GALACTORRHEA ASSOCIATED WITH LYMPHOCYTIC ADENOHYPOPHYSITIS

CASE REPORT

BY

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Summary

A young woman, 14 months post partum, committed suicide when she noticed milk discharging from her nipples and thought she was pregnant. At autopsy the uterus was found to be non-gravid and the pituitary gland enlarged. Histological examination revealed lymphocytic adenohypophysitis, a rarely identified condition usually associated with hypopituitarism. Immunoperoxidase studies of the pituitary demonstrated prolactin cell hyperplasia. None of the other known causes of galactorrhea was present suggesting that this may be a new addition to the differential diagnosis of galactorrhea. To this date lymphocytic adenohypophysitis has been reported only in women, the majority within 14 months post-partum, and is usually identified only at autopsy.

LYMPHOCYTIC adenohypophysitis is rarely identified, occasionally causing sellar enlargement and associated with hypopituitarism (Duff and Bernstein, 1933; Goudie and Pinkerton, 1962; Hume and Roberts, 1967; Egloff et al, 1969; Lack, 1975; Gleason et al, 1978; Mayfield et al, 1980). Both decreased thyroid and adrenal cortical function have been reported in these cases, six of which were studied post mortem, all dying of presumed hypopituitarism. Increased pituitary function has never been associated with an inflammatory process of the pituitary and is usually ascribed to neoplasia. This report describes a patient with galactorrhea who at autopsy was found to have lymphocytic adenohypophysitis. Immunocytochemical examination revealed prolactin cell hyperplasia. These findings may indicate another variant of the disease or an earlier phase and suggests a new addition to the differential diagnosis of galactorrhea.

CASE REPORT

A 22-year-old black woman with three previous pregnancies, including one spontaneous abortion, noticed milk discharging from her nipples and thought she was pregnant. She had last seen a doctor six weeks after the birth of her last child, 14 months previously, when all was
well, but she had complained recently of headaches without visual disturbances. She had not used oral contraceptives at any time since the birth of her last child and was taking no other medication. An accurate menstrual history could not be obtained. She had bottle-fed her last baby. Wanting only two children and depressed because her husband had recently started a second full-time job, she committed suicide by hanging herself.

A complete autopsy was performed at the Cuyahoga County Coroner's Office. Findings, other than those of trauma, included a milky discharge easily expressed from the breasts, a non-gravid uterus, and grossly atrophic adrenal glands. The pituitary gland was enlarged, measuring $1.8 \times 1.2 \times 1.0$ cm compared to normal average of $1.5 \times 0.9 \times 0.6$ cm (Doniach, 1977). It bulged from the sella turcica producing slight compression of the optic tracts.

Methods

In addition to routine staining with hematoxylin and eosin, PAS-Orange G and Wilder’s reticulin stain, adjacent sections of the pituitary were also stained for prolactin (PRL), growth hormone (GH), corticotrophin (ACTH), thyrotrophin (TSH), luteinizing hormone (LH) and follicle-stimulating hormone (FSH) with the peroxidase-anti-peroxidase (PAP) method of Sternberger (1979). Incubations with anti-hPRL (diluted 1:1000), anti-hGH (1:1000), anti-pACTH$_{1-24}$ (1:1000), anti-hTSH $\beta$ (1:4000), anti-hLH $\beta$ (1:1000) and anti-hFSH $\beta$ (1:4000) were carried out. The regions of antibody-antigen binding were finally revealed by 3,3′-diaminobenzidine tetrahydrochloride (DAB) (Sigma) according to Graham and Karnovsky (1966). The specificity of immunostaining was verified by replacing the primary antiserum with normal rabbit serum. For control purposes, pituitary glands from unselected autopsies were immunostained applying the same antisera.

Findings

Microscopically, the adenohypophysis was involved with a widespread inflammatory process characterized by a diffuse, interstitial infiltrate of lymphocytes and plasma cells which pushed apart the epithelial cell cords (Fig. 1). Several

![Fig. 1](image_url)

Diffuse mononuclear inflammatory infiltrate compressing the pituitary cell cords. Note the lymphoid follicle with prominent germinal center in lower right field. (Hematoxylin and eosin, $\times 70$).
lymphoid follicles, many of which had pale germinal centers, occasionally contained polymorphonuclear leucocytes and small foci of necrosis. The alveolar compartments, outlined by the reticulin stain, were widely separated by the interstitial infiltrate and contained compressed pituitary cell cords. Nowhere was there evidence of fragmentation of the reticulin meshwork, a feature which helped to exclude the presence of adenomatous tissue (Velasco et al., 1977). The inflammatory process involved approximately 70 per cent of the adenohypophysis. The small residual fragment of uninvolved gland contained normal proportions of acidophil, basophil and chromophobe cells, and was sharply separated from the inflammatory process by a clear line of demarcation.

The immunoperoxidase study revealed that the pituitary cell cords enveloped by the inflammatory infiltrate contained predominantly prolactin cells (Fig. 2). Some cords showed an admixture of GH and ACTH containing cells (Figs. 3 and 4) and others were populated solely by prolactin cells. The TSH, LH and FSH containing cells were noted, but they were abundant and cytologically unremarkable in the uninvolved portion of the gland. The neurohypophysis was unremarkable.

The breasts showed areas of lactational activity, lobular proliferation and acinar formation in an otherwise apparently unstimulated gland. A lymphocytic and plasmocytic interstitial infiltrate was noted within the lobules. The ovaries showed many primordial follicles below a cortex of normal thickness. Some follicles were cystic and essentially in the same phase of development. They were largely devoid of granulosa cells and had a theca interna which was partially luteinized. The endometrium was too autolytic for accurate assessment.

