Spectrum of Different Types of Hypophysitis: A Clinicopathologic Study of Hypophysitis in 31 Cases

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Abstract

Hypophysitis has been histologically classified into five types: lymphocytic hypophysitis (LYH), granulomatous hypophysitis (GRH), xanthogranulomatous hypophysitis (XGH), xanthomatous hypophysitis (XH), and necrotizing hypophysitis. The present study evaluated 31 cases of hypophysitis to clarify their characteristic clinicopathologic features. The lesions were histologically classified into four groups: LYH (22 cases) including lymphocytic adenohypophysitis (LAH) (19 cases) and lymphocytic infundibuloneurohypophysitis (LINH) (3 cases), GRH (5 cases), XGH (2 cases), and XH (2 cases). In each group, the pituitary gland showed lymphocytic infiltration associated with focal or diffuse hypophysial destruction of variable severity and fibrosis. Histologic and clinical overlap among different types of hypophysitis, especially between LAH and LINH, suggest that these entities may have similar etiologic background and/or represent different stages of the same lesion. Considering the sampling sites and clinical manifestations, LAH may not usually involve the neurohypophysis, but LINH may often extend to the adenohypophysis. A selective loss of adrenocorticotrophic hormone–positive cells was seen in two patients with LAH despite only very slight lymphoplasmacytic infiltration. This suggests that there may be at least two causative mechanisms for hypopituitarism in hypophysitis: nonspecific destruction of all types of adenohypophysial cells by severe inflammation and selective destruction of specific adenohypophysial cells.

Key Words: Hypophysitis; pituitary; histology.

Introduction

Hypophysitis is an infrequent inflammatory disease of pituitary gland and gives rise to clinical symptoms, such as diabetes insipidus (DI), headache, and visual disorder. Since the first report in 1962, more than 100 cases of hypophysitis have been described [1–51]. Histologically, hypophysitis includes five types: lymphocytic hypophysitis (LYH), granulomatous hypophysitis (GRH), xanthogranulomatous hypophysitis (XGH), xanthomatous hypophysitis (XH), and necrotizing hypophysitis (NH). In terms of the site of inflammation, hypophysitis is also classified into two types: adenohypophysitis and infundibuloneurohypophysitis.

Lymphocytic adenohypophysitis (LAH) commonly affects females and is related to pregnancy or the postpartum period, but also occurs in nonpregnant women and even in men [1–12]. LAH may cause complete or partial hypopituitarism, headache,
and visual disorders mimicking nonfunctioning adenomas on clinical and radiologic grounds [7]. Some reports suggest an autoimmune pathogenesis in LYH [2–5,7,13–18], and approximately one third of cases of LAH have complications with autoimmune disease. These include thyroiditis, adrenalitis, Sjögren’s syndrome, hepatitis, and atrophic gastritis [2–4,7,13–19]. Both isolated and multiple anterior pituitary hormone–secreting cell deficiency have been described, such as adrenocorticotropic hormone (ACTH)–secreting cell loss in patients with LYH [2–5,13,15,17]. Recent reports on DI in LYH have led to an appreciation of the more varied settings in which this disorder may present [10,20,21]. Nonetheless, the natural history of this form of LYH is still uncertain.

Lymphocytic infundibuloneurohypophysitis (LINH) was first reported by Iimura et al. [22] and is thought to be a different entity from LAH. Inflammation occurring in the posterior pituitary and/or pituitary stalk is known to be able to result in DI [22–24]. LINH, like LAH, may also be associated with autoimmune disease [10]. However, the etiology remains unclear.

GRH is a rare lesion that is histologically characterized by nodular aggregates of multinucleated giant cells, histiocytes, and extensive plasma cell infiltration constituting granuloma [6,25]. It may be a part of systemic granulomatous disorders, such as tuberculosis, sarcoidosis, histiocytosis X, Wegener granulomatosis, and syphilis, or an isolated pituitary disease of Rathke cleft cyst or pituitary adenoma [26–29]. Patients who have granulomatous involvement of the pituitary without evidence of systemic granulomatous disease have been considered to have a disorder known as idiopathic giant cell GRH.

Folkert et al. [30] first reported three patients with XH in 1998 and later, to the best of our knowledge, there is only one subsequent case of XH in the literature [31]. It was histologically described that fragments of intact normal anterior pituitary with preserved vascular and reticulin network and regions of anterior pituitary were infiltrated by foamy histiocytes. However, the etiology of XH remains obscure.

