Lymphoid "Hypophysitis" With End Organ Insufficiency

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A clinically hypothyroid patient had bilateral adrenal cortical atrophy and an extraordinary lesion of the pituitary gland. The parenchyma of the adenohypophysis was extensively replaced by a predominantly lymphocytic infiltrate with formation of nodules, many of which had pale germinial centers. There were areas of hyalinization with interstitial fibrosis and mild capsular thickening. A similar lesion of the adenohypophysis has been reported previously, but without the evidence of adenohypophyseal insufficiency present in this case. It is speculated that this lesion may be related to cell-mediated autoimmunity and other organ-specific autoimmune disorders.

The purpose of this case report is to present an extraordinary lesion of the pituitary gland that I have elected to term lymphoid "hypophysitis." Lymphocytic infiltrates have been described in various endocrine tissues such as adrenals, thyroid, parathyroid, ovary, pancreatic islet tissue, and pituitary. To my knowledge, there has been only one previously reported case in the literature in which the adenohypophysis was involved in a similar manner; however, this case demonstrates clinicopathologic evidence of end organ insufficiency.

REPORT OF A CASE

A 42-year-old woman had schizophrenia of several years' duration and was treated with 300 mg of chlorpromazine daily. As a young adult, she had had two uncomplicated miscarriages. A hysterectomy and unilateral salpingo-oophorectomy were performed in 1950 for clinically suspected endometriosis. Pathologic examination showed a proliferative endometrium, chronic endocervicitis, and cystic follicles of the ovary. In 1961, an adnexal mass prompted removal of the remaining tube and ovary, which showed a cystic corpus luteum. All of the original microscopical slides were reviewed and I am in accord with the diagnoses.

In January, 1972, she manifested symp-
toms referable to anemia. Laboratory studies demonstrated a normocytic-nor-
mochromic anemia with a hemoglobin level of 10.7 g/m/l. Thyroid studies showed
a T₂ uptake of 20% (normal range, 25% to 35%) and T₃ uptake of 3μg/100 ml (normal
range, 5.4μg to 13μg/100 ml). Therapy with 300 mg of desiccated thyroid daily was in-
stituted.

In September 1972, she was admitted to another hospital with complaints of nausea, vomiting, and diarrhea. She was ane-
mic. The hemoglobin level had dropped to 7.1 g/m/l, and the hematocrit reading
was 22.8%. The white blood cell count was 3,700/cu mm with the differential cell count
showing 41% segmented neutrophils, 45% lymphocytes, and 4% eosinophils. A bone
marrow biopsy yielded a minute quantity of marrow that was interpreted as sug-
gestive depression of marrow elements possibly due to chlorpromazine. This drug
was discontinued and she was transferred to the New England Deaconess Hospital
with complaints of weakness, anorexia, nausea, vomiting, diarrhea, and severe
weight loss.

On admission, she appeared dehydrated, pale, and mildly disoriented with an oral
temperature of 39.4°C (103°F). Her pulse rate was 110 beats per minute and blood
pressure was 140/80 mm Hg. The remain-
der of the physical examination was nor-
mal except for mild pretibial pitting edemas, sparse axillary and pubic hair, and
a mild conjunctivitis. Culture of the con-
junctiva showed sparse growth of Staphy-
lococcus, coagulase positive. Blood, urine,
and cerebrospinal fluid cultures were nega-
tive. Fecal cultures were negative for
pathogens, and throat cultures yielded
commensal organisms. At admission, elec-
trolytes showed a serum sodium of 135
mEq/liter (normal, 137 to 145 mEq/liter),
serum chloride of 106 mEq/liter (normal,

Fig 2.—Parathyroid with patchy infiltrate of lymphocytes and occasional plasma cells
(hematoxylin-eosin, x 150).

Fig 3.—Adrenal gland with severe generalized thinning of cortex and involvement of the zona fasciculata and zona reticularis and relative sparing of zona glomerulosa. Arrow indicates cortico-medullary junction (hematoxylin-eosin, x 33).
Fig 4.—Congestion and mild lymphocytic infiltrate of corticomedullary junction (hematoxylin-eosin, × 150).

Fig 5.—Lateral portion of adenohypophysis showing numerous lymphoid nodules, interstitial lymphocytic infiltrate, fibrosis, and capsular thickening (hematoxylin-eosin, × 50).

95 to 105 mEq/liter), serum potassium of 3.4 mEq/liter (normal, 3.5 to 5.0 mEq/liter), and serum carbon dioxide of 20 mM/liter (normal, 23 to 29 mM/liter). Coagulation studies showed a prothrombin time of 17.0 seconds (control, 11.1 seconds), and platelet count of 200,000/cu mm. The fibrinogen level was greater than 1,000 mg/100 ml. Total serum protein was 4.9 gm/100 ml, and serum albumin was 1.9 gm/100 ml (normal range, 3.7 to 5.0 gm/100 ml). The IgM level on serum protein electrophoresis was 950 mg/100 ml (normal range, 40 to 200 mg/100 ml). She was treated for possible sepsis with sodium cephalothin and gentamicin sulfate.

Her fever abated slightly, but she died unexpectedly on her sixth hospital day.

AUTOPSY FINDINGS

An autopsy was performed within six hours of death. Postmortem aerobic and anaerobic blood cultures were negative. Alcoholic zinc formol-fixed tissue was examined utilizing hematoxylin-eosin stain. The pituitary gland was additionally stained with PAS-orange G, reticulum stain, Mason-Goldner Trichrome stain, and Congo red. Adenohypophyseal cells were differentiated according to standard criteria.

