

The Spectrum and Significance of Primary Hypophysitis

CAROL C. CHEUNG, SHEREEN EZZAT, HARLEY S. SMYTH, AND SYLVIA L. ASA

The Freeman Center for Endocrine Oncology, Mount Sinai Hospital, Departments of Pathology and Laboratory Medicine (C.C.C., S.L.A.), Medicine (Endocrinology) (S.E.), and Surgery (H.S.S.), University of Toronto, Toronto, Ontario M5G 1X5, Canada

ABSTRACT

Hypophysitis can present clinically as a mass lesion of the sella turcica. Secondary hypophysitis occurs in cases where a definite etiologic agent or process inciting the inflammatory reaction can be identified. In contrast, primary hypophysitis refers to inflammation confined to the pituitary gland with no identifiable etiologic associations. We report three cases of primary hypophysitis to illustrate the spectrum of three clinicopathological entities that encompass this disease: lymphocytic hypophysitis, granulomatous hypophysitis, and xanthomatous hypophysitis. Our three patients underwent surgery, revealed a symmetrical superior bitemporal quadratic visual field defect. The remainder of the physical examination was unremarkable.

Inflammatiumary lesions of the pituitary gland, known as hypophysitis, are important for several reasons. They clinically and radiologically mimic tumors of the sellar region, causing mass effects such as headache and visual impairment (1). In addition, they may result in hypophysial and/or hypothalamic dysfunction from inflammatory destruction of the hypophysis or compression of the residual normal gland by edema (1–3). Hypophysitis secondary to infection or systemic disease, although common in the past, is relatively rare today. Idiopathic or primary hypophysitis is currently the most common form of pituitary inflammation. Three histopathological conditions are now recognized to fall within this category: lymphocytic hypophysitis, granulomatous hypophysitis, and xanthomatous hypophysitis. We describe three patients to illustrate the spectrum of primary hypophysitis.

Clinical Presentations

Case 1

A 39-yr-old nulliparous woman presented with rapidly progressive frontal headaches, nausea, vomiting, anorexia, weight loss, and cold and hot flashes. As a teenager, she had primary hyperthyroidism for which she received radioactive iodine treatment; she had been on thyroid hormone replace-


Address correspondence and requests for reprints to: Dr. Sylvia L. Asa, Department of Pathology, University Health Network, 610 University Avenue, Suite 4-302, Toronto, Ontario M5G 2M9, Canada. E-mail: sylvia.asa@uhn.on.ca.

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ment since that time. Other significant past medical history included psoriasis. The patient had five sisters; three were hypothyroid, and one had undergone thymectomy for myasthenia gravis. There was no family history of endocrine neoplasms. She had no visual field deficits.

Endocrine laboratory investigations revealed modest hypoprolactinemia of 84 mg/L but marked reduction in random plasma cortisol (35 nmol/L), LH, FSH (<1 mIU/L), and GH (0.1 μg/L) levels. A MRI of the head revealed a 1.9-cm sellar mass with suprasellar extension (Fig. 3A).

The patient underwent trans-sphenoidal resection of the lesion. A postoperative MRI showed significant resolution of the lesion (Fig. 3B). In addition to her persistent anterior pituitary failure, which required replacement with glucocorticoids, T4, and estrogen/progestin, she also developed postoperative central diabetes insipidus requiring desmopressin supplements. Histological examination of the resected lesion showed necrotizing granulomatous inflammation (Fig. 4). There were variable numbers of plasma cells and foamy histiocytes with vacuolated cytoplasm. Areas of old hemorrhage with hemosiderin deposition were present. The lesion was well demarcated, and areas of interspersed normal adenohypophysis were identified. Investigations for infectious diseases including body fluid cultures and chest radiography were entirely negative. Six months later, her headaches returned and a MRI scan showed recurrence of the lesion (Fig. 3C). She was placed on high doses of dexamethasone (16 mg/day) with plans for a second trans-sphenoidal resection. She developed severe Cushing’s syndrome and type 2 diabetes mellitus. A MRI scan 3 months after treatment with corticosteroids showed complete resolution of her pituitary lesion, and surgery was, therefore, cancelled. Further investigations were unable to identify a cause for the pituitary inflammation. She was switched from dexamethasone to maintenance doses of cortisol acetate with resolution of her Cushingoid features and diabetes mellitus. Three years later, she remains disease free clinically and radiographically but continues to require full pituitary hormone replacement.

