

Inflammatory and Infectious Processes Involving the Pituitary Gland

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Abstract: Inflammatory and infectious diseases of the pituitary gland are rare, and imaging diagnosis may be difficult. They encompass a wide spectrum of pathology including autoimmune (lymphocytic) hypophysitis, granulomatous hypophysitis, local manifestations of systemic disease, and a multitude of infectious processes. Based on extensive review of the literature, this article will present a classification scheme, description of pathology, and imaging findings of the various inflammatory and infectious entities, along with selected images from our case material.

Key Words: hypophysitis, sarcoidosis, langerhans cell histiocytosis, wegener granulomatosis

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Inflammatory conditions of the pituitary gland are rare and occur much less commonly than primary tumors. The exact classification of these disorders varies among authors, but they are generally divided into primary and secondary processes (Table 1). Secondary hypophysitis is usually associated with an underlying systemic disorder, whereas primary hypophysitis is isolated to the gland.¹ Histologically, inflammatory lesions of the pituitary gland are a heterogeneous group of diseases and include lymphocytic hypophysitis, giant cell granulomatous inflammation, xanthomatous hypophysitis, and pyogenic, tubercular, and fungal abscesses. Abscess may occur secondary to aseptic necrosis of a pituitary adenoma or as a complication of bacterial meningitis.² Mucocles and noninfectious granulomatous disease, particularly sarcoidosis and histiocytosis X, may affect the hypothalamus and pituitary gland.³

The pituitary gland may also be injured by radiation resulting in an inflammatory process that may also involve the optic chiasm.⁴ In this article, we review the imaging appearance of the most common inflammatory and infectious processes affecting the pituitary gland.

Primary Hypophysitis

Idiopathic or primary hypophysitis is currently the most common form of pituitary inflammation. Three histopathological conditions are now recognized within this category: lymphocytic hypophysitis, granulomatous hypophysitis, and

xanthomatous hypophysitis. Unlike secondary hypophysitis, these conditions are usually confined to the pituitary gland and thus require a higher level of clinical suspicion to ensure that the correct diagnosis is made and that the clinical management is optimal.⁵

