Hypophysitis in surgical and autopsial specimens

Abstract We present the clinical and histological findings of 11 cases of inflammatory anterior pituitary lesions, 8 of which were obtained during surgery and 3 of which were obtained from autopsies. Additionally, we extended the conventional classification of pituitary inflammatory disease by the new entity "secondary hypophysitis". Of the surgically obtained specimens 5 consisted of inflammatory extension into the pituitary gland out of the surrounding tissue. In all of these patients the inflammation originated from an additional tumor in the sellar region (4 craniopharyngiomas, 1 prolactinoma). These will be referred to as "secondary hypophysitis", an entity which has not yet been mentioned in the literature. Of the remaining 6 cases, 2 were granulomatous hypophysitis, 2 pituitary abscesses, 1 lymphocytic hypophysitis, and 1 showed extensive scarring of the anterior pituitary lobe due to preceding lymphocytic hypophysitis. At histological examination the basic structure of the anterior pituitary was maintained in all cases. Relative counts of hormone-producing cells were normal. In secondary hypophysitis, the affected area was composed of fibrous tissue and granulation tissue. B and T lymphocytes were present in equal amounts. Granulomas were not found. Inflammatory infiltrates, granulation tissue and fibroses were seen in different proportions. Based on our results and three other cases reported in the literature so far, we think that the presently used classification of pituitary inflammatory diseases lacks an entity which describes a non-abscess-forming inflammation of the pituitary gland originating from an associated pathological process. Therefore, we introduced the term secondary hypophysitis to describe this fourth entity of pituitary inflammatory disease.

Key words Hypophysitis - Pituitary abscess - Pituitary tumor - Immunocytochemistry

Introduction

Inflammatory diseases of the pituitary gland are rare and are mostly published in the form of case reports. Most cases of granulomatous hypophysitis and pituitary abscess which were described in the first half of this century had their origin in systemic inflammatory diseases [3, 17, 19, 43, 57]. In contrast to these, case reports of pituitary inflammations without pathological agents (lymphocytic hypophysitis [4, 5, 10, 11, 16, 20, 27, 29, 35, 42, 51], idiopathic granulomatous hypophysitis [8, 14, 41, 43, 48, 53, 55], and sterile, i.e., aseptic pituitary abscesses [13, 30, 34, 44, 45, 50]) dominated the literature in the second half of this century. Regarding the epidemiology of inflammatory pituitary lesions, symptomatic inflammations have to be distinguished from those which are asymptomatic. According to Buchfelder et al. [8] and our own data, approximately 0.5% of patients who were operated because of sellar processes, turned out to have an inflammatory pituitary disease. Assuming an incidence of sellar tumors of 20 cases per 1,000,000 per year [2, 36], one can estimate a yearly incidence of pituitary inflammatory diseases of 1 case per 10,000,000 population. This incidence is much lower than the rate of lymphocytic (7.2%) and of granulocytic (0.7%) inflammations within the pituitary gland, which was found in an unselected post mortem series of 1,030 cases by Saeger et al. [46]. However, in only one of these autopsialy examined patients, could lymphocytic hypophysitis be diagnosed, being supported by clinical signs of pituitary insufficiency prior to death.

In the present study, we focus on the histological features of the different types of pituitary inflammatory diseases, based on the experience that we gained in eight sur-
gical and three autopsy cases of inflammatory pituitary processes. Additionally, we try to establish "secondary" hypophysitis as a fourth separate entity of pituitary inflammatory disease.

Materials and methods

Patients

In our collection of more than 2,000 surgical specimens of sellar tumors (1971–1993), we found 8 cases of inflammatory pituitary disease (0.4%). Additionally, we have been examining the pituitaries of our postmortem cases routinely since 1991. Among the 1,077 pituitaries examined, 2 pituitaries revealed an inflammation (0.2%). Another case was obtained from a neighboring hospital.

Staging of the endocrine function

In the surgical patients, the evaluation of the preoperative endocrine function was based on basal plasma levels of all hormones of the anterior pituitary gland. Lowered growth hormone (GH) plasma levels were seen as an indicator of pituitary insufficiency only in adolescents, but not in adults. Diabetes insipidus was diagnosed when clinical symptoms and signs were present. According to the scheme used previously, we staged the pituitary function as follows [40]: intact pituitary function: all hormones of the anterior pituitary lobe within the normal range; partial pituitary insufficiency: one or two hormones of the anterior pituitary lobe below the normal range; and complete pituitary insufficiency: more than two hormones of the anterior pituitary lobe below the normal range.