NH, first described by Ahmed et al. [32] in 1993, consists of inflammation with necrosis in the hypothalamus, pituitary stalk, adenohypophysis, and infundibuloneurohypophysitis and is accompanied by pituitary hypofunction and DI.

Because biopsy or surgical specimens of inflammatory lesions of the pituitary are usually very small and the histologic image is variable in different sampling regions, interpretation of the whole image is quite difficult. Additionally, because hypophysitis can reportedly be diagnosed by magnetic resonance imaging (MRI) [22,33,34], though it is still controversial, biopsy in the future may be infrequently performed. Up to now there are only a few reports that discuss mutual relations of the different types of hypophysitis [20,33,35]. The present study assessed 31 hypophysitis cases, which may be the largest number histologically examined, in order to clarify further their mutual relations, clinicopathologic relations, mode of extension of LYH, and etiology.

Materials and Methods

Thirty-one formalin-fixed and paraffin-embedded hypophysitis specimens, from 23 female and 7 male patients, whose mean age was 43.8 yr (range: 27–72 yr), were obtained from 1980 to 2001 at the University of Tokushima (Tokushima, Japan), University of Toronto (Toronto, Canada), Tokyo Medical University (Tokyo, Japan), and Toranomon Hospital (Tokyo, Japan), and
six other hospitals (Japan) and were eligible for the primary study. Four cases of hypophysitis were from autopsy and the others were from biopsy or surgery. Standard hematoxylin and eosin stain and periodic acid-Schiff reaction were used for histologic examination. Electron microscopic studies were not performed in our series.

**Immunohistochemistry**

Immunohistochemistry using commercially available antibodies was used to characterize inflammatory areas for the presence of growth hormone (GH) (1:400 dilution, polyclonal; Dako, Kyoto, Japan), prolactin (PRL) (1:100 dilution, monoclonal; Immunotech S.A., Marseille, France), adrenocorticotropic (ACTH) (1:200 dilution, monoclonal; Dako), β-thyrotropin (thyroid-stimulating hormone [TSH]) (1:100 dilution, monoclonal; Dako), β-follicle-stimulating hormone (FSH) (1:100 dilution, monoclonal; Immunotech S.A.), β-luteinizing hormone (LH) (1:100 dilution, monoclonal; Immunotech S.A.), α-subunit (1:100 dilution, monoclonal; Immunotech S.A.), S-100 protein (1:500 dilution, polyclonal; Dako), CD3 (1:100 dilution, polyclonal; Dako), and CD79a (1:30 dilution, monoclonal; Dako). Immunostains were performed on 5-μm formalin-fixed and paraffin-embedded sections using the labeled streptavidin-biotin method (Dako), after routine sections deparaffinization, rehydration, blockade of endogenous peroxidase activity, and antigen retrieval. Sections to be stained for S-100 protein, CD3, and CD79a were pretreated with 10 μg/mL of proteinase K (Dako) in phosphate-buffered saline (PBS) for 10 min at room temperature prior to antigen retrieval. Sections were incubated at 4°C overnight in the primary monoclonal antibody (MAb), and for 1 h each at room temperature in biotinylated link antibody and peroxidase-labeled streptavidin. Sections were washed in PBS after each step. Antigen–antibody complexes were detected with the 3,3'-diaminobenzidine/H₂O₂ reaction, and sections were counterstained with hematoxylin. For negative controls, primary MAb were substituted with PBS in duplicate sections. Normal pituitary tissues were used for positive controls.

**Results**

**Clinical Findings**

The major presenting symptoms of each patient are summarized in Table 1. The distribution of different types of hypophysitis in two lobes is summarized in Table 2. Hypophysitis was located in the anterior pituitary in 24 of 31 cases (77.4%) and in the posterior pituitary in 9 of 31 cases (29.0%). Two cases involved both pituitary lobes. The ratio of men to women with anterior pituitary lesions was 5 to 17 and the ratio of men to women with posterior pituitary lesions was 2 to 7. The patient’s age and sex in case 6 and the age in case 17 were unknown.