Case 3

A 32-yr-old G1, P1 woman presented with oligomenorrhea and hyperprolactinemia 3 yr after an uneventful pregnancy. She had resumed normal menses 8 weeks postpartum and did not have persistent galactorrhea. Her PRL level was 96 μg/L (normal, <27 μg/L). Magnetic resonance imaging revealed a 1-cm inhomogeneous lesion that was bright on T1- and T2-weighted images, strongly suggestive of a cyst (Fig. 5). She was started on bromocriptine (up to 5 mg/day), which resulted in normalization of her PRL levels and menstrual function. Two years later, however, the size of the lesion did not regress on repeat magnetic resonance imaging. Preoperative evaluation of her pituitary function using insulin-induced hypoglycemia, TRH, and GnRH revealed no evidence of compromise including GH (peaking to 6.8 μg/L) concentrations. At the time of surgery, a cyst filled with syrupy orange/amber material with floating crystals was noted. The cavity appeared smooth with a fibrous wall. An apparently normal gland was visualized separately. Histological examination of the resected lesion showed chronic hypophysitis with fibrosis, lymphoplasmacytic infiltration, necrosis, hemorrhage, hemosiderin deposition, and foamy histiocytes (Fig. 6). There was no evidence of either an adenoma or of cyst wall remnants. Postoperatively, the patient’s PRL levels normalized (11 μg/L) without dopaminergic inhibition. Two years later, she continues to have
normal pituitary function, including PRL levels (10 µg/L) and regular menstrual function.

**Discussion**

We describe three cases of primary hypophysitis to illustrate the histological and clinical spectrum of this entity. Although the most common pituitary mass is adenoma, other mass lesions include metastatic tumors, cysts, hyperplasia, infections, and inflammation (4). The potentially transient endocrine and compressive features of inflammation require a high index of suspicion because conservative management may eliminate the need for aggressive pituitary surgery. Primary hypophysitis should be considered in the differential diagnosis of pituitary lesions in women around the time of pregnancy, in those with rapidly progressive lesions, and in those in whom PRL levels are discordant with the size of the lesion or response to dopaminergic therapy.

Hypophysitis can be primary or secondary. In secondary hypophysitis, an etiologic agent or defined systemic disease is implicated (5). Bacterial, viral, and fungal pathogens have been reported; opportunistic infections are usually associated with HIV (6). Systemic inflammatory diseases that can involve the pituitary include sarcoidosis (7), Wegener’s granulomatosis (8), Takayasu’s disease (9), Crohn’s disease (10), and Langerhans cell histiocytosis (11, 12).

The causative agent(s) of primary hypophysitis is currently unknown. However, three distinct clinicopathological entities have been described (Table 1).

Since the first report of lymphocytic hypophysitis in 1962 (13), more than 100 cases have been described. Females are affected more frequently than males (8:1). The mean age of diagnosis is 34.5 yr for females and 44.7 yr for males. In females, lymphocytic hypophysitis classically presents during late pregnancy or early postpartum (14). In our earlier review of 16 cases (1), the most common manifestations were hypopituitarism (63%), mass effects (56%), hyperprolactinemia (38%), and diabetes insipidus (19%). Unrecognized and untreated hypopituitarism can result in death. In most cases, radiological studies suggest a pituitary tumor (15–17). Features indicative of lymphocytic hypophysitis, however, include loss of the hyperintense “bright spot” signal of the posterior pituitary, thickening of the pituitary stalk, or enlargement of the posterior gland (18–20). Histologically, lymphocytic hypophysitis is characterized by diffuse infiltration of the pituitary by inflammatory cells, predominantly lymphocytes that form lymphoid follicles; there is variable reactive fibrosis. Although the pathogenesis of lymphocytic hypophysitis is unknown, it is thought to be an autoimmune phenomenon. The histopathology resembles that of other autoimmune endocrine disorders (4), and up to one quarter of patients have other autoimmune disorders. Antipituitary antibodies have been detected in a few patients (21, 22). Most cases involve the anterior lobe and are assumed to be due to antibodies against adenohypophysial cells. In some patients, the clinical presentation and biochemical findings implicate a single hormone-secreting cell type as the target (23–25). Rarely, patients present with isolated diabetes insipidus and the inflammatory process is restricted to the posterior lobe and stalk, which can exhibit localized enlargement; this disorder has been named infundibular neurohypophysitis (18, 26, 27).

