HYPOPHYSITIS: IT’S NOT YOUR MOTHER’S PITUITARY ADENOMA

Consideration of the differential diagnosis of a sellar mass most commonly leads to the diagnosis of pituitary adenoma. The pituitary gland, however, can also be the target of inflammatory reactions, either independent from or related to systemic infections, autoimmune reactions, or neoplasms. Hypophysitis, which refers to inflammation of the pituitary gland, is an important diagnosis to consider when a space-occupying lesion of the sella turcica is assessed. Although these disorders are less common than pituitary adenomas, accurate and early diagnosis of hypophysitis is imperative to allow for appropriate treatment targeted to endocrine replacement, neurologic impairments, and possible underlying systemic disorders.

Primary hypophysitis occurs in a spectrum of histopathologic varieties. Autoimmune, or lymphocytic hypophysitis (LH), is the most common subtype, although the actual incidence of LH is difficult to assess because of confusion with Sheehan syndrome and spontaneous recovery of subclinical or undiagnosed cases (1). With its dense lymphocytic infiltration and fibrosis, LH is further classified on the basis of anatomy, depending on the extent of inflammation through the anterior pituitary (lymphocytic adenohypophysitis) or posterior pituitary and infundibulum (lymphocytic infundibuloneurohypophysitis). It affects women more frequently than men, and it often occurs during late pregnancy or the postpartum period (2). There is an autoimmune pathogenesis, and an association with coexistent autoimmune disorders in up to 50% of patients, although no specific autoantigen has been identified as the culprit (3-6). In addition, the initial manifestation or evaluation can reveal isolated adrenocorticotrophic hormone deficiency or diabetes insipidus, which differs substantially from the typical presentation of a pituitary adenoma (7).

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In this issue of Endocrine Practice, Demetri et al (8) focus attention on granulomatous hypophysitis (GRH) (8). This form of hypophysitis has been described in association with several different systemic conditions, as reviewed by Demetri et al (8) and by others (3,9). The current case presented, however, was that of primary GRH, in which no systemic condition was identified. Primary GRH has also been reported in association with Rathke cleft cysts (10,11). Although not as common as LH, the GRH variant occurs in about 1% of sellar lesions (12). There is frequent suprasellar extension and cavernous sinus invasion, and more rarely, involvement of the sinuses occurs, as described in the patient of Demetri et al (8). The histologic features include histiocytes, multinucleated giant cells, and variable numbers of lymphocytes and plasma cells. Although the cause is not clear, autoimmunity may have a role, similar to that with LH, and this disease may, in fact, be on a continuum with LH.

Xanthomatous hypophysitis has been described in a small number of cases. This subtype is more likely to be cystic in nature, and it includes foamy (lipid-rich) histiocytes with varied numbers of lymphocytes. Its cause is unknown, although it may be related to changes after a cyst has ruptured (13).

Necrotizing hypophysitis, the least described subtype of primary hypophysitis, has been suggested in 3 cases reported from 2 different medical centers (14,15). The cases in adults manifested clinically with diabetes insipidus, with magnetic resonance imaging (MRI) features typical of hypophysitis, including an enlarged, enhanced pituitary gland with thickened, expanded infundibulum, suggesting involvement up to the hypothalamus. Necrotizing hypophysitis has been considered an entity distinct from LH on the basis of both the anatomic extent of inflammation and the histopathologic features of necrosis and fibrosis in conjunction with the infundibulohypophysitis.

The initial manifestations of most forms of hypophysitis usually consist of symptoms of mass effect, chiasmal compression, hypopituitarism, or some combination of these factors, similar to those of pituitary adenoma. Although there are no pathognomonic clinical, biochemical, or radiographic criteria, there has been continued analysis of methods to distinguish hypophysitis from pituitary adenoma before surgical intervention (16). The former can be suggested clinically, particularly in cases with current or recent pregnancy, presentation with diabetes insipidus or adrenocorticotrophic hormone or thyroid-stimulating hormone deficiency, hypopituitarism of rapid onset or out of proportion to the size of pituitary lesions, and associated autoimmune diseases (1).

MRI technology has vastly improved the ability of clinicians to diagnose pituitary pathologic conditions. Although hypophysitis accounts for only 10% to 15% of all pituitary lesions, the advent of MRI in the mid-1980s facilitated increased identification of this inflammatory pituitary disease. Characteristic MRI features are best
seen with use of a contrast agent and dedicated thin-section pituitary sequences and include a contrast-enhancing, homogeneous, symmetrically enlarged sellar mass, with relatively low signal on T1-weighted and high signal on T2-weighted images (17). These findings may be more specific to hypophysitis than to a pituitary macroadenoma. The pituitary stalk may be enlarged, with inflammatory extension up to the hypothalamus.

Overall, the natural history of hypophysitis is unclear, and appropriate management has not been well established. In rare cases, close observation has resulted in complete resolution of inflammation, radiologic abnormalities, and endocrine dysfunction, indicating a benign and transient nature of this disease (18,19). Nevertheless, observation alone has also been described to lead to chronic hypophysitis, granuloma and fibrosis formation, and death (20). Selective hormone replacement should be initiated promptly when pituitary dysfunction is detected. Evaluation can also include investigation of possible underlying systemic disease, treatment of which may ameliorate pituitary function or neurologic symptoms.

In contrast to the management of pituitary adenoma, additional medical therapy may be appropriate in the absence of visual compromise (21) and includes use of antinflammatory agents—namely, corticosteroids or methotrexate to induce regression of inflammatory tissue and improvement of pituitary function (22-24). Although improvement has been described, particularly in cases of LH treated with high-dose corticosteroids, results are not consistently reproducible among any subtype of hypophysitis, and relapses have occurred after withdrawal of corticosteroid therapy. Surgical intervention for hypophysitis with use of a transsphenoidal approach has been undertaken for cases misdiagnosed as pituitary adenoma, for failed medical therapy, or for progressive signs of mass effect or hypopituitarism. Surgical treatment allows rapid decompression of the mass and determination of a histologic diagnosis, which can clarify the cause and eliminate the need for high-dose corticosteroid therapy. In addition, reports have suggested that if intraoperative frozen section suggests the presence of hypophysitis, the surgical goal should focus on decompression of the sella turcica without causing hypopituitarism, rather than extensive debulking of the lesion, as may be the objective for other sellar lesions. Radiotherapy has been described infrequently, although gamma knife radiosurgery with low-dose irradiation may be effective (22). Regardless of the choice of therapy, long-term follow-up with repeated imaging and hormonal evaluation will facilitate early identification in the case of a recurrent mass or symptoms.

In conclusion, careful identification and classification of hypophysitis are necessary to guide management. As demonstrated by the case described by Demetri et al (8), distinguishing hypophysitis from other causes of a sellar lesion can affect the interpretation of operative success and the subsequent clinical course. The role of either medical or surgical therapy is not well established, but both have been associated with improvement of pituitary endocrine function and mass-related symptoms. In fact, the literature suggests that optimal management involves achieving a high index of suspicion through use of clinical and radiologic criteria. This approach can provide patients, particularly those with milder disease, a more conservative management without initiation of an extensive, and possibly unnecessary, surgical procedure. To date, however, despite the advent of MRI to assist in the assessment of pituitary lesions, many cases of hypophysitis are presumed to be pituitary adenoma and are still diagnosed either on surgical pathology examination or at autopsy. Further study is still needed to assist in understanding the appropriate evaluation and management of this rare but interesting condition.

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