>FSH**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000–2000</td>
<td>1 of 2 (50)</td>
<td>0 of 2 (0)</td>
<td>1 of 2 (100)</td>
<td>1 of 2 (50)</td>
<td>0 of 2 (100)</td>
<td>1 of 2 (50)</td>
</tr>
<tr>
<td>&gt;2000</td>
<td>6 of 8 (75)</td>
<td>5 of 9 (56)</td>
<td>3 of 9 (33)</td>
<td>4 of 8 (50)</td>
<td>6 of 8 (75)</td>
<td>6 of 8 (75)</td>
</tr>
<tr>
<td>≥4000</td>
<td>2 of 3 (67)</td>
<td>1 of 3 (33)</td>
<td>1 of 3 (33)</td>
<td>0 of 3 (0)</td>
<td>1 of 3 (33)</td>
<td>3 of 3 (100)</td>
</tr>
</tbody>
</table>

* The probability values for comparisons between all pituitary endocrine functions and size of RCC were greater than 0.05. Abbreviations: APH = anterior pituitary hormone; PRL = prolactin.
† Two patients in whom GH examination was not performed are excluded.
‡ One patient in whom TSH examination was not performed is excluded.
§ One patient in whom PRL examination was not performed is excluded.
¶ One patient in whom LH examination was not performed is excluded.
** One patient in whom FSH examination was not performed is excluded.
stage neurohypophysitis suffered from permanent diabetes insipidus, whereas one patient in whom there was no inflammation and two who exhibited subacute neurohypophysitis did not have this disease (Table 5). The presence of diabetes insipidus significantly correlated with advanced stages of inflammation (p = 0.025), but not with the volume of the RCC or with the type of operative procedure (p > 0.05).

Discussion
Pathophysiological Mechanisms of Hypophysitis in Patients With RCCs

Although inflammatory lesions of the pituitary gland are rare, various forms have been reported. Autoimmune disorders, such as lymphocytic adenohypophysitis and lymphocytic infundibuloneurohypophysitis, have been considered to be causative factors in the development of hypophysitis. Other inflammatory lesions are characterized by a chronic granulomatous process containing multinucleated giant cells; such a profile can occur in cases of syphilis, tuberculosis, and sarcoidosis.

In patients who presented with an absence of caseous granuloma, tuberculosis and syphilis could be ruled out and systemic sarcoidosis could be viewed as unlikely because of a lack of evidence of multiorgan involvement. In addition, autoimmune hypophysitis was also unlikely, given that the inflammatory cells infiltrating the RCC epithelium or hypophysis in patients in our series were primarily composed of T and B lymphocytes. Therefore, the hypophysitis might have been caused by the RCC.

One cause of inflammation of the RCC is thought to be infection and abscess formation in the cyst.17 In the pres-

---

**TABLE 3**

| Surgical Approach | GH† | Cortisol | TSH‡ | PRL§ | LH|| | FSH** |
|-------------------|-----|---------|------|------|-----|-----|-----|
| preop state       |     |         |      |      |     |     |     |
| TS                | 11 of 16 (69) | 5 of 16 (31) | 6 of 15 (40) | 6 of 16 (38) | 10 of 16 (63) | 10 of 16 (63) |
| TC                | 2 of 2 (100)  | 2 of 4 (50)  | 1 of 4 (25)   | 1 of 3 (33)   | 2 of 3 (67)    | 1 of 3 (33)    |
| postop state      |     |         |      |      |     |     |     |
| TS                | 8 of 16 (50)  | 5 of 16 (31) | 5 of 15 (33) | 4 of 16 (25) | 8 of 16 (50) | 11 of 16 (69) |
| TC                | 2 of 2 (100)  | 2 of 4 (50)  | 3 of 4 (75)   | 1 of 3 (33)   | 2 of 3 (67)    | 2 of 3 (67)    |

* The probability values for comparisons between all pituitary endocrine functions and surgical approaches were greater than 0.05. Abbreviations: TC = transcranial; TS = transsphenoidal.
† Two patients in whom GH examination was not performed are excluded.
‡ One patient in whom TSH examination was not performed is excluded.
§ One patient in whom PRL examination was not performed is excluded.
|| One patient in whom LH examination was not performed is excluded.
** One patient in whom FSH examination was not performed is excluded.

---

**TABLE 4**

| Stage of Adeno-hypophysitis | GH† | Cortisol | TSH‡ | PRL§ | LH|| | FSH** |
|-----------------------------|-----|---------|------|------|-----|-----|-----|
| preop state                 |     |         |      |      |     |     |     |
| none                        | 4 of 8 (50) | 2 of 8 (25) | 2 of 7 (29) | 2 of 8 (25) | 4 of 8 (50) | 4 of 8 (50) |
| acute                       | 2 of 3 (67)  | 1 of 3 (33)  | 1 of 3 (33)  | 1 of 3 (33)  | 3 of 3 (100)  |
| subacute                    | 2 of 2 (100) | 0 of 2 (0)   | 0 of 2 (0)   | 1 of 2 (50)  | 2 of 2 (100) | 1 of 2 (50)  |
| chronic                     | 3 of 3 (100) | 2 of 5 (40)  | 2 of 5 (40)  | 2 of 4 (50)  | 3 of 4 (75)  | 2 of 4 (50)  |
| end                          | 2 of 2 (100) | 2 of 2 (100) | 2 of 2 (100) | 1 of 2 (50)  | 2 of 2 (100) | 1 of 2 (50)  |
| postop state                |     |         |      |      |     |     |     |
| none                        | 2 of 8 (25)†† | 1 of 8 (12)‡‡ | 2 of 7 (29)§§ | 2 of 8 (25) | 3 of 8 (38) | 5 of 8 (63) |
| acute                       | 2 of 3 (67)†† | 1 of 3 (33)‡‡ | 0 of 3 (0)§§ | 0 of 3 (0)   | 1 of 3 (33) | 3 of 3 (100) |
| subacute                    | 1 of 2 (50)†† | 0 of 2 (0)†† | 0 of 2 (0)§§ | 0 of 2 (0)   | 1 of 2 (50) | 1 of 2 (50) |
| chronic                     | 3 of 3 (100)†† | 3 of 5 (60)‡‡ | 4 of 5 (80)§§ | 1 of 4 (25) | 3 of 4 (75) | 2 of 4 (50) |
| end                          | 2 of 2 (100)†† | 2 of 2 (100)‡‡ | 2 of 2 (100)§§ | 2 of 2 (100) | 2 of 2 (100) | 2 of 2 (100) |

