We report a rare case of lymphocytic hypophysitis followed by dacryoadenitis. Lymphocytic hypophysitis is a rare disease that can easily be mistaken for neoplastic proliferation. Because combination with rheumatoid arthritis, thyroiditis, or pernicious anemia is frequent, an immunological pathogenesis is likely.

To our knowledge, this is the first description of lymphocytic hypophysitis in association with dacryoadenitis. Histologically, both hypophysitis and dacryoadenitis demonstrate a lymphocytic infiltrate consisting of CD3+ T cells and CD20+ B cells. Lymphoproliferative diseases, infectious diseases, and vasculitis should be included in the differential diagnosis.

Swelling of the lacrimal gland can be caused by infectious dacryoadenitis, which in turn often results from obstruction of the nasolacrimal duct or changes in the canaliculi. Secondary acute dacryoadenitis is usually caused by systemic infection, such as endemic parotiditis, herpes zoster ophthalmicus, or infectious mononucleosis. Inflammatory changes of the lacrimal gland are seen in association with Graves disease, granulomatous diseases such as sarcoidosis, or Sjogren syndrome. A unilateral infiltration of the lacrimal gland without systemic disease is rare.

About 100 cases of lymphocytic hypophysitis have been reported in the literature. Like lymphocytic dacryoadenitis, hypophysitis is often seen in patients with autoimmune disorders like adrenalitis, gastritis type A, or Hashimoto thyroiditis. However, there is, to our knowledge, no report of an association of lymphocytic hypophysitis with dacryoadenitis. Although knowledge about immunological diseases is growing, the origin and pathophysiology of this symptom complex are still unknown. In this study we describe the histological and immunocytochemical findings in the symptom complex of lymphocytic hypophysitis and dacryoadenitis.

REPORT OF A CASE

HISTORY

A 22-year-old woman was first seen at our clinic in August 1996 with a swelling of the left lacrimal gland that persisted for 3 weeks. She reported that swelling and pain did not respond to 1 week of systemic antibiotic treatment with 300 mg of clindamycin. She was also using steroid eye drops and topical ointment at night. Ibuprofen (600 mg) was being taken orally to relieve pain. The patient was receiving a hormone substitution therapy owing to insufficiency of the hypophysis after transsphenoidal hypophysectomy. This had been performed in March 1995 for a suspected hypophysal tumor. Prior to the operation the patient had had amenorrhea, but did not suffer from visual disturbances. Eighteen months after surgery, her medication regimen consisted of 37.5 mg of prednisolone, estrogen and gestagen, and somatropin.

CLINICAL APPEARANCE AND LABORATORY TEST RESULTS

The patient had a painful, tender swelling of the lacrimal gland with a section-mark-shaped upper eyelid (Figure 1) without inflammatory signs. On ophthal-
mic examination there was full visual acuity for both eyes and no signs of inflammation of the anterior segment. The fundus and optic nerve showed no pathological changes. Perimetry confirmed normal outer visual field borders for both eyes.

Findings from physical examination revealed no signs of systemic rheumatoid or lymphatic disease. There was no sign of peripheral lymphadenopathy. Abdominal and thyroid ultrasonographic tests yielded normal results, as did the chest x-ray film.

All hematological parameters were within normal limits, as were protein electrophoresis and immunoglobulin fractions. Rheumatological screening did not indicate a systemic collagenous or rheumatological disease. There was no vitamin B₁₂ deficiency.

Serologically there were no titers for human immunodeficiency virus, herpes simplex virus, varicella zoster virus, or Epstein-Barr virus infection. Gonorrhea, salmonellosis, borreliosis, yersiniosis, syphilis, and mycoplasmosis had also been excluded. There was no evidence for viral or bacterial infection in the lacrimal fluid. Parasitological screening for toxoplasmosis and *Toxocara canis* and screening of the stool for worm infection were negative.

Thyroid hormone screening showed all parameters within normal limits. Computed tomography and magnetic resonance imaging of the orbits and neurocranium showed a significant enlargement of the left lacrimal gland, most likely due to dacryoadenitis and compression of the chiasma, which could be growing residual pituitary tissue (as indicated by the history of partial hypophysectomy).

**THERAPY**

After the possibility of infectious disease was ruled out, systemic antibiotic treatment was stopped. A biopsy specimen was obtained to exclude a lymphoblastomatous infiltration of the lacrimal gland. Because of the possible immunological cause of the disease, the patient was treated with high-dose steroids (prednisolone, 100 mg/d intravenously, in addition to her hormone substitution therapy). A few days after initiation of the steroid therapy, regression of the periorbital and lacrimal gland swelling was observed. The associated pain also vanished during treatment. Steroid therapy was slowly tapered and the appearance of the orbit returned to normal.