Primary Lymphocytic Hypophysitis

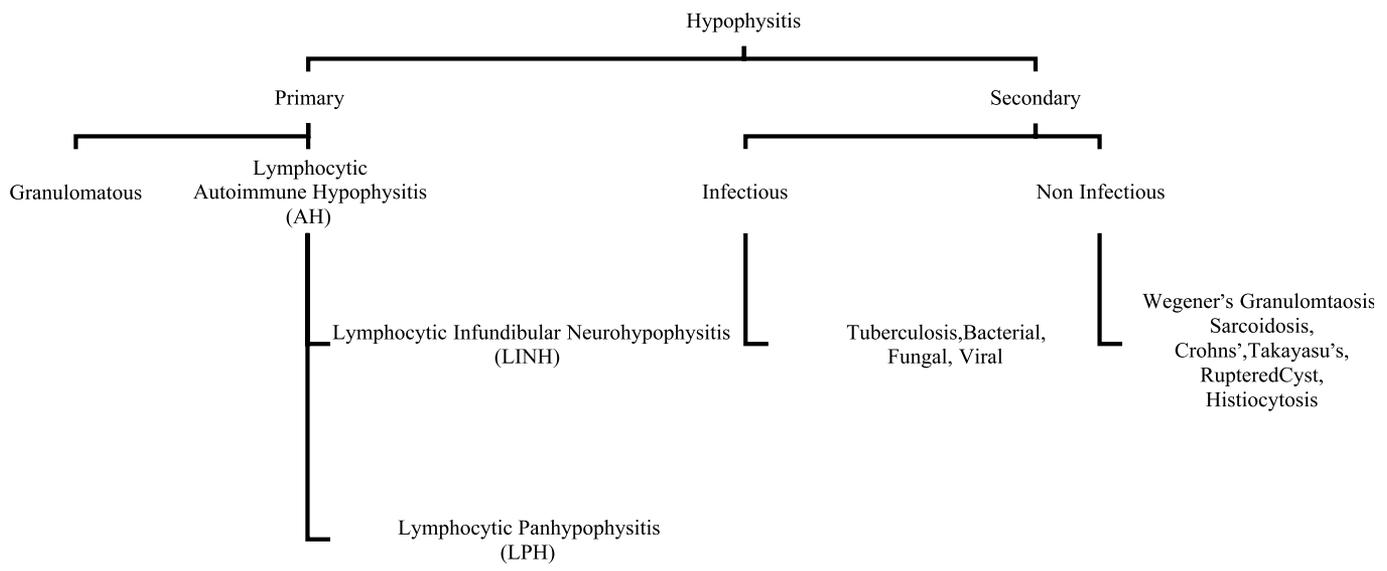
Lymphocytic hypophysitis is the most common among the chronic inflammations that primarily affect the pituitary gland, surpassing granulomatous and xanthomatous lesions.⁶ Lymphocytic hypophysitis is an autoimmune disorder. Autoimmune hypophysitis (AH) is frequently associated with Hashimoto thyroiditis, adrenalitis, ovarian failure, atrophic gastritis, and pernicious anemia.⁷ Lymphocytic hypophysitis may be associated with systemic lupus erythematosus.⁸ Most inflammatory pituitary lesions occur in women, during the postpartum period. Most commonly, these represent AH.⁹ When occurring in pregnancy, AH does not cause complications on the fetus or on the outcome of pregnancy, which typically concludes at term with spontaneous vaginal delivery.⁶ Lymphocytic hypophysitis is characterized by diffuse infiltration of the pituitary gland by lymphocytes and plasma cells.⁹ It was originally labeled *lymphocytic adenohypophysitis* (LAH) because the inflammation was thought to be limited to the anterior hypophysis.⁹ Later, it was found that the autoimmune infiltrates could involve the infundibular stem and the posterior lobe and the term *lymphocytic infundibuloneurohypophysitis* (LINH) was created. Finally, it was recognized that the adenohypophysis, infundibulum, and neurohypophysis can be affected, giving rise to the term *lymphocytic panhypophysitis*. Headache and visual disturbances due to compression of adjacent structures are the most common, and usually the initial, complaints. Other common symptoms are due to partial or complete deficits of anterior pituitary hormones, most commonly corticotropin followed by thyrotropin, gonadotropins, and prolactin (PRL). These deficiencies are considered to be the direct result of the autoimmune attack on the pituitary acinar cells and result in the classic signs and symptoms of hypoadrenalism, hypothyroidism, and hypogonadism. The deficit of PRL manifests itself in the postpartum as an inability to lactate.

Primary lymphocytic hypophysitis also results in symptoms due to deficits of the hormones produced by the posterior pituitary (mainly diabetes insipidus), which can be attributed either to direct immune destruction or to compression of the posterior lobe and infundibular stem. Diabetes insipidus is the cardinal feature of LINH. Diabetes insipidus can also be seen in pure LAH, despite the absence of lymphocytic infiltration in the neuroinfundibulum, because swelling of the pars tuberalis of the adenohypophysis, which

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TABLE 1. Suggested Classification Scheme: Inflammatory and Infectious Hypophysitis

covers the infundibulum anterolaterally, may inhibit the axonal transport of antidiuretic hormone. Less common manifestations are hyperprolactinemia, mainly resulting in amenorrhea/oligomenorrhea and galactorrhea. Several mechanisms have been invoked to explain this increase in PRL. Stalk compression, with resulting decrease in dopamine delivery to the anterior pituitary, is certainly the best characterized mechanism and accounts for the hyperprolactinemia associated with many suprasellar masses. It is very unusual for AH to present as an incidental finding in the absence of clinical pituitary disease. The main diagnostic issue is the distinction between the rare cases of AH and the overwhelmingly more common pituitary tumors, especially nonsecreting adenomas.⁶ The differential diagnosis of LINH also includes meningioma, which may enlarge considerably during pregnancy as do adenomas.³ At present, such distinction can be achieved with certainty only by microscopic examination of the pituitary tissue obtained from surgery. Even with magnetic resonance imaging (MRI) studies, approximately 40% of LINH cases are diagnosed preoperatively as pituitary adenomas.⁶