Clinical symptoms in each type of hypophysitis are summarized in Table 3. Five patients (cases 1, 10, 11, 18, and 23) (16.1%) suffered from headache, and two of those (cases 1 and 23) also had visual disturbances. Nine patients (29.0%) had thyroid dysfunction (cases 3–9, 14, and 27), associated with pregnancy (cases 3–5), hypothyroidism (cases 4, 7, and 8), Hashimoto’s disease (cases 3, 9, and 27), or chronic thyroditis (cases 5 and 6). One patient (case 5) had chronic pancreatitis, and two (cases 5 and 14) had atrophy of the adrenal glands. In four patients (cases 7, 11, 29, and 30) (12.9%), partial or total pituitary hypofunction was documented. Five patients (cases 3, 20, 22, 25, and 30)
<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Site</th>
<th>DI</th>
<th>Headache</th>
<th>Pregnancy</th>
<th>Amenorrhea</th>
<th>Galactorrhea</th>
<th>Visual disorder</th>
<th>Autoimmune disease</th>
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<tbody>
<tr>
<td>1</td>
<td>54/F</td>
<td></td>
<td>AP</td>
<td>+</td>
<td>Postpartum</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lymphocytic adenohypophysitis</td>
</tr>
<tr>
<td>2</td>
<td>29/F</td>
<td></td>
<td>AP</td>
<td>+</td>
<td>Pregnancy (7 mo)</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ Hashimoto disease, thyroiditis, adrenal insufficiency</td>
</tr>
<tr>
<td>3</td>
<td>54/F</td>
<td></td>
<td>AP</td>
<td>+</td>
<td>Postpartum (4 mo)</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No ACTH cells, germinal centers</td>
</tr>
<tr>
<td>4</td>
<td>52/F</td>
<td></td>
<td>AP</td>
<td>+</td>
<td>Postpartum (9 mo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>5</td>
<td>51/F</td>
<td></td>
<td>AP</td>
<td>+</td>
<td>Postpartum (5 mo)</td>
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<td>Thyroiditis, pancreatitis, atrophy of adrenal gland</td>
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</tr>
<tr>
<td>6</td>
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<td></td>
<td>AP</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thyroiditis, Hypothyroidism</td>
</tr>
<tr>
<td>7</td>
<td>50/F</td>
<td></td>
<td>AP</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Severe fibrosis</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>59/F</td>
<td></td>
<td>AP</td>
<td>+</td>
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<td></td>
<td></td>
<td>Hypothyroidism, rheumatoid arthritis</td>
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<tr>
<td>9</td>
<td>50/F</td>
<td></td>
<td>AP</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hashimoto disease</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>51/M</td>
<td></td>
<td>AP</td>
<td>+</td>
<td></td>
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<td>Pernasal sinusitis, Hypoadrenocorticicism, severe fibrosis</td>
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</tr>
<tr>
<td>11</td>
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<td></td>
<td>AP</td>
<td>+</td>
<td></td>
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<td></td>
<td></td>
<td>Aromegaly, no adenoma</td>
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</tr>
<tr>
<td>12</td>
<td>54/M</td>
<td></td>
<td>AP</td>
<td>+</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Hypothyroidism, atrophy of adrenal gland</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>30/F</td>
<td></td>
<td>AP</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No ACTH cells</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>30/F</td>
<td></td>
<td>Both lobes</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Germinal centers</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>66/F</td>
<td></td>
<td>AP</td>
<td>+</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Germinal centers</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>53/F</td>
<td></td>
<td>AP</td>
<td>+</td>
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<td></td>
<td></td>
<td>Germinal centers</td>
<td></td>
</tr>
<tr>
<td>17</td>
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<td>AP</td>
<td>+</td>
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<td></td>
<td>Germinal centers</td>
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<tr>
<td>18</td>
<td>30/F</td>
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<td>Both lobes</td>
<td>+</td>
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<td></td>
<td></td>
<td></td>
<td>Germinal centers</td>
<td></td>
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<tr>
<td>19</td>
<td>30/F</td>
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<td>Both lobes</td>
<td>+</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>Germinal centers</td>
<td></td>
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</tbody>
</table>

**Lymphocytic infundibuloneurohypophysitis**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Site</th>
<th>DI</th>
<th>Headache</th>
<th>Pregnancy</th>
<th>Amenorrhea</th>
<th>Galactorrhea</th>
<th>Visual disorder</th>
<th>Autoimmune disease</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>27/F</td>
<td></td>
<td>PP</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>Lymphocytic infundibuloneurohypophysitis</td>
</tr>
<tr>
<td>21</td>
<td>56/F</td>
<td></td>
<td>PP</td>
<td>+</td>
<td>Dizziness</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stalk only</td>
</tr>
<tr>
<td>22</td>
<td>31/F</td>
<td></td>
<td>PP</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Stalk only</td>
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**Granulomatous hypophysitis**