Gross and Microscopical Findings

Microscopical sections revealed a small vessel necrotizing vasculitis of hypersensitivity type involving kidneys, ureters, esophagus, small intestine, colon, lung, skeletal muscle, and periadrenal tissue. There were multiple small fibrocaseous granulomas confined to the lungs. Sections stained with Ziehl-Neelsen, PAS, and methenamine silver stains were negative for acid-fast organisms or fungi. The spleen weighed 170 gm and microscopically showed congestion with scattered polymorphonuclear leukocytes. Lymphatic follicles were normal. The liver showed slight congestion. Lymph nodes sampled above and below the diaphragm were normal. Vertebral bone marrow was slightly hypercellular, and there was normal maturation of myeloid and erythroid precursors.

Thyroid Gland

The gland weighed 11.0 gm, had a normal external appearance, and microscopically showed flattened follicular epithelium (Fig 1). Colloid was present and appeared normal. There was no lymphocytic infiltration, and no oxyphilic cell change of thyroid epithelium.

Parathyroid Glands

One gland was examined and showed focal lymphocytic infiltration with a small plasma cell component (Fig 2). The gland was populated by chief cells, and there was no evidence of hyperplasia.

Adrenal Glands

Both glands were examined, and their respective weights reflect some adherent adipose tissue. The right adrenal gland weighed 3.0 gm and the left 4.0 gm. The normal weight of adrenal glands in this laboratory is 5 to 8 gm each. The cortex of each gland measured less than 0.1 cm in thickness throughout (Fig 3). The cytoplasm of scattered cortical cells was compact and devoid of vacuoles. There was severe hyperemia at the

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corticomedullary junction along with a mild lymphocytic infiltrate (Fig 4).

**Pituitary Gland**

The 550-mg gland appeared grossly normal and was sectioned in the horizontal plane. Step microscopical sections were examined. The adenohypophysis showed diffuse infiltration by mature lymphocytes with formation of numerous nodules, many of which had pale germinal centers (Fig 5 and 6). The infiltrate was in part composed of plasma cells. There was moderate interstitial fibrosis with capsular thickening. There were no vascular changes. The residual adenohypophysis was populated by acidophils, basophils, amphophils, and chromophobes with nests of smaller cells that were difficult to identify. There was an abrupt line of demarcation between the adenohypophysis and the neurohypophysis (Fig 7). Hyalinized areas did not stain for amyloid. The brain in general, and, in particular, the infundibulum and hypothalamus appeared normal.

**COMMENT**

Any lymphocytic infiltration with nodule formation within the adenohypophysis of the pituitary gland is extraordinary. This process occurred to a severe extent in this case, and was accompanied by germinal center formation within lymphoid nodules and by interstitial fibrosis. This adenohypophyseal lesion and its end organ effects appeared unrelated to the fibrocaseous pulmonary granulomas or the hypersensitivity type of necrotizing vasculitis. The pulmonary granulomas did not resemble those seen in Wegener granulomatosis, nor did they resemble rheumatoid nodules. The clinically documented hypothroidism and the pronounced adrenal cortical atrophy were probably a result of extensive replacement of the adenohypophysis.

A dependence of pituitary function on gland volume has been noted. When the primary lesion producing adenohypophysyal insufficiency is in the adenohypophysis itself, no symptoms are detectable unless approximately 70% of the gland is ablated. The usual order of hormone loss in chronic hypopituitarism is growth hormone, gonadotropins, corticotropin, and thyrotropin; however, some patients may exhibit different patterns of deficiency. The degree of adenohypophysyal replacement in this case is sufficient to explain the end organ insufficiency observed.

Lymphocytic infiltration within the pituitary gland has been noted previously, but the extent of adenohypophysyal involvement in this case is extraordinary. In 1926, Schmidt described several patients with non-

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**Fig 6.**—Adenohypophysis showing pale germinal center within lymphoid nodule and interstitial lymphocytic infiltrate. Nests of epithelial cells represent residual parenchymal cells of adenohypophysis (hematoxylin-eosin, × 175).

**Fig 7.**—Abrupt line of demarcation between adenohypophysis and uninvolved neurohypophysis (N). Numerous lymphoid nodules are evident in adenohypophysis. A portion of capsule (C) is present (hematoxylin-eosin, × 40).
tuberculous Addison disease and chronic lymphocytic thyroiditis giving rise to adrenal and thyroid insufficiency. The subject of this case report does not represent Schmidt syndrome. In association with Schmidt syndrome, there have been several reports of mild lymphocytic and plasmacytic infiltration of the adrenocortical tissue occasionally with tiny foci of necrosis; however, there was nothing to suggest that the extent of adenohypophyseal involvement was functionally important.

In 1962, the coexistence of anterior hypophysisis and Hashimoto disease was described in a young woman. The pituitary was involved by a process similar to that which occurred in my case. Her death was presumed to be secondary to acute adrenal insufficiency, although the adrenal glands were not found at autopsy. In the case that I am reporting, there was clinical hypothyroidism, but there was no lymphocytic infiltration of the thyroid gland and the follicular epithelium was flattened.

The possibility that this lesion was related to chlorpromazine is remote. Chlorpromazine has been associated with galactorrhea and gynecomastia through its inhibitory effect on the secretion of prolactin. However, there have been no reports of histologic changes within the adenohypophysis.

There has been recent evidence linking organ-specific disorders such as autoimmune thyroiditis, adrenalitis, and oophoritis. Edmonds et al. have suggested that these disorders and others such as pernicious anemia may be the result of cell-mediated autoimmunity. It is tempting to speculate that, in this case, the severe lymphoid infiltrate in the adenohypophysis was related to an autoimmune phenomenon.

References