Concurrent lymphocytic hypophysitis and pituitary adenoma

Case report and review of the literature

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Lymphocytic hypophysitis (LyH) is an uncommon intrasellar lesion characterized by lymphocytic infiltration of the adenohypophysis. Evidence suggests that the cause is autoimmune, and the symptoms are usually related to either a mass effect or endocrine dysfunction. Lymphocytic hypophysitis has been described rarely in the setting of other simultaneous pathological processes that involve the pituitary and sella turcica, and is postulated to arise from an intrinsic inflammatory response.

The authors report the case of a 43-year-old woman who presented with a 2-month history of galactorrhea and pseudohyperprolactinemia secondary to a 10-mm lesion within an enlarged pituitary gland. She was nulliparous and had no contributory medical history. Serial neuroimaging performed over a 2-year period demonstrated lesion growth, and visual deficits had developed; together these warranted surgical intervention. A transphenoidal resection was performed. Microscopic and immunohistopathological examinations revealed a nonsecreting pituitary adenoma with concurrent lymphocytic adenohypophysitis.

This is the first documented case of LyH in the setting of a null-cell pituitary adenoma. The authors review the related literature and outline potential mechanisms for the concurrent development of LyH and a pituitary adenoma.

KEY WORDS • adenoma • lymphocytic hypophysitis • CD45 • pituitary

YMPHOCYTIC hypophysitis is a rare, idiopathic intrasellar lesion that presents with a mass effect and pituitary dysfunction; fewer than 400 cases have been reported to date.5 Lymphocytic hypophysitis has a marked female predominance and most commonly becomes symptomatic during pregnancy or the postpartum period. The lesion usually presents as a compressive lesion of the anterior pituitary, hypothalamus, or optic apparatus, or appears as endocrinological dysfunction including diabetes insipidus and hormone deficiency. The hypophysitis is hypothesized to be autoimmune in nature, with florid B-cell, T-cell, and plasma cell infiltration of the adenohypophysitis.

Hyphophysitis has also been identified in the setting of various systemic autoimmune and infectious diseases.5 The presence of immune cells in these processes as well as in idiopathic hypophysitis is postulated to reflect an autoimmune-flammatory process triggered by unknown exogenous or endogenous target antigens. In animal models, however, intrinsic pituitary proteins are thought to be able to initiate this autoimmune process and have been implicated in this disease.17,32 Additional evidence to support this hypothesis has been derived from rare case reports of intrasellar lesions that have been identified histologically in conjunction with hypophysitis. In the setting of a functional adenoma LyH has been reported twice. We present the first case of LyH concurrent with a nonsecreting pituitary adenoma.

Case Report

History. This seemingly healthy 43-year-old woman presented with galactorrhea of 2 month’s duration. She complained of fatigue and malaise, but no weight change, muscle weakness, cramping, or paresthesia. She denied visual complaints. There had been no polyuria, polydipsia, loss of libido, or temperature intolerance, although her menstrual cycles were irregular.

Her medical history was significant for postprandial hypoglycemia, mitral valve prolapse, and migraine headaches; medications included propranolol and multivitamins. She

Abbreviations used in this paper: GH = growth hormone; IL = interleukin; LyH = lymphocytic hypophysitis; MR = magnetic resonance.
was married and had no children (gravida 0). Her family history did not show anything unusual.

Examination. On initial evaluation, the patient was neurologically intact, with full visual fields on formal testing. There were no physical stigmata of endocrine dysfunction. Her serum hormone levels were significant only for a slightly elevated prolactin concentration of 30.8 ng/ml (normal range 2.8–29.2 ng/ml). Treatment with bromocriptine yielded symptomatic relief from the fatigue and a decrease in the prolactin concentration to 18.6 ng/ml, but the bromocriptine therapy was discontinued because of adverse side effects including headaches, dizziness, and nausea.

The patient was referred to our institution. Physical examination, including neurological and formal visual field testing, was unrevealing. On endocrine testing, the patient was found to have normal thyroid function as well as normal baseline and provocative cortisol and GH concentrations before and after cosyntropin stimulation and insulin tolerance testing. Magnetic resonance imaging of the sella turcica demonstrated a hypodense 10 × 8 × 8–mm lesion in the inferior, paramedian aspect of the sella. There was no enhancement of the infundibulum after administration of a contrast agent.

Operation. In view of the patient’s progressive visual loss, she underwent surgery via a transsphenoidal approach to the sella turcica. On wide exposure of the sellar contents, a slightly brown–gray, soft, and mostly mucoid lesion, clearly demarcated from the surrounding tissues, was identified approximately 2 mm beneath the surface of the anterior pituitary gland. This lesion had the appearance of an adenoma and was removed completely. Immediately behind the tumor, the white posterior pituitary gland was identified and preserved. Above the tumor, there was a more firm and rubbery, white–tan region of the anterior pituitary gland that was distinct from both the tumor and the remainder of the adenohypophysis, which was red–brown in color and slightly gritty. A portion of this periaxial fasciculus was also removed.