<table>
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<tr>
<th>Case</th>
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<th>Sex</th>
<th>Site</th>
<th>DI</th>
<th>Headache</th>
<th>Pregnancy</th>
<th>Amenorrhea</th>
<th>Galactorrhea</th>
<th>Visual disorder</th>
<th>Autoimmune disease</th>
<th>Remarks</th>
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</thead>
<tbody>
<tr>
<td>23</td>
<td>51/F</td>
<td></td>
<td>AP</td>
<td>+</td>
<td>Postpartum</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lymphocytic infundibuloneurohypophysitis</td>
</tr>
<tr>
<td>24</td>
<td>57/F</td>
<td></td>
<td>AP</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Multinucleated giant cells, epithelial cells,媾血 lobes intact</td>
</tr>
</tbody>
</table>
| 25   | 51/F    |     | PP  | +  | Postpartum | +         |            |             |                |                 | Adenomas, epithelial granulomas, 
Fuchs' dystrophy, 
giant cells, germinal centers |
| 26   | 53/F    |     | Both lobes | + | Pregnancy | +         |            |             |                |                 | Granulomas, 
epithelial cells |
| 27   | 47/F    |     | Both lobes | + |          | +         |            |             |                |                 | Lymphocytic infundibuloneurohypophysitis |

**Xanthogranulomatous hypophysitis**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Site</th>
<th>DI</th>
<th>Headache</th>
<th>Pregnancy</th>
<th>Amenorrhea</th>
<th>Galactorrhea</th>
<th>Visual disorder</th>
<th>Autoimmune disease</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>48/M</td>
<td></td>
<td>PP+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Xanthogranulomatous hypophysitis</td>
</tr>
<tr>
<td>29</td>
<td>57/F</td>
<td></td>
<td>Both lobes</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Antinuclear antibody</td>
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**Xanthomatous hypophysitis**

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<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Site</th>
<th>DI</th>
<th>Headache</th>
<th>Pregnancy</th>
<th>Amenorrhea</th>
<th>Galactorrhea</th>
<th>Visual disorder</th>
<th>Autoimmune disease</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>42/F</td>
<td></td>
<td>AP</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Xanthomatous hypophysitis</td>
</tr>
<tr>
<td>31</td>
<td>72/F</td>
<td></td>
<td>Both lobes</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypoadrenocorticicism</td>
</tr>
</tbody>
</table>

*AP, anterior pituitary; PP, posterior pituitary; amenorrhea, amenorrhea; galacto., galactorrhea. Not apparent.
Table 2. Number of Cases of Different Types of Hypophysitis in Two Lobes

<table>
<thead>
<tr>
<th>Site/histologic diagnosis</th>
<th>Anterior pituitary (16 cases)</th>
<th>Both lobes (12 cases)*</th>
<th>Posterior pituitary (3 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAH</td>
<td>14 (14)</td>
<td>5 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>LINH</td>
<td>0 (0)</td>
<td>0 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>GRH</td>
<td>1 (1)</td>
<td>3 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>XGH</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>XH</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Numbers given in parentheses represent number of observed cases.
*AP, anterior pituitary; PP, posterior pituitary.

Table 3. Number of Cases Showing Clinical Symptoms in Each Type of Hypophysitis

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>Clinical symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>LAH</td>
<td>6</td>
</tr>
<tr>
<td>LINH</td>
<td>0</td>
</tr>
<tr>
<td>GRH</td>
<td>0</td>
</tr>
<tr>
<td>XGH</td>
<td>1</td>
</tr>
<tr>
<td>XH</td>
<td>0</td>
</tr>
</tbody>
</table>

(16.1%) had galactorrhea, and four of them (cases 3, 20, 25, and 30) had amenorrhea as well. Eight cases (cases 1–5, 23, 25, and 26) (25.8%) were associated with pregnancy: presenting during pregnancy in two patients (cases 2 and 26) and during the postpartum period in six (cases 1, 3–5, 23, and 25). The symptoms of the latter were noted up to 9 mo after delivery. Interestingly, only LAH or GRH were associated with pregnancy.