Idiopathic Granulomatous Hypophysitis

Idiopathic granulomatous hypophysitis, a rare chronic inflammatory condition, is distinct from secondary granulomatous hypophysitis associated with systemic disorders such as sarcoidosis, syphilis, tuberculosis, or histiocytosis X.^{6,10} The relationship, if any, between lymphocytic and idiopathic granulomatous hypophysitis is unclear. Some authors feel these conditions are different or are opposite ends of the spectrum of same disease, with fibrosis representing the end stage of the inflammatory process.⁹ Granulomatous hypophysitis is, however, distinct from lymphocytic hypophysitis because it lacks the key epidemiological features that are present in lymphocytic hypophysitis such as its female

preponderance,^{5,6} association with pregnancy, occasional spontaneous resolution, and association with other well-established autoimmune diseases.⁶ Granulomatous hypophysitis presents with headache, visual disturbances, nausea, vomiting, diabetes insipidus, and hyperprolactinemia.^{5,6,10}



FIGURE 1. Lymphocytic hypophysitis mimicking a macroadenoma. Coronal T1WI. The pituitary gland is diffusely and symmetrically enlarged, extending into the suprasellar region. Note that the floor of the sella is intact.

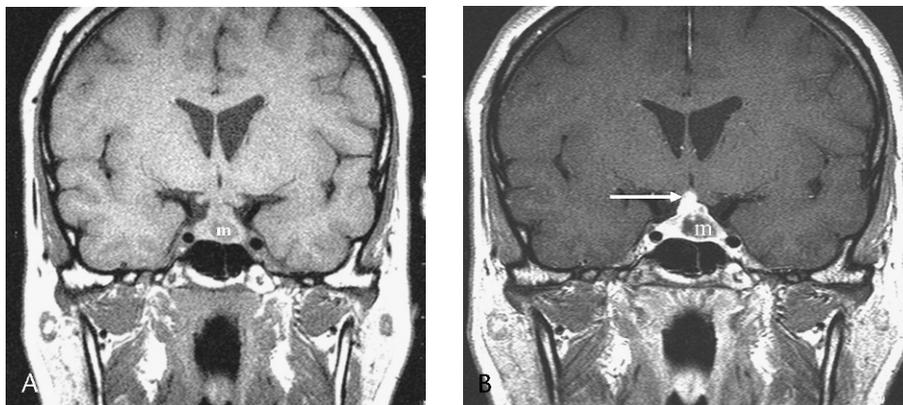


FIGURE 2. A and B, Lymphocytic hypophysitis. Coronal pre- and postgadolinium T1WI. In this case, note the ring enhancement of a large hypointense pituitary mass (m) extending into the suprasellar cistern, with thickening and enhancement of pituitary stalk (arrow).

