Acta Neurochir (Wien) (1993) 121: 152–158

Acta Neurochirurgica

Pituitary Granuloma and Chronic Inflammation of Hypophysis: Clinical and Immunohistochemical Studies

M. Higuchi[1], N. Arita[1], S. Mori[1], B. Satoh[2], H. Mori[3], and T. Hayakawa[1]

Department of [1] Neurosurgery and [2] Third Department of Internal Medicine, Osaka University Medical School, and [3] Second Department of Pathology, Osaka Medical College, Osaka, Japan

Summary

We describe five patients with chronic inflammation of the hypophysis including three pituitary granulomas of unknown aetiology. In contrast to the previously reported cases, the involvement of neurohypophysis or hypothalamus was a distinct clinical feature in these patients. Impairment of anterior pituitary function was less prominent, while polyuria and polydipsia occurred in all cases. Enlargement of the sella turcica was absent in three and slight in two cases. CT scan and MR images demonstrated a contrast-enhanced sellar mass in all patients; abnormally thickened pituitary stalk and infundibulum with contrast-enhancement was observed in four. The fibrous tissues were removed by the transsphenoidal approach in four patients, and by the subfrontal approach in one case. In all patients, the endocrinological dysfunction was prolonged. No increase in the size of the remaining pituitary mass was demonstrated on repeated MR images in any of the patients.

On histological examination, granulomatous formation was present in three samples, and multinucleated Langhans' giant cells were seen in one. The epithelioid cells and multinucleated giant cells constituting the granulomas were positive for anti-macrophage antibody. No firm laboratory or histological evidence was obtained supporting the presence of systemic disease leading to granulomas. In the other two cases, the pituitary lesions were composed of chronic inflammation tissue, and serum antipituitary antibodies were present in a patient with concurrent Hashimoto's thyroiditis.

Our experiences with chronic inflammation of the hypophysis indicate that these patients are best managed by histological confirmation of the lesion followed by adequate hormonal replacement.

Based on our findings and those reported in the literature, we propose that patients with granulomatous hypophysitis or chronic inflammation of the hypophysis be managed as follows: When an underlying disease is detected, the patient should begin to receive conservative treatment for the causative disease plus hormonal replacement therapy, as necessary. However, when visual disturbance is progressive and uncontrollable by conservative means, surgical decompression of the chiasma is required. If the pathogenesis of the pituitary lesion cannot be identified, surgical exploration is essential for a precise pathological diagnosis. When a granulomatous or chronic inflammatory process is evident intra-operatively, partial removal or biopsy are recommended. Radical resection of fibrous and adhesive tissue with infundibular impairment will lead not only to exacerbation of the pre-existing anterior- and/or posterior pituitary dysfunction, but also to grave hypothalamic injury.

Keywords: Pituitary granuloma; giant cell granuloma; chronic inflammation of hypophysis; diabetes insipidus.

Introduction

Granulomatous hypophysitis is an almost unknown clinicopathological entity. Occasionally, the pituitary gland is affected by systemic granulomatous disorders, such as tuberculosis, sarcoidosis and histiocytosis X [3, 4, 7, 11, 15]. In rare cases, granulomatous lesions are confined to the pituitary gland[4, 6, 11], or hypophyseal dysfunction precedes other symptoms[2].

When such specific aetiologies are excluded, there remain a very few patients with granulomatous hypophysitis of unknown origin[3, 7, 15, 16]. According to published reports, 8 cases were diagnosed as idiopathic granulomatous hypophysitis based on surgical specimens[3, 7, 15, 16, 17].

We have performed more than 300 trans-sphenoidal operations for sellar mass lesions, the majority of which were tumourous disorders such as pituitary adenoma and craniopharyngioma, coinciding with the pre-operative diagnosis. We have encountered a few patients with non-tumourous lesions, in these cases, correct diagnosis and appropriate management during and after surgery were of utmost importance.

In this report, we describe five patients with chronic inflammation of the hypophysis including three pituitary granulomas of unknown origin. We present their endocrinological, radiological, and histopathological

features, and discuss the treatment of choice for this disorder.