DI was present in 10 patients (cases 11, 12, 15, 16, 20, 22, 25, 28–30) (32.3%) (3 males and 7 females). Four patients with anterior pituitary lesions had LAH (two males and two females). For six patients with posterior pituitary lesions, there were two LINH cases, one GRH case, two XGH cases, and one XH case. The patients with LAH did not have autoimmune disorders and were not pregnant. One patient (case 25) had an onset during the postpartum period. The specimens in the four LAH cases were obtained only from anterior pituitary.

One patient (case 24) had pituitary adenoma and one patient (case 13) had acromegaly without evident pituitary adenoma.

Histological Findings

Lymphocytic Adenohypophysitis

Almost all cases of LAH showed an infiltration of both lymphocytes and plasma cells. In particular, case 1 showed severe infiltration of plasma cells and slight infiltration of lymphocytes and cosinophils. Multinucleated giant cells were characteristically absent. Epithelioid histiocytes were also not observed. Variable inflammation was sometimes found within the same case (cases 3 and 7). Scattered islands of preserved anterior pituitary cells were observed in inflamed or fibrotic areas (Fig. 1).
Fibrosis was noted in all of the 19 LAH cases, 5 of which (cases 1, 6, 9, 11, and 18) showed severe fibrosis. The specimens of cases 18 and 19 were obtained from both pituitary lobes. Case 18 showed mild lymphocytic infiltration in the posterior lobe,
and case 19 had severe lymphocytic posterior lobe infiltration. Lymphoid follicles were found in six cases (cases 3, 4, 7, 11, 18, and 19), four of which (cases 3, 11, 18, and 19) had secondary follicles with germinal centers (Fig. 2). In our LAH series, no necrosis or adenoma was observed.

Immunohistochemically, although the infiltrating lymphocytes were variable in the ratio of B- to T-cells among the adenohypophysitis cases, the overall ratio of B- to T-cells was equal (Fig. 3A, B). S-100 protein-positive folliculostellate cells (FSCs) were nearly absent in the inflammatory lesions, whereas these cells were found in residual normal pituitary tissue. A complete loss of ACTH immunopositive cells was demonstrated in five cases (cases 3, 5, 7, and 14). Two of them, autopsy cases (cases 5 and 14), were affected by a very slight lymphoplasmacytic infiltration (Fig. 4). The other three cases (cases 3, 4, and 7) showed severe lymphoplasmacytic inflammation with loss of ACTH cells.

**Lymphocytic Infundibuloneurohypophysitis**

The histologic findings of LINH were similar to those of LAH, showing diffuse infiltration of lymphocytes and plasma cells with fibrosis in the posterior pituitary or stalk (cases 20–22) (Fig. 5). The specimens of cases 20 and 21 were obtained only from pituitary stalk and the infiltrating cells were mainly lymphocytes. Granulomas or multinucleated giant cells were not seen.

**Granulomatous Hypophysitis**

Five GRH cases were found in the biopsy specimens, including four cases (cases 23, 24, 26, and 27) in the anterior pituitary gland and one (case 25) in the posterior pituitary. Two specimens (cases 24 and 27) had epithelioid granulomas. Multinucleated giant cells, but not epithelioid histiocytes, were observed in case 23.

In less involved areas, the lobular architecture of the pituitary gland was preserved. Sparse plasma cells and varying numbers of lymphocytes were present in the interstitial tissue. Each case had various degrees of lymphocytic infiltration, and fibrosis was present in the interstitial tissue. A high degree of lymphocytic infiltration with foreign body giant cells concomitant with Rathke cleft cyst was noted in two cases (cases 25 and 26). The cyst was lined by columnar epithelium, and the cyst walls and surrounding regions were mainly infiltrated by lymphocytes. Foreign body giant cells were identified in the area with lymphocytic infiltration (Fig. 6). Immunohistochemically, B- and T-cells were present in equal proportion.

**Xanthogranulomatous Hypophysitis**

XGH (cases 28 and 29) was located mainly in the posterior pituitary. Multinucleated giant cells and epithelioid cells accompanied by xanthoma cells were observed in association with lymphocytic infiltration (Fig. 7). In case 29, abscess associated with neutrophilic exudates was found in the periphery. Neutrophilic exudates and xanthoma cells around the region of the lymphocytic infiltration were seen in case 28. As in LYH and GRH, in less involved areas, the lobular architecture of the pituitary glands was preserved. Rathke cleft cyst or neoplasia was not identified in the specimens. Immunohistochemically, S-100 protein immunopositive FSCs were not demonstrated.