In the postmortem patients, the evaluation of the endocrine function prior to death was based on the presence of clinical signs of hypopituitarism reported by the colleagues of the referring departments and the relatives of the patients. In addition, the functions of the endocrine glands controlled by the anterior pituitary lobe were examined by searching for signs of atrophy in case 11.

Surgical procedure

All eight patients whose surgical specimens of the anterior pituitary gland led to the diagnosis of a pituitary inflammatory disease, were operated by the transnasal-submucosal-transphenoidal approach. None of these patients had undergone previous pituitary surgery. In patients with an additional sellar tumor (nos. 1–5), small biopsies of the anterior pituitary lobe were taken to discriminate clearly between the pituitary gland and the tumor capsule [40]. In the patient with a pituitary abscess (no. 6), the abscess was evacuated. In the two patients with granulomatous hypophysitis (nos. 7 and 8), the operation was terminated after diagnosis of frozen sections showed a pituitary inflammation and that a pituitary tumor could be excluded.

Morphological methods

Pituitary tissue was fixed in 4% formaldehyde, embedded in paraffin and stained with hematoxylin-eosin and periodic acid-Schiff stain (PAS). Immunohistochemical studies were carried out using the following polyclonal (pc) or monoclonal (mc) antibodies (Dakopatts, Hamburg, Germany): GH (pc), rabbit, dilution 1:100; prolactin (pc), rabbit, 1:300; adrenocorticotropic hormone (pc), rabbit, 1:300; thyroid-stimulating hormone (pc), rabbit, 1:800; follicle-stimulating hormone (pc), rabbit, 1:250; luteinizing hormone (pc), rabbit, 1:700; α-subunit (pc), rabbit, 1:600; S-100 protein (pc), rabbit, 1:500; 4KB 5 (B lymphocytes) (mc), mouse, 1:20; BL 26 (B lymphocytes) (mc), mouse, 1:100; UCHL 1 (T lymphocytes) (mc), mouse, 1:150; and CD43 (T lymphocytes) (mc), mouse, 1:30.

For detection of the immunoreaction we used the Vectastain-ABC kit (Vector Laboratories, Burlingame, USA), consisting of a biotinylated anti-immunoglobulin antibody, an avidin solution and a solution of biotinylated horseradish peroxidase forming an avidin-biotinylated horseradish peroxidase complex. The substrate of the peroxidase was diaminobenzidine.

Results

The clinical symptoms, endocrinological findings, as well as the clinical and morphological diagnosis of our eight surgical and three postmortem patients with inflammatory pituitary disease are given in Table 1. Based on histological appearance and pathophysiological mechanism, we divided the pituitary lesions into the five following groups of inflammatory pituitary disease: secondary hypophysitis, pituitary abscess, granulomatous hypophysitis, lymphocytic hypophysitis and pituitary scarring due to preceding lymphocytic hypophysitis.

Secondary hypophysitis

The basic structure of the pituitary gland was maintained and only focally loosened. In all cases, granulation tissue was seen, which partially invaded the neighboring anterior pituitary tissue. In case 2, we also found giant cells of the foreign body type. In cases 1 and 4, the pituitary tissue showed focal interstitial fibrosis (Fig. 1). Cases 1, 3, and 4 revealed lymphocytic infiltrates of different intensities (Fig. 2). B and T lymphocytes were always seen in equal amounts. Granulomas were never encountered in secondary hypophysitis. In case 5, the abscess first developed in the necrotic tumor tissue and later on spread into the anterior lobe tissue. Necrosis and fibrin exudation were seen here. Some fibrin deposits and edema zones were also noted in case 4. Case 1 showed discrete bleeding and fibrin exudations and in case 2 a few iron-containing macrophages could be seen, indicating former hemorrhage. In all cases, however, we also found anterior pituitary tissue that was not invaded by granulation tissue or inflammatory infiltrates.