Case Reports

We encountered five patients with chronic inflammation of the hypophysis including three pituitary granulomas since 1979. One patient underwent craniotomy, in the others, the trans-sphenoidal approach was used. For histopathological examination, we performed haematoxylin and eosin (H & E)-, Ziehl-Neelsen-, and PAS staining. Immunohistochemical staining for macrophage and anterior pituitary hormones was by the PAP method (DAKO LSAB Kit, DAKO Japan Co. Ltd., Kyoto, Japan). The clinical findings of the five patients are summarized in Table 1 and Table 2.

Case 1

This 46-year-old female developed bitemporal hemianopsia, polyuria and polydipsia. Neurological examination was normal, except for bitemporal hemianopsia. Skull X-ray films showed normal-sized sella turcica. A CT scan revealed a sellar mass lesion, which was homogeneously enhanced with contrast material. On endocrinological examination, both the basal and post-stimulation values of serum GH and LH were low, while the basal value of serum PRL was slightly elevated (36.0 ng/ml). A water deprivation test disclosed normal water metabolism.

On November 21, 1979, a hard, calcified mass was removed subtotally by right frontotemporal craniotomy. Microscopic examination of the surgical specimen revealed granulomas composed of epithelioid histiocytes, which were positive for anti-macrophage antibody. Langhans' multinucleated giant cells were not evident. There was no caseous necrosis, and Ziel-Neelsen stain did not reveal tubercle bacilli. The normal pituitary structure was not found, and a test for anterior pituitary hormones was immunohistochemically negative. The pathological diagnosis was granulomatous hypophysitis of unknown aetiology.

The patient's immediate postoperative course was satisfactory, and she showed good improvement in the visual fields. She has been receiving replacement of corticosteroid and thyroid hormones for three years. The remaining pituitary lesion did not increase in size on repeated post-operative follow-up MR images.

Case 2

This 55-year-old male was admitted for evaluation of polyuria and polydipsia. He had been diagnosed with pulmonary tuberculosis at the age of 23, which had been treated successfully by chemotherapy. He had otherwise been well. Chest X-ray films revealed a nodular infiltrate in the middle lobe of the left lung, and an intradermal tuberculin test was strongly positive. Skull X-ray films revealed slight enlargement of the sella turcica. T1-weighted MR images demonstrated a sellar iso-intensity mass associated with thickening of the pituitary stalk and infundibulum. These lesions were homogeneously enhanced upon the administration of Gd-DTPA. Endocrinological studies disclosed normal anterior pituitary function, including a normal basal value of serum PRL (17.5 ng/ml). However, a water deprivation test revealed diabetes insipidus of central origin.

On July 6, 1987, trans-sphenoidal exploration of the sella was performed, and abnormal fibrous tissue located posteriorly to the anterior lobe was removed subtotally. No normal posterior pituitary was identified. Microscopic examination of the surgical specimen

Table 1. *Summary of Pre-Operative Clinical Data in Five Cases*

Patient	Age (yrs), sex	Symptoms	Endocrinological findings	Neuroradiological findings	Other clinical findings
Case 1	46, F	bitemporal hemianopsia → polyuria and polydipsia	hypopituitarism (GH ↓, LH ↓), basal PRL : 36.0 mg/ml	intra- and suprasellar enhancing mass	
Case 2	55, M	polyuria and polydipsia	diabetes insipidus, basal PRL : 17.5 ng/ml	intra- and suprasellar enhancing mass, thickened infundibulum	past history of pulmonary tuberculosis (at 23 y.o.), intradermal tuerbculin test (+ + +)
Case 3	56, F	polyuria and polydipsia	hypopituitarism (GH ↓, ACTH ↓), diabetes insipidus, basal PRL : 58.0 ng/ml	intra- and suprasellar ring-like enhancing mass	
Case 4	54, F	deterioration of rt-visual acuity → polyuria and polydipsia, headache, subfever	diabetes insipidus, basal PRL : 2.4 ng/ml, primary hypothyroidism	intra- and suprasellar enhancing mass, thickened infundibulum	association with Hashimoto's disease, serum antipituitary antibody (+), intradermal tuberculin test (+ + +)
Case 5	55, M	polyuria and polydipsia → decreased libido, bitemporal hemianopsia	panhypopituitarysm, basal PRL : 2.2 ng/ml	intra- and suprasellar enhancing mass, thickened infundibulum	intradermal tuberculin test (+ + +)