**Xanthomatous Hypophysitis**

In case 31, an autopsy case, xanthoma cell infiltration with foamy granular cytoplasm and slight lymphocytic infiltration, was noted in both lobes, with the anterior pituitary comparatively spared (Fig. 8). Infiltration of xanthoma cells was also present in the hypothalamus. Intracellular
or interstitial hemosiderin was absent. In the other XH case (case 30), many xanthoma cells were present in the anterior pituitary and posterior pituitary tissue was not identified in the specimen. No necrosis or granuloma was found in either case. Xanthoma cells had PAS-positive cytoplasmic granules and were immunonegative for S-100 protein.

Discussion

We histologically and immunohistochemically analyzed 31 cases of hypophysitis, which may be the largest series among similar studies reported. These cases included LYH, GRH, XGH, and XH. NH was not found in our series.

LYH is apparently an autoimmune disease in the anterior lobe of the pituitary and nearly 20–50% of LYH patients have associated autoimmune disorders [1, 3, 14–19]. Hypothyroidism and chronic lymphocytic thyroiditis have been reported as common findings [1, 2, 15, 16, 18]. In the present study, eight LAH cases (42%) presented with dysfunction of the thyroid and three cases (15.9%) showed atrophy of the adrenal glands. Engelberth et al. [36] reported that symptoms and signs of pituitary deficiency owing to LYH appeared to be most common at 6–12 mo after deliv-
ery and that 18% of normal women had antipituitary antibodies in the postpartum period, whereas all were negative for the antibodies during pregnancy and at delivery. These findings indicate that normal parturition may result in antipituitary antibodies. In our series, one LAH case presented during pregnancy and four were postpartum. Three of the latter were associated with autoimmune disorders, supporting the concept that LAH may involve postpartum autoimmune mechanisms.

Cosman et al. [7] reported that pituitary masses usually cause a characteristic, progressive hormone loss, with levels of GH and FSH/LH reduced first, followed by levels of TSH and ACTH and, last, PRL. By contrast, as seen in our study, LAH frequently results in isolated ACTH deficiency or combined adrenal and/or thyroid deficiencies in the presence of normal gonadal function. Patients presenting with these unusual patterns of pituitary hormone levels are clinically suspect to have LAH rather than a pituitary mass. Because ACTH cells are selectively vulnerable, LAH with selective loss of ACTH cells usually shows a very slight lymphocytic infiltration that is not visualized radiographically. Such cases may present the first stage of inflammation in LAH. In the present study, we observed two cases with selective loss of ACTH immunoreactive cells. As to the reason for the loss of ACTH cells, it has been speculated to be the result of a targeted autoimmune attack during late pregnancy or in the postpartum period [3, 4]. This hypothesis was supported by the finding of Poulard et al. [37] that human pituitary ACTH-secreting cells normally had an affinity for human antibody through the Fc portion of immunoglobulin.

Inflammation of the hypothalamic-neurohypophyseal system is known to be a cause of central DI [22–24]. Hoshimaru et al. [38] reported a case of LINH with DI, forming a small mass lesion in the neurohypophysis and/or infundibulum. The anterior lobes of these LINH cases were normal and signs of hypopituitarism were absent [7, 22, 23]. Recently, LINH patients with dysfunction of the adenohypophysis and isolated thickening of the stalk have been reported. DI also has been described in patients with LAH [5, 21, 32, 34, 39–42]. In the two LINH cases with DI reported by Nishioke et al. [20], inflammation of the adenohypophysis was demonstrated histologically and stalk thickening was indicated on MRI. Although inflammation of the neurohypophysis was not histologically identified, it was still suggested that the principal site of inflammation was in the neurohypophyseal system and that the adenohypophysitis might be secondarily affected by extension of the inflammatory process. Other studies describing that histologically diagnosed LYH cases with DI frequently have a thickened stalk resembling LINH on MRI support this hypothesis [5, 11].