Histologically, the mucoid lesion contained neoplastic tissue that was characterized by cells with moderately pleomorphic nuclei and moderate amounts of cytoplasm (Fig. 2A). No mitotic figures were evident. Reticulin staining demonstrated a disruption in the normal nested architectural pattern that marks the adenohypophysis (Fig. 2B). There was no immunoreactivity when antibodies to GH, prolactin, adrenocorticotropic, thyrotropin, leutinizing hormone, and follicle-stimulating hormone were applied; this finding was consistent with a nonfunctional adenoma. The other tissue sample that was resected contained normal anterior pituitary gland, which was heavily infiltrated by lymphocytes and plasma cells (Fig. 2C). The identity of the lymphocytes was confirmed by CD45 immunostaining (dilution 1:80; Dako Corp., Carpinteria, CA; Fig. 2D), as CD45 is a marker of nonerythroid hematopoietic cells. These findings were consistent with the presence of LyH.

Postoperative Course. Postoperative imaging demonstrated optic nerve decompression with complete removal of the adenoma. The patient’s visual fields returned to normal and repeated endocrine serology testing yielded normal findings. Perioperative steroid medication was not administered, and at 6 weeks postoperatively the endocrinological findings, including the prolactin level (7.6 ng/ml), were normal. No additional therapy has been necessary, and 9 months after surgery MR imaging revealed a normal pituitary gland within the sella.

Discussion

This case demonstrates two distinct, concurrent pituitary mass lesions. The patient’s initial presentation was believed to represent an asymptomatic nonsecreting pituitary adenoma—a common sellar lesion. We thought that the mild pseudohyperprolactinemia was secondary to distortion of the infundibulum by the enlarged gland and initially managed the case medically. The hypointense lesion believed to be an adenoma did not change significantly; however, given an overall increase in the sellar contents and progressive optic nerve compression, resection and definitive pathological diagnosis were indicated. The dual pathological condition was not suspected preoperatively, similar to the few cases previously described.

Lymphocytic hypophysitis is predominantly identified in women in the third and fourth decades of life. It often has a marked temporal relation to late pregnancy or the postpartum period. The nature of this relationship is not understood, but may stem from the marked hyperestrogenemia and increased pituitary blood flow that occurs during pregnancy. An autoantibody to α-enolase, a protein found in pituitary extracts and in placental tissue, has been identified in LyH and has been implicated in its connection with pregnancy.

The natural history of LyH is not well described, but the literature suggests that slow disease progression occurs if untreated. Treatment is often medical, including steroid therapy and hormone replacement, and surgery is reserved for neural and optic decompression. Ancodotal evidence supports the adjunctive use of immunosuppressants and radiotherapy for lesions refractory to steroid therapy. Long-term outcomes have not been well studied, although more than half of the patients require life-long hormone replacement. Rare cases resolve spontaneously; the overall mortality rate is approximately 8% and death is likely to result from adrenal insufficiency.

Although extremely rare, dual pathological processes involving LyH and a second lesion have been described. Eight cases have been reported in which LyH occurred concurrently with a ruptured Rathke cleft cyst. Inflammatory changes that have been described include lymphocytic and plasmacytic invasion; in three of these cases, granulomatous nodules were described. The mechanism by which these lesions arise has been proposed to be an autoimmune reaction incited by inflammation to the mucinous cyst content, with initial lymphocytic invasion followed by granulomatous changes. Although little direct evidence supports this hypothesis, the foreign nature of the cyst’s content may be expected to stimulate adenohypophysitis and pituitary dysfunction. The degree of lymphocytic and

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macrophage invasion around the cyst has been postulated to correlate with the severity of the presenting symptoms.\textsuperscript{10}

Concurrent neoplasia and hypophysitis have been demonstrated as well. Five intrasellar germinomas\textsuperscript{4,7,8,14} have been described in the setting of LyH. The patients harboring these lesions were young (range 6–21 years) and all presented with diabetes insipidus. On surgical exploration, all patients had lymphocytic invasion and the initial pathological diagnosis was LyH. Failure to respond to corticosteroids, however, led to repeated neuroimaging and surgical reexploration, at which time a diagnosis of concurrent germinoma was made. In these tumors, the inflammatory changes within the neighboring, normal anterior pituitary gland were postulated to result from an autoimmune reaction triggered by presence of the tumor, although there was no direct evidence to confirm this. The presence of overwhelming granulomatous changes has been described for intracranial germinomas, and may significantly mask the diagnosis when only small specimens are available for microscopic examination.

