Introduction

Lymphoepithelial hypophysis: A rare variant of the anterior hypophysis

Key Words: Lymphoepithelial hypophysis; primary tumor; morphology; immunocytochemistry

Abstract

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Light and electron microscopic findings and correlation to clinical appearance

Lymphoepithelial hypophysitis:
a dense lymphocytic infiltration of the anterior lobe of the pituitary. This disease was mostly seen at autopsies [1], but recently it has been reported with increasing frequency. Most of the patients are women during pregnancy or in the postpartum period [10–12], but it can also be seen in men [13–15]. Although the etiology so far is unclear, it is thought to be an autoimmune process, because it is often found in combination with rheumatic diseases, thyroiditis, parathyroiditis, pernicious anemia, or adrenalitis.

Lymphocytic hypophysitis often leads to enlargement of the pituitary gland, resulting in such symptoms as headache, visual disturbances, or endocrine disturbances such as partial pituitary insufficiency or panhypopituitarism [16,17]. The tentative diagnosis of pituitary tumor is reached when a space-occupying lesion within the sella turcica is found using CT or MRI scan in combination with endocrine, neurological, or visual disturbances, and surgery is performed. Histologic examination of lymphocytic hypophysitis shows infiltrates of lymphocytes and plasma cells and sometimes granulomas [4]. Feigenbaum et al. [11] showed that a patient who was given prednisone could regain normal vision as well as show a decrease in intrasellar mass size. If lymphocytic hypophysitis could be treated with corticosteroids to suppress the inflammatory response, it is important to distinguish it from the other forms of hypophysitis. Up to now, approx 100 cases of lymphocytic hypophysitis have been reported in the literature. Because of the increasing significance of this disease, we studied morphological structure, immunohistochemical staining, and, in one case, the ultrastructural morphology of six cases with lymphocytic hypophysitis and correlated the results to clinical features.

Materials and Methods

Patients

Six patients with lymphocytic hypophysitis were found in our files (about 2500 surgical pituitary specimens) collected from 1970–1996. Five of them underwent neurosurgery because of an expanding lesion within the sella turcica. The operations were performed by the transnasal-submucosal-transsphenoidal approach. Two of the patients were operated on at the Department of Neurosurgery, University of Heidelberg, one patient at the Department of Neurosurgery, University of Hamburg, and two patients at the Department of Neurosurgery, Hospital Berlin–Neukölln. One case was seen at a routinely performed autopsy. The clinical features of the patients are summarized in Table 1.

Morphological Methods

For light microscopy, tissue was fixed in 4% formaldehyde, embedded in paraffin, 4–6-μm thick sections were cut and stained with hematoxylin-eosin and periodic acid Schiff (PAS). Immunocytochemistry was performed by an indirect method using antibodies directed against human growth hormone (monoclonal, Biogenex, San Ramon, CA, 1:400), adrenocorticotropic hormone 24-39 (monoclonal, Dako, Glostrup, Denmark, 1:50), follicle-stimulating hormone (monoclonal, Coulter Immunotech, Marseilles, France, 1:200), α-subunit (monoclonal, Immunotech, 1:100), prolactin (monoclonal, Immunotech, 1:100), thyroid stimulating hormone (monoclonal, Immunotech, 1:100), luteinizng hormone (monoclonal, Immunotech, 1:200), S-100 protein (polyclonal, Dako, 1:800), CD 20 (clone L 26, monoclonal, Dako, 1:100), CD 45 RA (clone 4 KB 5, monoclonal, Dako, 1:20), CD 43 (clone DF-T 1, monoclonal, Dako, 1:40), CD
in all six cases. The intensity of the initial microscope showed lymphocytic infiltrates studies of the anterior pituitary by light

**Results**

Extramedullary lymphomas (ELS) (see the amount of fibrosis were assessed by an
and the number and distribution of cells and the

EM 9 72, sections were then examined

a transmission electron microscope (Z.E.L.)

with sectioned with immunohistochemistry and stained with


genius (DAKO, 1:200), antihuman lymphocyte antigen

human myeloid/histiocyte antigen M6

human lymphocyte antigen common an

1:200), antihuman lymphocyte common

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**Hypophysitis**
Table 2. Immunocytochemical Data of Cases

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* - no immunoreactivity; (+), very few cells immunoreactive; +, up to 10% of cells immunoreactive; ++, 11–30% of cells immunoreactive; ++++, more than 30% immunoreactive cells.

Fig. 1. Case 1: Anterior pituitary with fibrosis and differently dense infiltration of lymphocytes. Some preserved acini. Hematoxylin-eosin (magnification ×330).

Fig. 2. Case 2: Anterior pituitary with dense infiltration of lymphocytes. Many preserved prolactin cells. Anti-prolactin ABC (magnification ×330).

three small cysts. Three cases contained posterior lobe tissue. One case showed a lymphocytic infiltrate adjacent to slight invasion of basophil cells. Another case showed an increased number of transformed glial cells and the third a loose arrangement of pituicytes. In one case, tissue of the capsule was obtained, which was interspersed with lymphocytes. The folliculo-stellate cells were not affected by the inflammation.

The results of the immunocytochemistry are summarized in Table 2. The residual adenohypophyseal cells comprised different cell types. Prolactin and growth hormone reactive cells were seen (Fig. 2). TSH immunoreactive cells were only occasionally observed. The number of gonadotropic cells varied.