Cortical thickness of the adrenal glands was reduced to less than 0.5 mm, rather than the usual 1 to 2 mm. All layers of the adrenal cortex were atrophic, with the zona fasciculata showing the most marked shrinkage. The thyroid gland was unremarkable histologically. Parathyroid glands were not identified.

**DISCUSSION**

Lymphocytic adenohypophysitis as an auto-

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**Fig. 2**

Immunoperoxidase staining showing marked hyperplasia of prolactin cells. Anti-human prolactin was used as primary antiserum (PAP method). (No counter-stain, x115).
Fig. 3

Same field as in Figure 2 stained with anti-human GH as primary anti-serum. Note presence of GH cells at the periphery of cell cords. PAP method. (No counterstain, ×115).

Fig. 4

Adjacent field of Figures 2 and 3 showing the distribution of ACTH cells within the cords. Anti-porcine ACTH1-24 as primary antiserum. PAP method. (No counterstain, ×115).
immune disease was first postulated by Goudie and Pinkerton (1962). Since then evidence has steadily accumulated in a series of case reports and experimental work to verify this hypothesis. Lymphocytic infiltration of the target organ has been consistently described (Duff and Bernstein, 1933; Goudie and Pinkerton, 1962; Hume and Roberts, 1967; Egloff et al, 1969; Lack, 1975; Gleason et al, 1978; Mayfield et al, 1980). The disease has been produced in experimental animals by injection of pituitary extracts in Freund’s adjuvant (Levine, 1967). It has been reported in association with other known autoimmune diseases, namely Hashimoto’s thyroiditis (Goudie and Pinkerton, 1962), pernicious anaemia (Hume and Roberts, 1967), and idiopathic Addison’s disease (Duff and Bernstein, 1933; Goudie and Pinkerton, 1962; Hume and Roberts, 1967). And, finally, the presence of circulating anti-pituitary antibodies has been demonstrated (Mayfield et al, 1980).

Analysis of the reported cases reveals that all those affected were women and five, including our patient, were within 14 months post partum when the first onset of symptoms or actual death occurred. This observation corresponds to the preliminary experimental evidence that adenohypophysitis can be induced in pregnant rats and may be increased in severity in post partum animals (Levine, 1967). The explanation which has been offered is that pituitary antigens and, in some cases, antigens from other endocrine glands released during puerperal involution of these glands, trigger an autoimmune reaction (Goudie and Pinkerton, 1962). Indeed, 23 of 128 women tested at the fifth or seventh day after delivery demonstrated adenohypophyseal antibodies; 25 per cent of these women had decreased pituitary function 6 to 12 months post partum as compared with 4 percent of the remainder of the group (Engelberth and Jezkova, 1965).

Morphologically, the case reported here resembles those reported previously. In two cases the pituitary was smaller than usual (Goudie and Pinkerton, 1962; Hume and Roberts, 1967), in one it was normal in size (Lack, 1975), and in three others it was enlarged (Egloff et al, 1969; Gleason et al, 1978; Mayfield et al, 1980), as in our case. Microscopically, precisely the same appearance was found. However, in the present case there was definite prolactin cell hyperplasia as shown by immunocytochemical techniques. This finding correlated with the presence of galactorrhea.

Several possible explanations for the differences in hormonal behaviour can be postulated. The disease as found here could be a variant of a general autoimmune disorder of the pituitary gland with a similar relation to the hypo-functioning form as Grave’s disease has with Hashimoto’s thyroiditis. In other words, instead of a circulating antipituitary antibody, a stimulating-type of antibody similar to LATS may have been present. The existence of an auto-antibody to prolactin-secreting cells has already been demonstrated but its physiologic significance is as yet unclear (Bottazzo et al, 1975). It was not detected in cases of panhypopituitarism (Bottazzo et al, 1975). The finding of autoimmunity to a single pituitary cell-type, however, suggested that such a mechanism may underlie isolated pituitary hormone deficiencies or, as possible here, account for single hormonal increases, namely that of prolactin.

It is also possible that initially an inflammatory process is associated with cellular hyperplasia which may not be clinically manifest. Then, at a later stage, the associated necrosis, possibly ischemic in nature due to an enlarged and compressing gland occluding its own vascular supply, may destroy enough of the cellular components to produce a partial or complete hypopituitarism.

As a last possible mechanism, compression of the hypothalamus by the enlarged and inflamed gland may have prevented the release of prolactin inhibitory factor. Galactorrhea in association with non-functioning sellar tumours such as craniopharyngioma have been reported (Kleinberg et al, 1977). Only slight compression of the optic tracts, however, was noted in the present case and no clinical symptomatology was reported to suggest significant structural alteration. On the other hand, bulging pituitary tumours producing clinical symptomatology are well known to occur without an associated galactorrhea. Indeed, the three other cases of adenohypophysitis with gland enlargement and attendant clinical symptomatology were not associated with galactorrhea (Egloff et al, 1969; Gleason et al, 1978; Mayfield et al, 1980).
Regardless of the mechanism, the association of galactorrhea with adenohypophysis in the absence of other known causes suggests a new addition to the list of possible aetiologies. The largest category in a series of 235 patients with galactorrhea was that of idiopathic (41 per cent) (Kleinberg et al., 1977). Thus we suggest considering it when evaluating women presenting with galactorrhea.

The prevalence of adenohypophysitis is as yet unknown; it has previously only been associated with hormonal deficit rather than increase. This entity should be considered in patients not only presenting with hypopituitarism but also in cases with increased pituitary hormonal secretions.

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REFERENCES


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