Two years later, the patient has not experienced any recurrence. Medication was stopped except for hormone substitution therapy.

**HISTOLOGICAL FINDINGS**

Specimens of both the hypophysis and lacrimal gland were fixed in 4% formaldehyde, embedded in paraffin, and cut into 4- to 6-µm sections. Sections were stained with hematoxylin-eosin and periodic acid–Schiff. Immunocytochemistry was performed by an indirect method using antibodies. Sections were examined and the number and distribution of cells were assessed.

Both specimens of the hypophysis and the lacrimal gland showed lymphocytic infiltrates (**Figure 2** and **Figure 3**). Both hypophysis and lacrimal gland tissue showed a normal glandular and acinar pattern. There was no evidence of caseous necrosis, epitheloid granulomas, or abscesses within the infiltrates.

The medium-dense infiltrate of lymphocytes in the specimen of the anterior pituitary gland spread among the interstitium and partly into the alveoli. The structure of the remaining anterior lobe was normal. There was fibrosis, which led...
to broadening of the septa. The residual adenohypophysal cells comprised different cell types. Immunocytochemistry showed multiple growth hormone– and prolactin-reactive cells (Figure 4). Thyroid-stimulating hormone immunoreactive cells were only occasionally observed. There were a few corticotropin-positive cells.

The biopsy specimen of the lacrimal gland showed a well-differentiated lacrimal gland parenchyma. The interstitial septae were broadened and infiltrated by lymphocytes. In small areas the periductal infiltrate invaded the acini and the excretory ducts. A few excretory ducts showed signs of obstruction with granulocytes. Immunoglobulin staining of the specimen showed a low expression of \( \lambda \) as well as \( \kappa \) light chains. There were IgG- and IgM-positive plasma cells (Figure 5).

Immunostaining of the infiltrate of both specimens showed a mixed population of CD3+ T cells and CD20+ B cells. Common leukocytic antigen was expressed in the infiltrates. In neither specimen were there signs of a lymphoblastomatous infiltrate. The similarity of the infiltration of the pituitary and lacrimal glands indicated an autoimmune process.

**COMMENT**

We report the symptom complex of lymphocytic hypophysitis followed by lymphocytic dacryoadenitis in a healthy young woman. If systemic disorders are apparent, lacrimal glands are usually bilaterally affected and the disease is chronic. Our patient had an acute onset of dacryoadenitis, which remained unilateral. A lymphoblastomatous cause of the infiltration was excluded by immunohistochemistry.

In the literature, there is evidence that lymphocytic hypophysitis has an autoimmunopathic cause. However, we did not find any association with other autoimmunological diseases such as rheumatoid arthritis, thyroiditis, or pernicious anemia. Although there was no systemic correlation, another type of glandular tissue (the lacrimal gland) was affected. This association has not been reported before.
Histologically, the lymphocytic infiltrate consisted of B and T lymphocytes. Other authors report that, in hypophysitis, infiltrates mainly consist of T lymphocytes. As the infiltration pattern found in those cases was similar to the pattern found in the hypophysitis of our patient, a common cross-reacting antigen may be responsible.

Lymphocytic hypophysitis leads to an enlargement of the pituitary gland, which may result in the diagnosis of pituitary tumor as in our patient, whose tentative diagnosis was macroadenoma. The magnetic resonance imaging scan of the neurocranium at the time of the dacryoadenitis, 1 year after transsphenoidal hypophysectomy, showed enlargement of the residual pituitary gland, suggesting recurrence of the lymphocytic hypophysitis. While the patient continued the hormone substitution therapy, no evidence of progressing insufficiency of the residual hypophysis was found after examination of her hormone levels. When we compared the results of immunostaining of the hypophysis (growth hormone and prolactin highly positive) with the peripheral hormone level before hypophysectomy, we found a coincident low level of growth hormone. Other pituitary hormones might have low immunoreactivity due to edema and inflammatory infiltrate.

It is important to distinguish these forms of lymphocytic adenitis from other forms of expanding pituitary lesions or lacrimal gland swelling. Systemic immunomodulatory treatment is necessary. The differential diagnosis should include expanding pituitary and lacrimal gland lesions as well as lymphoproliferative and vasculitic diseases. This symptom complex can mimic pituitary adenoma or infectious dacryoadenitis but requires a different therapy.

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