* Unless otherwise specified, the probability values for comparisons were greater than 0.05.
† Two patients in whom GH examination was not performed are excluded.
‡ One patient in whom TSH examination was not performed is excluded.
§ One patient in whom PRL examination was not performed is excluded.
|| One patient in whom LH examination was not performed is excluded.
** One patient in whom FSH examination was not performed is excluded.
†† p = 0.019 for comparison with stage of adenohypophysitis.
‡‡ p = 0.027 for comparison with stage of adenohypophysitis.
§§ p = 0.039 for comparison with stage of adenohypophysitis.
ent cases, however, no organisms were demonstrated in the inflamed tissue. The inflammation was therefore aseptic rather than septic. In previous reports, many authors have described the mechanisms underlying inflammation in the RCC epithelium.\(^1,7,11,13,14,20\) Oka, et al.\(^13\) have suggested that granulation tissue surrounding the RCC epithelium might be induced by mucus secreted by the goblet cells of the cyst wall. Past studies have included cases of granulomatous hypophysitis that were caused by ruptured intrasellar RCCs.\(^1,7,11,13,14,20\) The mucus is a strong stimulator of tissue. These observations indicate that the inflammation within and surrounding the RCC epithelium in the present cases might have been a reactive response to cyst contents.

Changes in the Epithelium of an RCC

In some cases, the acute stage of the inflammation process subsides, but the stimulus persists long enough to evoke subsequent chronic inflammation, followed by rearrangement of the injured epithelium, resulting in a stratified columnar cell layer with or without hyperplasia.\(^12\) Under some circumstances, these regenerated cells can transform into metaplastic squamous cells.\(^12\) This stratified change in the epithelium is presumably a reaction to a deleterious factor in which the reaction may be protective rather than harmful.

Endocrinological Features

In this study, all patients underwent aspiration of cyst contents with partial surgical excision of the cyst wall, which should have brought about a global cessation of compression without inducing additional damage to hypophysial tissue. The surgical procedure—transsphenoidal or transcranial—did not correlate with postoperative pituitary dysfunction. Deficiency in GH, cortisol, and TSH secretion following surgery and the presence of diabetes insipidus significantly correlated with the progressive staging of inflammation in the adenohypophysis or neurohypophysis. Therefore, postoperative pituitary function was thought to be affected not by surgical damage, but mainly by inflammatory hypophysial damage. Moreover, all patients with RCC and end-stage adenohypophysitis also had panhypopituitarism. The destructive changes would likely have overwhelmed the entire pituitary gland if the duration of hypophysitis had been prolonged by persistence of the causative factor. Thus, hypophysitis must be identified in patients with RCCs as soon as possible to avoid total destruction of the hypophysis by RCC inflammation.

Clinical Considerations

Exposure to inflammation causes the RCC epithelium to stratify as inflammation progresses. The inflammation spreads into the subjacent hypophysis, resulting in pituitary dysfunction. Stratification of the RCC epithelium may be an index of the duration of hypophysitis. Moreover, the sudden onset of pituitary dysfunction at the time of follow-up in asymptomatic patients with RCC indicates epithelial inflammation, which results in an overwhelming of the hypophysis. As demonstrated in the present cases, hypophysitis does not diminish as long as causative factors, such as the contents of the RCC, remain in the hypophysis. In such cases, surgical removal should be considered.
Conclusions

Inflammation in the cyst epithelium and subjacent stroma was more advanced in the stratified epithelial group than in the single epithelial group. This suggests that exposure to inflammation causes RCC epithelium to stratify as the inflammation progresses.

The transsphenoidal excision of an RCC that is associated with hypophysitis, which is easily detected by endocrinological examination, should be considered as a possible treatment option. In particular, surgical intervention may be justified in cases in which there is a sudden onset of pituitary dysfunction, but the nature of the association between these disorders should be clarified prior to selection of surgery as the first-line treatment.

Acknowledgments

The authors thank Megumi Nishimura and Hiroaki Ueki for their excellent technical assistance.

References


Manuscript received August 15, 2000. Accepted in final form September 25, 2001. Address reprint requests to: Seiji Hama, M.D., Department of Neurosurgery, Hiroshima University School of Medicine, 1-2-3 Kasumi, Minami-ku, Hiroshima 734–8551, Japan. email: ml-hns@hiroshima-u.ac.jp.