Lymphocytic adenohypophysitis of pregnancy simulating a pituitary adenoma: a distinct pathological entity

Report of two cases

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Diffuse lymphocytic infiltration of the adenohypophysis occurring in temporal relation to pregnancy was found in two patients, each of whom had an intrasellar mass with suprasellar extension that caused compression of the optic chiasm. The pathology and etiology of this lesion is discussed. This entity should be considered when evaluating patients with a pituitary mass lesion that presents in temporal association to pregnancy, particularly if there is evidence of hypopituitarism rather than a hypersecreting, endocrine-active adenoma.

KEY WORDS • lymphocytic adenohypophysitis • pituitary tumor • pregnancy • autoimmune disease • transsphenoidal microsurgery

Pregnancy produces a variety of changes throughout the body, including alterations in the immune system and in the structure and function of the pituitary gland, which may lead to the development of hypopituitarism. We report two patients with hypopituitarism and an intrasellar mass with suprasellar extension that caused compression of the optic chiasm. In both cases, the pituitary lesion occurred in temporal association to pregnancy. Although the presumed diagnosis in both cases was pituitary adenoma, detailed histological analysis of the surgical specimens revealed lymphocytic adenohypophysitis.

Case Reports

Case 1

This 33-year-old oriental woman was first seen during her 8th month of pregnancy. She complained of a progressive loss of visual acuity in the left superior temporal field over the preceding 4 weeks. Her medical history included Pott's disease of the spine at 8 years old; treatment consisted of surgical debridement and fusion, and then long-term antibiotic therapy (isoniazid and streptomycin).

Preoperative Course. Formal visual field testing on August 13, 1980, revealed a bitemporal superior quadrantanopia which was worse in the left eye than in the right. The patient was otherwise normal neurologically. Laboratory evaluation on August 14, 1980, revealed a prolactin level of 6 ng/ml (normal, greater than 200 ng/ml during pregnancy). Sellar polytomography on August 14, 1980, showed expansion of the sella turcica with marked thinning of the sellar floor and demineralization of the dorsum sellae. A computerized tomography (CT) scan with magnified coronal and sagittal reconstructions showed a rounded, contrast-enhancing sellar mass extending into the suprasellar cistern and the inferior portion of the third ventricle (Fig. 1).

Labor was induced successfully on August 16, 1980, and the patient gave birth to a normal child. Six days later, a second visual field examination showed mild resolution of the deficit in the patient's left eye. On August 25, 1980, her serum prolactin level was 6 ng/ml (normal value postpartum, less than 20 ng/ml in...
our laboratory), and the fasting morning cortisol level was less than 2 μg/ml (normal, 5 to 25 μg/ml).

A second CT scan performed on August 29, 1980, showed no change from the previous study. Selective arteriograms of the right and left internal carotid artery and the left vertebral artery were normal. Formal visual field examination on September 9, 1980, showed improvement in both eyes. The fasting morning cortisol level on September 10, 1980, was 2 μg/dl (normal, 5 to 20 μg/dl), the human growth hormone (HGH) level was 2.9 ng/ml (normal, less than 10 ng/ml), and the serum prolactin level was less than 1 ng/ml.

On September 15, 1980, the thyroid function was evaluated: the thyroxine (T\textsubscript{4}) radioimmunoassay revealed 5.7 μg/dl (normal, 5 to 12 μg/dl); triiodothyronine (T\textsubscript{3}) uptake was 26% (normal, 26% to 35%); the T\textsubscript{3} index, 1.5 (normal, 1.3 to 4.2); and thyroid-stimulating hormone (TSH) less than 2 μg/ml (normal, 0 to 10). Serological evaluation for syphilis was negative.

Operation. On September 12, 1980, transsphenoidal exploration of the sella was performed. When the dura was incised and opened, a firm, dull white mass was evident. Tissue was sent for pathological analysis by frozen section, but a diagnosis could not be made from the specimen. The mass was then gently dissected free from the arachnoid and dura that formed its suprasellar capsule. With gentle depression of the suprasellar component, the pituitary stalk was identi-
D. S. Baskin, J. J. Townsend and C. B. Wilson

then gradually resolved completely. A CT scan obtained on August 12, 1980, revealed a contrast-enhancing mass lesion in the sellar and suprasellar regions. The patient was referred to the Neurosurgery Service for further evaluation. Her menses had returned. She denied any symptoms of a specific endocrine disturbance, but reported that, beginning in September, 1980, she had vomited after breakfast every day.