Immunostaining of the infiltrate showed, that it consisted mainly of T-lymphocytes as determined by CD 45 RO (Fig. 3) and CD 43 positivity. There were sparse B-lymphocytes, being positive for L 26 and CD 45 RA. In two cases, B-lymphocytes could not be detected. The infiltrating macrophages showed an immunoreactivity for CD 68 and Mac 387. Common leucocytic antigen was expressed in the infiltrates.

The electron microscopical findings showed some ruptured acini and remnants of damaged adenohypophyseal cells (Fig. 4). The acini were mingled with lymphocytes. An inflammation accompanied by plasma cells, lymphocytes, macrophages and sparse eosinophils and neutrophils could be seen. Single pituitary cells contained enlarged lysosomal bodies or oncocytic changes.
Lymphoctic Hypophysitis is a rare condition where the lymphocytic infiltration of the pituitary gland results in the destruction of hormone-producing cells. This leads to hormone deficiencies and clinical manifestations that resemble hypopituitarism.

**Discussion**

We examined six cases of lymphocytic hypophysitis and found an infiltration of lymphocytes and plasma cells in the hormone-producing areas of the pituitary gland. These findings suggest a possible mechanism for the development of hypopituitarism in patients with lymphocytic hypophysitis. The infiltration of lymphocytes in the portal areas is a critical feature in the pathogenesis of this condition.

**Figure 1**

A photomicrograph of a lymphocytic infiltrate with a granular and some lymphocytes (hematoxylin).

**Figure 2**

A case of a patient with bundles of collagen, damaged adenosine.

**Figure 3**

A case of a patient with infiltration of lymphocytes and anti-CD20.
ysin and rheumatoid factor. Autoantibodies against pituitary tissue were not tested in this patient.

We could also show the dominance of the female sex in patients with lymphocytic hypophysitis. However, none of the women in our study was pregnant or postpartum when undergoing neurosurgery.

In a former study, we found lymphocytic infiltrates in a collective out of 1030 (7.2%) post-mortem pituitaries [20]. In the majority of cases these were seen in the intermediate zone [21]. The findings in the autopsy case in our study agree with these results. We found lymphocytic infiltrates in the intermediate zone, spreading to the posterior lobe and the anterior lobe. The alveolar structure was maintained.

Nishioka [22] described in his study the proportion of the residual adenohypophysial cells revealed by immunocytochemistry. The results of the immunocytochemistry in our study showed a different amount of residual adenohypophysial cells in each pituitary. As Nishioka presented the case report of only one patient, this cannot be regarded as representative. Further studies performed on a larger sample might aid the evaluation of residual adenohypophysial cells and help to answer the question whether certain adenohypophysial cells may be more susceptible to destruction than others.

We were not able to show a correlation between hyperprolactinaemia and location of the infiltrate. One possible explanation for hyperprolactinaemia in patients with lymphocytic hypophysitis could be stalk compression resulting in negative inhibitory action of dopamine by decreased dopamine delivery [1]. One of the patients showed in MRI an intrasellar mass that seemed to wall in the pituitary stalk. In our three cases with hyperprolactinaemia, no surrounding tissue was obtained, so that histologically we cannot give a statement about possible destruction of posterior lobe tissue. But the edema associated with the inflammation could lead to enlargement of the pituitary and this mass in turn could account for patients' complaints of headache and visual disturbances.

Lymphocytic hypophysitis leads to an enlargement of the pituitary gland resulting in the tentative diagnosis of pituitary tumor and surgery. Two such patients were included in our study. One patient had an intrasellar mass, the pituitary stalk was walled in, and the tentative diagnosis was a macroadenoma. In the other patient, MRI showed an intrasellar cystic space occupying lesion with slight suprasellar expansion leading to the tentative diagnosis of a craniopharyngioma.

Abe et al. [14] suspect the origin of diabetes insipidus as a result of inflammation extending to the neurohypophysis. In our study, two patients were preoperatively diagnosed as having a diabetes insipidus, one patient postoperatively. No neurohypophysial tissue was obtained from any of these patients, so we could not investigate whether the neurohypophysis was involved in the inflammation and following destruction of posterior lobe tissue. A further explanation could be inhibition of the axoplasmatic transport of vasopressin from the hypothalamus to the posterior lobe by mass effect of the inflammation and enlargement of the pituitary.

Puchner et al. [23,24] reported three cases of associated lymphocytic hypophysitis in patients with cystic craniopharyngiomas. They assumed a local induction of the lymphocytic hypophysitis by rupture of the cystic wall and consecutive extravasation of the cystic fluid into the parenchyma [25]. This has to be regarded as a secondary hypophysitis. In our study, the histological examination of two patients revealed a hypophysitis next to the remnants of a cyst. There was extensive cica-
References

To examine the issue of this paper,

Acknowledgment

Different therapies

numerous primary treatments, but requires a
show lymphocytic hypophysitis come
of expanding primary lesion, we can see
of expanding primary lesion. In the different
It is important to include lymphocytic
causes from other forms of lymphopapillitis
Taken together, lymphocytic hypophysitis
because of the extremely high incidence and
treatment difficult to detect when
have sign of a lymphocytic hypophysitis
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