Granulomatous hypophysitis may coexist with lymphocytic hypophysitis.⁶

Imaging of Primary Hypophysitis

On precontrast T1-weighted MR images, the normal adenohypophysis demonstrates a homogenous signal, approximately isointense to gray matter, whereas the normal neurohypophysis is hyperintense. The hyperintensity of the neurohypophysis is believed to reflect the high phospholipid content in antidiuretic hormone and oxytocin neurosecretory granules (see article by Castillo in this issue). After gadolinium administration, there is a physiological and homogeneous enhancement of the entire gland.⁶ LH should be included among the differential diagnosis of cystic, ring-enhancing sellar masses. The presence of such lesion is typical of LH and may aid in reaching the correct diagnosis.¹¹ LH should also be considered in patients with a triad of empty sella, hyperprolactinemia, and hypopituitarism.¹ Primary inflammatory disorders of the pituitary such as AH may account for some cases of “sterile pituitary abscesses” in which no species are cultured and only inflammation is seen¹¹ (Fig. 1). In LAH, the typical precontrast MRI findings include a symmetric enlargement of a homogeneous pituitary gland, a thickened but rarely displaced stalk, and a usually intact sellar floor (Fig. 2). This is in contrast to pituitary macroadenomas, which are asymmetric, displace the infundibular stalk, depress or erode the sellar floor, and only rarely obscure the posterior pituitary “bright spot.” The pattern of signal enhancement after gadolinium may be helpful in differentiating LAH from a macroadenoma. Intense and homogenous enhancement of the anterior pituitary, similar to that of the cavernous sinuses, is suggestive of an inflammatory infiltrative process such as LAH rather than a macroadenoma. Macroadenomas generally enhance less and more slowly than the normal pituitary tissues on dynamic contrast-enhanced MRI. Pituitary adenomas may develop secondary inflammatory changes and show intense and homogenous contrast enhancement, making distinction from LAH difficult. In LINH, there is the loss of T1 hyperintensity of the neurohypophysis. This is a nonspecific

finding, as various infiltrative, inflammatory, and neoplastic processes can result in a similar appearance.⁶ Often, the MRI findings of AH are not specific enough to distinguish this rare entity from the far more prevalent pituitary adenomas. However, the symmetry of the pituitary enhancement, lack of erosive changes of the sellar floor, homogeneity of the pituitary mass, and its intense enhancement after gadolinium can be diagnostic in the proper clinical context. Careful correlation with clinical history and endocrine findings is therefore important for a proper interpretation of the MRI findings in AH.^{5,6} Preoperative diagnosis of idiopathic granulomatous hypophysitis is usually difficult; however, stalk thickening and loss of posterior pituitary bright spot on MRI are clues to the diagnosis.¹²

Treatment of Primary Autoimmune Hypophysitis

The treatment of AH is currently directed at the relief of symptoms and includes reducing the size of the pituitary mass and replacing deficient hormones. Mass reduction can be achieved by surgery, lympholytic drugs (glucocorticoids, azathioprine, or methotrexate), or radiotherapy.⁶ The role of surgery in the definitive treatment of AH remains controversial, but current literature suggests a limited utility. When the preoperative diagnosis of a pituitary mass is still undefined, surgery should be performed only in the presence of serious and progressive deficits of visual fields, acuity, and ocular movements not responsive to medical treatment. Patients presenting with hypopituitarism, diabetes insipidus, or hyperprolactinemia rarely benefit from surgery because their defects are secondary to diffuse lymphocytic infiltration, rather than to compression of the normal glandular parenchyma. During surgery, if frozen sections suggests AH, the surgeon should try to achieve decompression of the sella turcica rather than extensive debulking of the lesion, as is the objective for pituitary adenomas.⁶ Surgery, in addition to providing a histological diagnosis, is effective in achieving decompression of the sellar mass, thereby resolving headaches and visual deficits. Only rarely, however, does surgery improve preexisting endocrine deficits. Complications of surgery such as bleeding, cerebrospinal fluid leaks, and

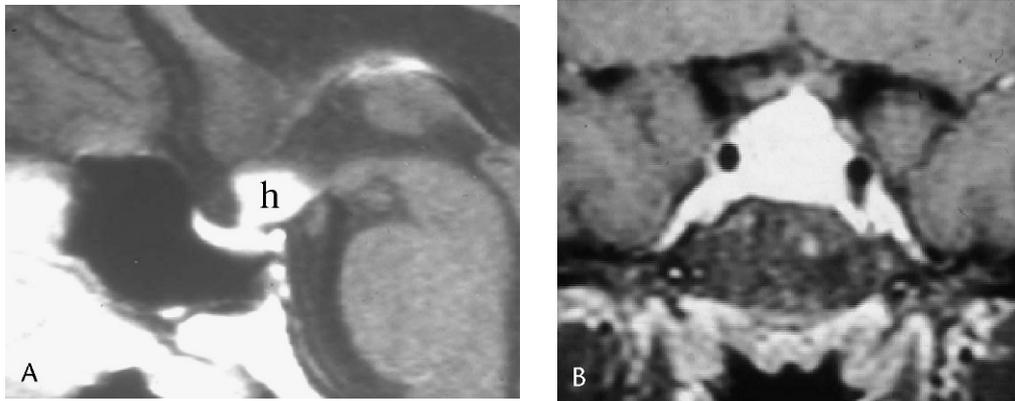


FIGURE 3. A and B, Pituitary sarcoidosis. Sagittal and coronal postgadolinium T1WI demonstrate diffuse intense enhancement of enlarged gland, thickened and intensely enhancing stalk and hypothalamus (h).