Granulomatous hypophysitis, first described in 1917, has
an annual incidence of 1 in 10 million and accounts for less than 1% of all pituitary disorders (5). In contrast to lymphocytic hypophysitis, there is no gender predilection. The mean age of diagnosis is 21.5 yr for females and 50 yr for males. Most reported cases are diagnosed at autopsy. Patients present with nausea, vomiting, meningitis, hyperprolactinemia, and/or diabetes insipidus. Radiologically, there is an intrasellar mass that may show suprasellar extension. Histologically, granulomatous hypophysitis is characterized by collections of histiocytes, multinucleated giant cells, and variable numbers of lymphocytes and plasma cells (4). Although some cases are attributable to infection, most are idiopathic. An autoimmune pathogenesis has also been proposed for this disorder (28, 29), and some authors believe that granulomatous and lymphocytic hypophysitis are different manifestations of the same disease, but epidemiological data do not support this hypothesis.

Xanthomatous hypophysitis, the least common form of primary hypophysitis, was first described in three cases in 1998 (3). It is defined histologically by the presence of lipid-rich foamy histiocytes with variable numbers of lymphocytes and resembles xanthomatous inflammatory processes elsewhere, such as xanthomatous cholecystitis, endometritis, or pyelonephritis, in which the inflammation is attributed to cell debris of endogenous or infectious origin. Unlike the other hypophysitisides, these lesions are more likely to be cystic on radiological or surgical evaluation. It may be that the inflammation is a response to components of a ruptured cyst, however, no confirmation of a preexisting cyst has been identified. No infectious process has been implicated. Any attempt to characterize this entity based on the few cases reported would be speculative.

Currently, it is unclear whether these three conditions are truly distinct entities, or merely different manifestations of the same disease. They share clinical and radiological features, and there is no reliable way to distinguish the hypophysitisides from each other without histological examination. Nevertheless, they are important in the differential diagnosis of the sellar mass.

Conservative management may lead to resolution without the need for surgery (30). Transsphenoidal surgery is, however, both diagnostic and therapeutic and, therefore, should be performed in cases with progressive compression or those in whom radiographical and/or clinical progression occurs during conservative medical management (1, 31, 32). Hyperprolactinemia (33–35) and pituitary insufficiency (36, 37) resolve after pituitary surgery, in most cases (1). In rare instances, surgical intervention has resulted in further deterioration of visual field deficits (38) and/or hypopituitarism (33, 38–40). These complications highlight the importance of early suspicion of the diagnosis and conservative management in patients with nonprogressive disease. In the event of surgery, intraoperative pathology consultation will confirm the diagnosis and prevent aggressive resection of potentially viable pituitary tissue (1, 2, 41).
Since most cases of primary hypophysitis present clinically like neoplasms, they usually undergo surgical resection; histological examination reveals their true nature. This, and their variable natural history, makes it difficult to accurately assess the efficacy of nonsurgical treatments. For example, all reported cases of xanthomatous hypophysitis have been diagnosed after surgical resection, and, therefore, there are no data reflecting the effects of medical treatment on this entity (3).

Spontaneous recovery of pituitary function with resolution of the pituitary mass has been described in cases with histologically proven hypophysitis (36, 37, 42, 43). Some patients, however, require active treatment. Although the administration of bromocriptine can improve visual field deficits and lower the hyperprolactinemia, the beneficial impact of this agent on the course of the disease is unproven. Moreover, lack of tumor shrinkage, as in our cases, should raise suspicion of xanthomatous hypophysitis. Glucocorticoid therapy has been advocated to reduce inflammation and has been temporarily effective in some patients (35, 37, 39). The true efficacy of corticosteroid therapy in this condition, however, also remains uncertain.

In summary, the hypophysitides are a heterogeneous group of inflammatory conditions involving the pituitary gland. Secondary hypophysitis is more easily diagnosed because patients will likely have other systemic manifestations of their underlying disorder. Primary hypophysitis encompasses three clinicopathological entities: lymphocytic hypophysitis, granulomatous hypophysitis, and more recently, xanthomatous hypophysitis. Unlike secondary hypophysitis, these conditions are usually confined to the pituitary gland and, therefore, require a higher level of clinical suspicion to ensure optimal management.

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