Physical and neurological examinations upon admission, including evaluations of the visual acuity and fields, showed no abnormalities. Laboratory values were also normal; her serum prolactin level was 3 ng/ml (normal, less than 20 ng/ml in our laboratory).

Sellar polytomography revealed sellar expansion, predominantly in an anterior inferior direction, with marked thinning of the sellar floor. The dorsum sellae was demineralized and truncated. A CT scan of the sella with magnified coronal and sagittal reconstructions demonstrated an expanded sella with an irregular area of decreased attenuation in the midportion, and a contrast-enhancing density extending superiorly into the suprasellar cistern (Fig. 3). Marked upward bulging of the enhancing component of this lesion was noted in the coronal and sagittal images.

Operation. On November 14, 1980, the patient underwent transphenoidal exploration of the sella. When the dura was incised, abnormally firm yellow tissue, with areas of orange and gray specks, was immediately apparent. Further exploration exposed a normal but hyperemic pituitary gland. It was impossible to separate normal gland from abnormal tissue. A frozen section biopsy specimen revealed chronic inflammation and fibrosis. Our experience with Case 1 led us to suspect that this was another case of lymphocytic adenohypophysitis. After additional biopsy specimens were obtained for further pathological study, the procedure was terminated without attempting radical excision of the mass.

Pathological Studies. Pathological analysis of the specimens showed an anterior pituitary gland with extensive fibrosis and scattered small nests of pituitary cells. There were numerous lymphocytes and plasma cells within the gland, and several nodules composed entirely of lymphocytes and plasma cells were seen (Fig. 4). Analyses with special stains for bacteria, fungi, and acid-fast organisms were negative.

Postoperative Course. During the postoperative period, the patient developed moderate diabetes insipidus that was controlled with occasional intramuscular injections of Pitressin. She continues to use DDAVP nasal spray to control her diabetes insipidus, and has had no recurrence of symptoms. Her child has continued to develop normally.

Discussion

In 1909, Erdheim and Stumme were the first to describe changes in the human adenohypophysis dur-
Adenohypophysitis and pregnancy

Fig. 3. Case 2. Computerized tomography scan with magnified views of the sella in the midcoronal (upper) and midsagittal (lower) planes showing a sellar mass lesion with a low-density center and suprasellar extension.

Fig. 4. Case 2. Photomicrograph of the biopsy specimen. Arrows indicate scattered pituitary cells with surrounding fibrosis. A small nodule of lymphocytes is evident. H & E, × 200.

ing pregnancy. They reported a marked increase in the size and weight of the normal pituitary gland that they attributed to an increase in the number of chromophobe cells, which they called "pregnancy cells." These cells have since been identified as the lactotrophs producing prolactin; the increase in the size and weight of the pituitary during pregnancy is the result of hypertrophy and hyperplasia of these prolactin cells.6,11

Pregnancy also causes changes in the immune system.6,5,10,20 An intriguing problem for the immunologist is the question of how the fetus, with its full complement of paternal antigens, escapes immunological rejection by its mother.9 A number of studies suggest that one factor involved in the privileged immunological state of pregnancy is the fetal production of suppressor cells6,10,20 that are capable of inhibiting maternal rejection of the fetal allograft.

The transplacental protein exchange that occurs during pregnancy exposes the mother to a variety of foreign antigens, to which an antibody response may occur. Even if the fetus can successfully defend against these antibodies by producing suppressor cells and/or substances, these new antibodies may cross react with maternal antigens to cause either new autoimmune disease or a severe exacerbation of preexisting disease in the mother during pregnancy or during the postpartum period.