Pituitary abscess

Patient 6 was treated because of a meningitis 1 year prior to operation at an external hospital. Several cerebrospinal fluid (CSF) examinations at that time revealed a pleocytosis (380/3 cells). However, all CSF cultures remained sterile. The computed tomography (CT) scan, performed during this hospital stay, revealed an empty sella with a hyperdense weakly contrast-enhancing left-suprasellar mass. At endocrinological investigation, a complete pituitary insufficiency was detected. One year later, the suprasellar mass was unchanged on CT control examination. At endocrinological testing, the patient was still completely pituitary insufficient. The overall condition of the
<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Hypopituitarism</th>
<th>Preoperative clinical diagnosis</th>
<th>Morphological diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>f</td>
<td>Loss of vision</td>
<td>Hypogonadotropic hypogonadism</td>
<td>Cranioopharyngioma</td>
<td>Cranioopharyngioma with inflammation leading to secondary hypophysitis</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>m</td>
<td>Failure of sexual development</td>
<td>Complete, hyperprolactinemia: PRL = 28 µg/l (normal: 15 µg/l)</td>
<td>Cranioopharyngioma</td>
<td>Cranioopharyngioma with inflammation leading to secondary hypophysitis</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>m</td>
<td>Fatigue, impotence, loss of vision</td>
<td>Complete</td>
<td>Cystic pituitary tumor</td>
<td>Cranioopharyngioma with inflammation leading to secondary hypophysitis</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>f</td>
<td>Sec. amenorrhea, anorexia nervosa</td>
<td>Complete</td>
<td>Pituitary tumor (probably granular hypophysitis)</td>
<td>Cranioopharyngioma obviously originating from a regressed hypophysitis</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>f</td>
<td>Loss of vision headache, diabetes insipidus</td>
<td>Partial, hyperprolactinemia: PRL = 98 µg/l (normal: 26 µg/l)</td>
<td>Cystic pituitary tumor, hypophysitis?</td>
<td>Sparserly granulated prolactin-cell pituitary adenoma with necrosis leading to secondary hypophysitis</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>f</td>
<td>Intermittent signs of pituitary insufficiency, menigitis</td>
<td>Complete, diabetes insipidus</td>
<td>Pituitary abscess</td>
<td>Chronic pituitary abscess</td>
</tr>
<tr>
<td>7</td>
<td>41</td>
<td>f</td>
<td>Sec. amenorrhea, galactorrhoea</td>
<td>Partial, hyperprolactinemia: PRL = 29 µg/l (normal: 26 µg/l)</td>
<td>Hormone-inactive pituitary adenoma</td>
<td>Granulomatous hypophysitis</td>
</tr>
<tr>
<td>8</td>
<td>49</td>
<td>m</td>
<td>Loss of libido, fatigue</td>
<td>Complete</td>
<td>Hormone-inactive pituitary adenoma</td>
<td>Granulomatous hypophysitis</td>
</tr>
<tr>
<td>9</td>
<td>66</td>
<td>m</td>
<td>No pituitary related symptoms</td>
<td>None</td>
<td>Polytrauma</td>
<td>Lymphocytic hypophysitis</td>
</tr>
<tr>
<td>10</td>
<td>89</td>
<td>m</td>
<td>No pituitary related symptoms</td>
<td>None</td>
<td>Perforating carcinoma of sigmoid colon leading to septicopyemia</td>
<td>Pituitary abscess</td>
</tr>
<tr>
<td>11</td>
<td>65</td>
<td>m</td>
<td>Head injury, central dysregulation tumor suspected</td>
<td>Complete</td>
<td>Pituitary tumor</td>
<td>Pituitary fibrosis and scarring, as a residue of a former active lymphocytic hypophysitis, no tumor</td>
</tr>
</tbody>
</table>

*Presented at the 37th Symposium of the German Society of Endocrinology, 03-06 March 1993 in Berlin, Germany [38]
*Presented at the 4th Meeting of the European Neuroendocrine Association, 06-09 October 1993 in Lisbon, Portugal [39]
*Previously published [40]
*Presented at the 5th European Workshop on Pituitary Adenomas, 19-20 March 1991 in Venice, Italy [37]

Patient deteriorated continuously. Operation consisted of transnasal exposure of the cyst, drainage of the intrasellar abscess, and one biopsy of the anterior pituitary lobe. Histological examination showed granulation tissue, indicating an abscess wall. The neighboring anterior pituitary tissue showed focal fibrosis. One of our postmortem cases (no. 10) died of septicemia due to a perforating carcinoma of the sigmoid colon. This patient had no history of clinical signs of pituitary insufficiency. Autopsy revealed a small pituitary abscess measuring 0.2 cm in width (Fig. 3).