diabetes insipidus are often transitory, although occasionally they can be persistent.⁶

Secondary Hypophysitis

In secondary hypophysitis, an etiologic agent or a defined systemic disease is the cause of the pituitary lesion. Systemic inflammatory diseases that can involve the pituitary include sarcoidosis, Wegener granulomatosis, Takayasu disease, Crohn disease, and Langerhans cell histiocytosis.⁹ Secondary hypophysitis is easier to diagnose than is primary disease because patients will likely have other systemic manifestations of the underlying disorder.⁹ In the setting of immunosuppression, fungal infection (most commonly aspergillosis), tuberculosis, and toxoplasmosis may involve the pituitary gland either exclusively or as a part of disseminated infection. Any one of these inflammatory processes may mimic a pituitary neoplasm and result in mass effect and hypothalamic-hypophyseal endocrine dysfunction.² The inflammatory infiltrate is mainly lymphocytic or xanthogranulomatous in nature and usually surrounds the lesion rather than the entire gland.⁶ Xanthogranulomatous inflammation is thought to be a granulomatous foreign-body reaction to conditions including infection

and some systemic inflammatory processes. An adenoma, Rathke cleft cyst, or mucocoele may also be the cause of xanthogranulomatous inflammation.⁶ A ruptured Rathke cleft cyst can be a rare cause of giant cell granulomatous hypophysitis.¹³ Microscopically, in xanthomatous hypophysitis, the pituitary shows cyst-like areas of liquefaction, infiltrated by lipid-rich foamy histiocytes and lymphocytes.⁶ When an abscess involves the pituitary, visual disturbances may be caused by inflammation, without compression, of the optic nerves.¹⁴

Imaging Secondary Granulomatous Hypophysitis

Imaging findings in secondary granulomatous hypophysitis may mimic those of an adenoma and show variable contrast enhancement. The striking computed tomography features are an intrasellar mass with cystic areas and ring enhancement. On MRI, the lesion is usually isointense to brain on T1-weighted images and heterogeneous on T2 sequences. Abnormal thickening of the infundibulum has been described. Contrast enhancement is frequently homogeneous, but cystic areas with ring enhancement may be seen.¹⁰ A diffusely enlarged gland and extension of the enhancement to the optic chiasm may be seen. Involvement

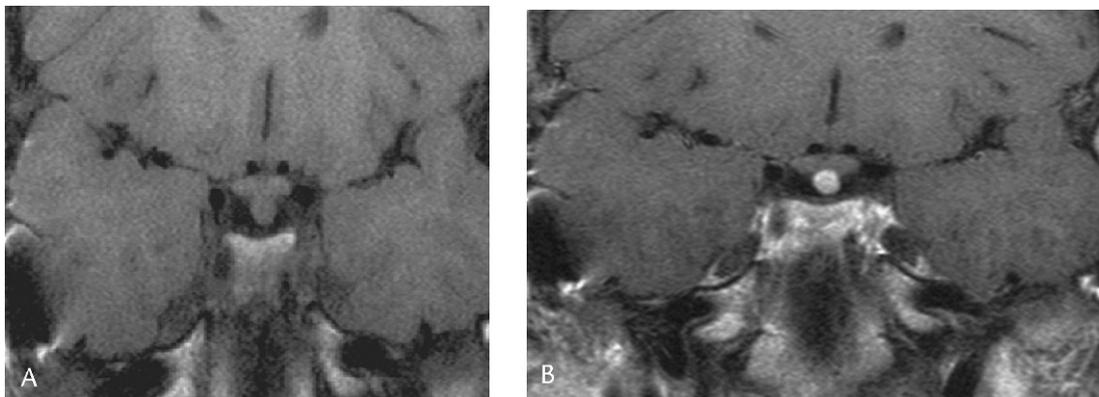


FIGURE 4. A and B, Pituitary Langerhans histiocytosis. Coronal T1WI pre- and postgadolinium. The stalk is thickened and enhances postgadolinium.