Puchner, et al.,\textsuperscript{25} described three patients with concurrent LyH and craniopharyngioma. These persons were older
(range 42–52 years) than those described earlier and they presented with pituitary dysfunction. The authors suggested that rupture of the cystic contents of the craniopharyngioma elicited a local inflammatory reaction, resulting in hypopituitarism, a mechanism similar to that postulated for ruptured Rathke cleft cysts. Craniopharyngioma cyst contents have been shown to incite local as well as remote inflammatory reactions, which may include aseptic meningitis in humans and vasculitis in animal models. Histological confirmation of tumor rupture into the pituitary parenchyma causing secondary LyH has not been demonstrated conclusively, however.

Some pituitary adenomas may contain lymphocytic infiltration. In a study of 1400 tumors, 2.9% demonstrated variable degrees of lymphocytic infiltration within the adenoma alone; normal anterior pituitary tissue was not in-
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filtrated. Thus, LyH is not an expected pathological finding in the setting of an adenoma.

We report the third case of a patient with simultaneous pituitary adenoma and LyH, and we describe the definitive findings of microscopic and immunohistochemical staining in this case. This is the first reported case of a concurrent null-cell adenoma and LyH. Holck and Laursen described a 54-year-old man with a prolactinoma and LyH. The authors postulated that a granulomatous reaction occurred as a reaction to an undefined substance elaborated by the adenoma. McConnon and associates described a 22-year-old woman with amenorrhea and galactorrhea that was caused by hyperprolactinemia from pituitary stalk compression.

Although the patient’s serum GH levels were normal and the tumor displayed minimal immunohistochemical staining for GH, the tumor exhibited the electron microscopic features of a GH-secreting adenoma. Furthermore, in situ hybridization confirmed the presence of GH messenger RNA. The normal surrounding anterior pituitary was infiltrated by lymphocytes and plasma cells. Finally, in a less conclusive report, Jenkins, et al., described a patient with a GH-secreting tumor. On pathological examination, a follicular, lymphoid infiltrate was identified within the adenoma. Although the authors described the characteristics of hypophysitis, no images were presented to show the concurrent presence of the adenoma and LyH, which makes it more difficult to ascertain whether this case represents true lymphocytic infiltration within the adenoma or separate, coincident pathological processes.

Experimental evidence suggests that the normal and neoplastic pituitary can support an inflammatory reaction via expression of multiple cytokines, including IL-1, IL-1 receptor agonist, IL-2, and IL-6. These cytokines play an incompletely understood role in normal and abnormal anterior pituitary physiology, but have been suggested to regulate trophic hormone secretion. In the setting of pituitary neoplasia, these cytokines may serve as an abnormal stimulant that elicits systemic or local inflammation, which can induce hypophysitis in the neighboring, residual normal gland. If this mechanism is operative, it is unclear why hypophysitis would not be identified more frequently in the setting of pituitary adenomas. With growing evidence indicating an autoimmune reaction in the setting of some pituitary adenomas, concurrent hypophysitis may be more common than previously appreciated. The normal pituitary gland is not intentionally resected during adenoma surgery and therefore evidence of inflammation may be unnoticed.

The presence of autoantibodies is frequently identified in the setting of a pituitary adenoma, however, suggesting that an immune reaction is more common than currently recognized and may be integral to disease progression and response to treatment. Additionally, pituitary adenomas may represent a heterogeneous class of tumors with variable stimulation of the immune system as well as varied responses to medical and radiation therapies. Despite the high frequency of pituitary adenomas in the general population, there may be subsets of tumors that interact with the immune system; these should be identified to clarify this relationship.

Tumor elaboration of hormones has been postulated to initiate a secondary hypophysitis, which is supported by evidence that antihormone antibodies are identified in patients with hypophysitis. Furthermore, in some experimental models, immunization with pituitary extract can induce hypophysitis. Finally, in the setting of a nonsecreting adenoma, such as that found in our patient, an autoimmune reaction may have been triggered by overexpression of other, nonhormonal proteins, which are not detected when standard assays are performed. Alternatively, the inflammatory reaction may have been triggered by cell-surface proteins and not a secreted protein, as has been suggested. Additional studies of future cases are likely to shed light on the pathogenesis of this disorder.

Conclusions

We present an unusual case in which lymphocytic hypophysitis and a null-cell pituitary adenoma presented simultaneously. This represents the third reported case of a rare combination of intrasellar pathological conditions, which may suggest an as yet undescribed, potential interaction between pituitary adenomas and the immune system.

References