Idiopathic granulomatous hypophysitis

The basic structure of the pituitary gland was focally altered in those cases with granulomatous hypophysitis. The relative number of hormone-producing cells was normal. In case 7, there was no increase of proactin cells. Hyperprolactinemia was reactive due to pituitary stalk compression. The granulomas, which were found in the anterior lobe of the pituitary, were composed of epitheloid cells, giant cells, and some folliculostellate cells. Inclu-
Fig. 1 Secondary hypophysitis (case 4). Granulation tissue and fibroses are infiltrating the anterior pituitary lobe (arrow). Hematoxylin-eosin, × 260

Fig. 2 Secondary hypophysitis (case 1). Dense infiltrates of lymphocytes in the anterior pituitary lobe. Hematoxylin-eosin, × 185

Fig. 3 Pituitary abscess (case 10). Dense granulocytic infiltration with indistinctive borderline towards the anterior pituitary lobe (left). Hematoxylin-eosin, × 255

Fig. 4 Granulomatous hypophysitis (case 7). Multiple granulomas of epithelial cell type and lymphocytic infiltrates, mainly of T cell type. Anti-UCHL 1-peroxidase-antiperoxidase-hematoxylin. × 230

Fig. 5 Granulomatous hypophysitis (case 8). Granuloma with giant cells and some lymphocytes in the connective tissue. Arrow indicates the anterior pituitary lobe tissue. Hematoxylin-eosin. × 260

Fig. 6 Lymphocytic hypophysitis (case 9). Focal lymphocytic infiltrate in the anterior pituitary lobe. Hematoxylin-eosin, × 180
Lymphocytic hypophysitis

The first of our postmortem patients (no. 9) died due to polytrauma on the day of hospital admission. Based on the data obtained from the surgical department of our hospital and from the relatives of the patient, he did not present any clinical signs of anterior pituitary insufficiency or diabetes insipidus. His pituitary gland showed a focal lymphocytic infiltrate which consisted mainly of T lymphocytes. The infiltrate was seen mainly in the intermediate zone, but also in the neurohypophysis and adenohypophysis (Fig. 6). According to Saeger et al. [46], lymphocytic infiltration was found in 7.2% of unselected pituitaries. The infiltrates were not examined by immunohistochemistry. These infiltrates should not be confused with those found in lymphocytic hypophysitis, as seen in our case. Our study revealed more pronounced lymphocytic infiltrates, sometimes leading to destruction of the alveoli. As no pituitary disease was suspected in this patient, other endocrine organs were not examined histologically.

Discussion

The clinical symptoms of hypophysitis and pituitary abscess typically include hypopituitarism and sometimes visual disturbances. Radiologically, hypophysitis usually appears as a solid intrasellar mass [8, 11, 12, 15, 20], whereas pituitary abscess shows a cystic formation [13, 21, 31, 50]. Establishing the correct diagnosis preoperatively is difficult. Either type of hypophysitis mimicks non-secreting pituitary adenomas or sometimes prolactinomas if associated with additional hyperprolactinemia [10, 29]. A pituitary abscess can be misdiagnosed as a Rathke’s cleft cyst, craniopharyngioma or cystic pituitary adenoma.

<table>
<thead>
<tr>
<th>Type</th>
<th>Etiology</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary hypophysitis</td>
<td>Originating from neighboring tissue</td>
<td>[1, 18, 26, 40]</td>
</tr>
<tr>
<td>Pituitary abscess</td>
<td>Originating from neighboring tissue</td>
<td>[3, 6, 13, 22, 24, 30, 31, 33, 34, 44, 45, 49, 50, 52, 54, 58]</td>
</tr>
<tr>
<td>Granulomatous hypophysitis</td>
<td>Septicpemyc</td>
<td>[8, 21, 31, 56]</td>
</tr>
<tr>
<td></td>
<td>Idiopathic</td>
<td>[8, 14, 41, 43, 48, 53, 55]</td>
</tr>
<tr>
<td></td>
<td>Sarcoïdosis</td>
<td>[12, 28, 43]</td>
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<tr>
<td></td>
<td>Tuberculosis</td>
<td>[15, 17, 43]</td>
</tr>
<tr>
<td></td>
<td>Syphilis</td>
<td>[43]</td>
</tr>
<tr>
<td></td>
<td>Actinomycosis</td>
<td>[19, 57]</td>
</tr>
<tr>
<td></td>
<td>Histiocytosis X</td>
<td>[32]</td>
</tr>
<tr>
<td></td>
<td>Wegener’s granulomatosis</td>
<td>[23]</td>
</tr>
<tr>
<td>Lymphocytic hypophysitis</td>
<td>Autoimmune disorder</td>
<td>[4, 5, 10, 11, 16, 20, 27, 29, 35, 42, 51]</td>
</tr>
</tbody>
</table>
Presently, the classification of hypophysitis is based on the histological type of inflammation. Granulomatous hypophysitis is differentiated from the lymphocytic type [9], and is characterized by a noncaseating granulomatous inflammation of the adenohypophysis with well-formed granulomas and prominent multinucleated giant cells. In contrast to previous descriptions [14, 41, 53], our two cases of granulomatous hypophysitis were free of anisotropin pro- lactin-containing cytoplasmic inclusions in the giant cells. However, as described by Püschel et al. [41], we mainly found T lymphocytes in the inflammatory infiltrates of our cases of granulomatous hypophysitis [41]. Lymphocytic hypophysitis is characterized by excessive lymphocytic infiltrations of the adenohypophysial interstitium, occasionally accompanied by plasma cells, histiocytes and lymphoid follicles with germinal centers. Well-formed granulomas and giant cells are not seen [9]. Pituitary abscess represents a third entity [3, 6, 8, 13, 21, 22, 24, 30, 31, 33, 34, 44, 45, 49, 50, 52, 54, 56, 58]. It is characterized by the formation of pyogenic necrosis within the pituitary gland [9]. However, inflammatory reactions within the surrounding pituitary tissue are found in only a minority of cases [13]. Cultures of pus reveal bacteria or fungi as causative agents in about 50% of the cases [6, 22, 31].