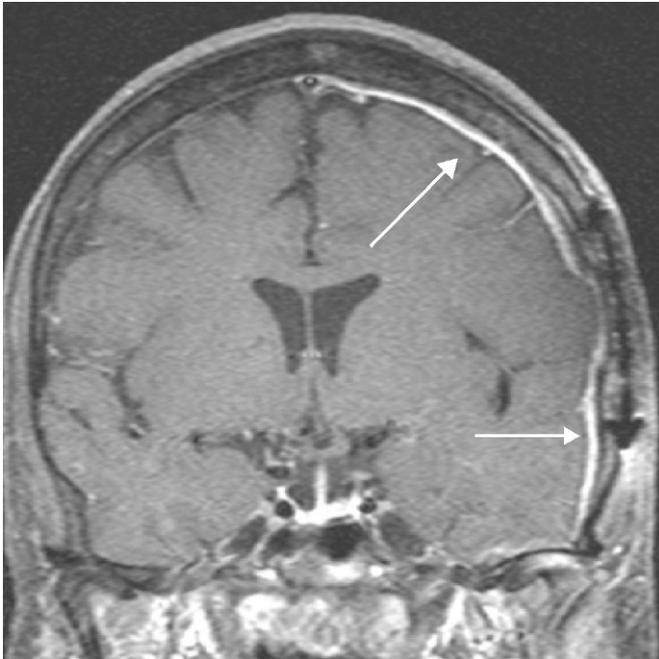


FIGURE 5. Pituitary Wegener granulomatosis. Coronal T1WI postgadolinium. In this case, there is a partially empty sella and the stalk is slightly thickened and enhancing. The diffuse dural enhancement (arrows) is a clue to a more diffuse inflammatory disease.

of the anterior lobe may result in a T1-weighted hyperintensity that is presumably due to hemorrhage. Contrast-enhanced studies may show a little central enhancement in the anterior pituitary.^{15,16} Findings suggesting inflammation, such as linear enhancement of the dura matter, sphenoid mucosal thickening, and adjacent bone marrow abnormality, may be also observed. However, these findings are non-specific and indistinguishable from those caused by neoplastic or inflammatory hypophysial processes. The diagnosis of secondary inflammatory hypophysitis may be suggested

when a history of sarcoidosis, histiocytosis X, tuberculosis, or a meningeal tear is obtained in the presence of hypopituitarism.¹⁰ Treatment is geared toward the systemic disease process.

Sarcoidosis

The most common symptom of pituitary sarcoidosis is headache. The most striking imaging feature is the presence of pituitary stalk thickening. Leptomeningeal involvement in the region of the hypothalamus and pituitary infundibulum may be seen as an isolated finding or associated with involvement of the basilar leptomeninges. Isolated involvement of the infundibulum mimics histiocytosis, lymphoma, metastatic carcinoma, and Langerhans cell histiocytosis.^{17,18} Hypothalamic and infundibular involvement may present as diabetes insipidus or amenorrhea. Disease isolated to the pituitary gland has been reported to have nonspecific imaging findings of an enhancing intrasellar mass with suprasellar extension¹⁷ (Fig. 3).