Sheehan6 noted that hypopituitarism in women was most commonly related to necrosis of the anterior hypophysis during the postpartum period. He reported several cases in which a postmortem analysis

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showed histological evidence of coagulation necrosis of the anterior pituitary gland in patients who had developed hypopituitarism postpartum. He believed that this necrosis was a consequence of local vascular changes and spasm in the artery supplying the anterior lobe and pituitary stalk.\(^{23-26}\) and postulated that spasm arrested portal blood supply for a variable period of time, which would account for variations in the size of the necrotic area. He related the spasm to a severe general circulatory collapse during delivery, although the specific localization of the vasospastic event to the anterior pituitary was not explained. Engelberth and Ježková\(^{6}\), however, noted high titers of antipituitary antibodies in the sera of 18% of randomly sampled women in the immediate postpartum period, as well as in a woman with clinical signs of Sheehan’s syndrome who had delivered a child 5 years earlier. Whereas 25% of the women with high antibody titers eventually developed signs of adenohypophysial dysfunction, only 3% of women with normal antibody levels developed a similar dysfunction. These data suggest that Sheehan’s syndrome may be a manifestation of pituitary autoimmunity disease that develops insidiously during pregnancy.

The concept of autoimmune disease of the pituitary is supported by the findings of Bottazzo, et al.,\(^{27}\) who identified specific autoimmune antibodies to prolactin-secreting cells in the anterior pituitary that react with the intracellular membranes belonging to the protein-synthesizing machinery of the cell. They found high titers of prolactin cell antibodies in two patients with hypopituitarism and in four patients with hypothyroidism. Antibodies against HGH-secreting cells were also identified in a young girl with growth retardation, and in her mother, who suffered from Addison’s disease and thyroiditis. In addition, several of their studies showed pituitary antibodies in sera that reacted with anterior pituitary cells that were neither lactotrophs, somatotrophs, nor thyrotrophs. Some of these antibodies may be directed against cells that secrete either luteinizing hormone or follicle-stimulating hormone. On the basis of these findings, it appears likely that antibodies to each of the anterior pituitary cell types will be identified.

A circumscribed accumulation of unicellular “lymph corpuscles” between Rathke’s cysts in the pars intermedia was first described by Erdheim,\(^{7}\) who noted that this histological appearance gave the impression of a lymphoid follicle. Simonds and Brandes\(^{28}\) performed serial sections of over 200 pituitary glands, and noted 21 cases in which there were areas of lymphocytic infiltration of various types. Although they considered this to be a pathological condition, clinical correlation was lacking. Shanklin,\(^{22}\) finding lymphocytes and lymphoid tissue in 43% of human pituitary glands obtained during routine postmortem examinations, suggested that their presence could be a normal finding.

In 1962, Goudie and Pinkerton\(^{13}\) reported the case of a young woman with histologically confirmed Hashimoto’s disease and lymphocytic infiltration of the adenohypophysis who died from adrenal failure during an acute attack of appendicitis. Since their report, 11 other cases of lymphocytic adenohypophysitis have been documented with similar pathological findings.\(^{1,4,6,10,12,14,16,17,19,21}\) Some of these cases occurred in association with diseases of other endocrine organs. All of the patients reported were women and, in 58%, the onset of the disease process was temporally related to pregnancy.

Triplet\(^{27}\) has reported that a frog will reject a graft of its own pituitary tissue if the pituitary gland is maintained apart from the animal during the period of immunological immaturity, although the microscopic appearance of the rejection process was not described. Levine\(^{18}\) has produced a pathological process in male and female rats that is identical to that seen in lymphocytic adenohypophysitis. The rats developed focal and diffuse infiltration of lymphocytes into the adenohypophysis within 13 to 20 days after receiving a single, intracutaneous injection of pituitary tissue with an immunological adjuvant. In a small subgroup of pregnant and postpartum rats, the adenohypophysitis in specimens from the postpartum group appeared more severe than it was in specimens from the pregnant rats.

Lymphocytic adenohypophysitis has emerged as a distinct and specific pathological disease process. It occurs exclusively in women, and appears to be related to disturbances in the immune system. In 58% (seven of 12) of the cases reported, it has occurred in close temporal proximity to pregnancy. The disease, although rare, should be considered when evaluating any women who has an intrasellar lesion that produces symptoms in temporal relation to pregnancy, particularly when there is no evidence of an endocrine-active pituitary neoplasm. If lymphocytic adenohypophysitis is suspected, a biopsy and pathological analysis of a frozen section should be obtained. If the histological appearance supports the diagnosis, simple decompression of the optic chiasm and subtotal removal of the mass is the optimal therapy.

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Adenohypophysitis and pregnancy


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