The presently used purely histological classification does not give information about the different pathophysiological mechanisms leading to the inflammatory diseases of the pituitary gland. However, various pathophysiological mechanisms are related to and are associated with the different histological types of hypophysitis. “Classical” lymphocytic hypophysitis has been designated as an autoimmune disorder [7, 25, 35]. It typically affects women during pregnancy or shortly after delivery [4, 5, 10, 11, 16, 27, 29, 42], and only rarely affects males [20, 35, 51]. “Classical” granulomatous hypophysitis can be either the manifestation of one of the systemic granulomatous diseases, as demonstrated in Table 2, or idiopathic [8, 14, 41, 43, 48, 53, 55].

In general, the majority of pituitary abscesses develop in a setting of bacterial meningitis, sinusitis, sepsis or immunosuppression, thereby giving a logical explanation for the pathogenesis of the lesion [9, 13, 21, 22, 24, 31, 56]. Some cases develop as a late complication after pituitary surgery [31]. Additionally, pituitary abscesses have been found to be associated with other pathological processes such as craniopharyngiomas [30, 34, 44], Rathke's cleft cysts [33, 49, 50] or pituitary adenomas [3, 31, 45, 52, 54, 58]. Therefore, a preceding necrosis of a coexisting tumor has been assumed to be the cause of sterile pituitary abscess formation [6, 13, 31].

In contrast, a non-abscess forming inflammation of the pituitary gland, which develops as an extension of an associated inflammation-inducing sellar process, is not included in the presently used classification. In previous reports, this form of inflammation was classified according to its histological appearance as either lymphocytic [26, 40], or granulomatous [1, 18] hypophysitis. However, as was noted by all authors, in all these cases the pathophysiological mechanism leading to the hypophysitis seems to be clearly different from the classical cases of lymphocytic and granulomatous hypophysitis [1, 18, 26, 40].

In the series of Puchner et al. [40], secondary hypophysitis occurred in 3 out of 28 craniopharyngioma patients examined (11%). Considering the extremely low incidence of either form of hypophysitis, this relatively high incidence of secondary hypophysitis in craniopharyngioma patients was explained by the fact that no systematic investigation of the anterior pituitary lobe in these patients – either in operative or in autopsy series – has been performed so far.

Of course, small biopsies are not representative of the entire anterior pituitary lobe. We cannot, therefore, evaluate to what extent the whole anterior pituitary is invaded by the inflammation. In addition to inflamed pituitary tissue, we always found some relatively unaffected pituitary tissue. Furthermore, we were able to demonstrate histo-

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Differential diagnosis between the different types of pituitary inflammatory diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>Granulomatous hypophysitis</td>
</tr>
<tr>
<td>Folliculostellate cells</td>
<td>Included in single granulomas</td>
</tr>
<tr>
<td>Inflammatory infiltrates</td>
<td>Granulomas, lymphocytes: mainly T lymphocytes</td>
</tr>
<tr>
<td>Granulomas</td>
<td>Containing giant cells</td>
</tr>
<tr>
<td>Basic structure</td>
<td>Focally coarsened or destroyed</td>
</tr>
<tr>
<td>Localization of inflammation</td>
<td>Dissimilated</td>
</tr>
</tbody>
</table>