Langerhans Cell Histiocytosis

Formerly called *histiocytosis X* and *eosinophilic granuloma*, this disease is a multisystem disorder involving the skin, bones, orbit, lungs, and the central nervous system. Proliferation of histiocytes form granulomas in and around the hypothalamus and infundibulum. Diabetes insipidus is the most common presentation, but patients can also develop other endocrine dysfunctions or visual impairment. MRI typically shows a thickened infundibulum or a hypothalamic mass that is isointense on T1, hyperintense on T2-weighted images, and enhances with contrast material (Fig. 4). The normal posterior pituitary bright spot is frequently absent.¹⁸

Wegener Granulomatosis

Diabetes insipidus is the most common manifestation of Wegener granulomatosis involving the pituitary gland. There are a few case reports of Wegener granulomatosis involving the anterior pituitary gland and resulting in hyperprolactinemia or panhypopituitarism. Characteristic

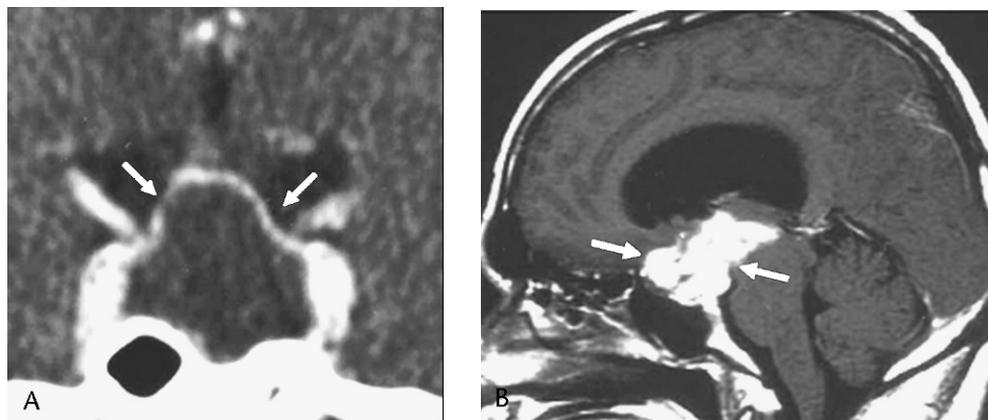


FIGURE 6. A and B, Pituitary tuberculosis. Coronal and sagittal T1WI postgadolinium images in 2 different patients. A, Large hypointense intrasellar and suprasellar mass demonstrates intense peripheral enhancement (arrows). B, There is intense solid enhancement of the pituitary gland, with tuberculomas in the suprasellar region (arrows).

MR imaging features include a diffusely enlarged pituitary gland, a relatively normal sized sella, a thickened stalk, and enhancement of the adjacent optic chiasm^{15,16} (Fig. 5).

Tuberculosis

Intrasellar tuberculomas are rare and have a female predominance. Imaging studies show involvement of paranasal sinuses and pituitary fossa, along with thickening of pituitary stalk. Simultaneous involvement of clivus may be an additional imaging feature of this disease.¹⁹ MR images in these patients will show a hypointense pituitary mass with or without an absent posterior pituitary bright signal. Tubercular pituitary abscesses appear isointense to hypointense on T1WI and hyperintense on T2WI. They may occasionally appear hyperintense on T1WI owing to high protein content. These signal characteristics are nonspecific and overlap those of pituitary adenomas. Tubercular abscesses may show peripheral contrast enhancement and adjacent meningeal enhancement on contrast-enhanced MR. There may be suprasellar extension or involvement of the optic chiasm^{20,21} (Fig. 6). The incidence of pituitary tuberculosis is likely to increase with a rise in the incidence of AIDS.¹⁹

CONCLUSIONS

Inflammatory diseases involving the pituitary gland are rare when compared with adenomas. Although primary autoimmune lymphocytic hypophysitis is more common than lesions secondary to a known systemic inflammatory or infectious processes, imaging findings are usually not specific enough to distinguish this disease from adenomas. Accurate diagnosis requires a high degree of suspicion and correlation with clinical signs and symptoms. Diagnosis of secondary hypophysitis may be suggested when appropriate imaging abnormalities are seen in a patient with a known systemic inflammatory or infectious process. Treatment of primary hypophysitis is aimed at symptomatic relief of the concomitant endocrine and/or visual disturbances. Treatment of secondary hypophysitis consists is targeted to the underlying systemic disorder.

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