In our study, four LAH cases (18.2%) and two LINH cases (9.1%) had a complication of DI. These LAH cases (two males and two females) did not have autoimmune disorders. The two female patients were not pregnant. The specimens of these four LAH cases were obtained from anterior pituitary alone, leaving open the possibility that the adenohypophysis may have been secondarily affected by extension of the inflammation of LINH. In other words, a primary lesion of the posterior pituitary may cause an inflammation to involve both pituitary lobes more easily than a primary lesion of the anterior pituitary. Thus, LYH involving both pituitary lobes may be diagnosed as LAH if the biopsy or surgical specimens of inflammatory lesions are very small or the specimens are obtained only from the anterior pituitary.
It has been reported that the infiltrating lymphocytes of LYH are mainly T-cells [22,23], but in the present study, the lymphocytes consisted of an equal ratio of B- and T-cells. Some germinal centers were also identified. There is only one report that described no FSCs demonstrable by S-100 protein staining in the inflammatory lesion [12]. In our series, some S-100 protein-positive FSCs were found in residual normal pituitary and in slight inflammatory lesions, but not in severe inflammatory lesions. Therefore, FSCs may gradually vanish with the progression of the inflammation in LAH.

GRH is rare and distinguished from LYH histologically by nodular aggregates of multinucleated giant cells, histiocytes, and numerous plasma cells [6,25]. GRH may be either part of a systemic granulomatous disorder or an isolated pituitary disease [26–29]. If other conditions are excluded by clinical and histologic examination, GRH is termed idiopathic. In our five GRH cases, systemic granulomatous diseases were not identified by clinical or histologic means, suggesting that they may be idiopathic. Rathke cleft cyst is occasionally accompanied by foreign body inflammatory cell infiltration around the cyst wall, sometimes involving the adjacent pituitary gland. The rupture of a Rathke cleft cyst may also be a cause of giant cell GRH owing to mucous spillage causing an inflammatory process in the pituitary gland. In two of our GRH cases, lymphocytic infiltration with foreign body giant cells concomitant with Rathke cleft cyst was found. It was considered that those cases were associated with ruptured Rathke cleft cyst, although rupture was not apparent in the sections. If Rathke cleft cyst or foreign body giant cells are not observed in very small pituitary sections, the diagnosis may be LYH.

There are pathologic similarities in ultrastructural findings between LYH and GRH. These include the presence of inactive, degenerated secretory cells; focal oncocytic changes in the secretory cells; and inflammatory cells within the periacinar membrane [33]. Moreover, the presence of Hashimoto’s thyroiditis in some GRH cases and the presence of GH, ACTH, and antimacrophage immunoreactivity in the cytoplasm of giant cells indicate an autoimmune pathogenesis in GRH as well as LYH [35]. In our series, GRH, like LYH, included one case (20%) with DI, three cases (60%) during pregnancy or in the postpartum period, and one case (20%) with thyroid dysfunction. In particular, the patients with pregnancy were identified only in LYH and GRH cases. These findings suggest that the two different groups have the same pathogenic background or represent different stages of the same lesion.

Folkerth et al. [30] first described three XH cases that showed fragments of residual anterior pituitary and the interstitium of anterior pituitary infiltrated by foamy histiocytes that were immunoreactive for CD68, the macrophage marker, and negative for S-100 protein and CD1a. Ultrastructurally, the foamy and granular cells contained abundant cytoplasmic lipid droplets and membrane-bound debris, as well as focal, electron-dense, amorphous debris; Birbeck granules were absent, and numbers of mitochondria and lysosomes were not increased. However, there are some reports that describe foamy macrophages in suprasellar Rathke cleft cyst or a colloid cyst of the third ventricle [52–57]. In our two cases with xanthoma cell infiltration diagnosed as XH, such a cyst was not identified. Furthermore, case 31 showed an infiltration of xanthoma cells also in the hypothalamus.

We encountered two hypophysitis cases showing granulomatous changes with
multinucleated giant cells, epithelioid cells, and lymphocytic infiltration accompanied by xanthoma cells. We considered the xanthoma cells in these cases to be different from those in the GRH and XH cases—possibly a reaction to debris or microorganisms occurring secondarily to inflammation with lymphocytes and neutrophils—and termed the cases XGH.

In summary, our study of 31 hypophysitis cases revealed that there are more than a few overlapping histologic and clinical findings among different classifications of hypophysitis, especially between LAH and LINH, suggesting that they may have similar etiologic background and/or represent different stages of the same lesion. In addition, considering the sampling sites and clinical manifestations, LAH may not usually involve the neurohypophysis but LINH may often extend to the adenohypophysis. Finally, there may be at least two causative mechanisms for adenohypophysial hypofunction in hypophysitis: nonspecific destruction of all types of the adenohypophysial cells by severe inflammation; and selective loss of specific adenohypophysial cells, such as ACTH cells.

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