Table 2. *Summary of Intra- and Postoperative Clinical Data in Five Cases*

Patient	Operative findings	Histopathological diagnosis	Postoperative medication	Neuroradiological findings in follow-up-period
Case 1	subtotal removal of fibrous firm tissue at craniotomy	granulomatous hypophysitis of unknown aetiology without giant cells	replacement of corticosteroid and thyroid hormone for three years after the operation	no enlargement of residual mass
Case 2	trans-sphenoidal partial removal of fibrous firm tissue	granulomatous hypophysitis of unknown aetiology without giant cells	replacement of corticosteroid and thyroid hormone, DDAVP therapy	no enlargement of residual mass
Case 3	trans-sphenoidal evacuation of creamy fluid and partial removal of fibrous cyst wall	granulation with chronic inflammatory infiltration	DDAVP therapy	no enlargement of residual mass
Case 4	trans-sphenoidal partial removal of fibrous firm tissue	granulation with chronic inflammatory infiltration	replacement of thyroid hormone, DDAVP therapy	no enlargement of residual mass
Case 5	trans-sphenoidal partial removal of fibrous firm tissue	granulomatous hypophysitis of unknown aetiology with multinucleated giant cells	replacement of corticosteroid and thyroid hormone	no enlargement of residual mass

revealed fibrosis, infiltration by inflammatory cells, including a few nodular aggregates of epithelioid cells. The specimen contained no normal pituitary structure. Neither caseous necrosis, nor acid-resistant bacteria were found. The pathological diagnosis was granulomatous hypophysitis of unknown aetiology.

The immediate postoperative course was uneventful. During the subsequent four years, the patients has received replacement of corticosteroid and thyroid hormones, and DDAVP therapy. During follow-up, the remaining pituitary lesions did not increase in size on repeated MR images since the operation.

Case 3

This 56-year-old female was referred for polyuria and polydipsia. The size of the sella turcia was within normal limits on skull X-ray films. MR images demonstrated a ring-like contrast-enhanced intrasellar mass with suprasellar extension. Endocrinological examination revealed low basal and post-stimulation values for serum GH and ACTH, and an elevated basal value for serum PRL (58.0 ng/ml). Diabetes insipidus of central origin was confirmed by a water deprivation test.

On November 9, 1987, the patient underwent trans-sphenoidal surgery. An intrasellar cystic lesion surrounded by a fibrous thick wall, containing a creamy, grayish fluid, was removed subtotally. Histopathological examination demonstrated fibrotic inflammatory tissue with lymphocytic infiltration. No normal pituitary tissue was found. A culture of the cyst content was sterile. The pathological diagnosis was granulation with chronic inflammatory infiltration.

The patient's immediate postoperative course was satisfactory. She received DDAVP therapy during the subsequent four years. The remaining pituitary lesion showed no increase in size on MR images taken repeatedly during four years after the surgery.

Case 4

This 54-year-old female developed headache, polyuria and polydipsia. Skull X-ray films showed a normal-sized sella turcica. MR images demonstrated a contrast-enhanced mass in the sellar region continuous with an abnormally thickened pituitary stalk and infundibulum (Fig. 1). Endocrinological survey revealed primary hypothyroidism, and normal function of the anterior pituitary, with a normal level of serum PRL (2.4 ng/ml). Diabetes insipidus of central origin was diagnosed by a water deprivation test. Positive thyroglobulin and microsome tests disclosed associated Hashimoto's disease. Serum antipituitary antibodies were also present. Blood analysis disclosed elevated ESR, indicative of an inflammatory process. An intradermal tuberculin test was strongly positive.

On October 1, 1990, trans-sphenoidal partial removal of the intrasellar mass was performed. The mass was composed of fibrous, hard, white-grayish tissue, which was situated behind the anterior pituitary. A normal posterior lobe was not evident. Light microscopic inspection of the surgical specimen revealed fibrotic inflammatory tissue with lymphocytic infiltration.

Normal pituitary tissue was absent. The Ziehl-Neelsen stain was negative, and no caseous necrosis was found. The pathological diagnosis was granulation with chronic inflammatory infiltration. The immediate postoperative course was uneventful and there was improvement in right visual acuity. During the subsequent year, the patient has received DDAVP therapy, and replacement of thyroid hormone for the pre-existing primary hypothyroidism. The remaining pituitary lesion has not increased in size on repeated MR images.

Case 5

This 55-year-old male developed polyuria, polydipsia, and decreased libido. Neurological examination was normal, except for

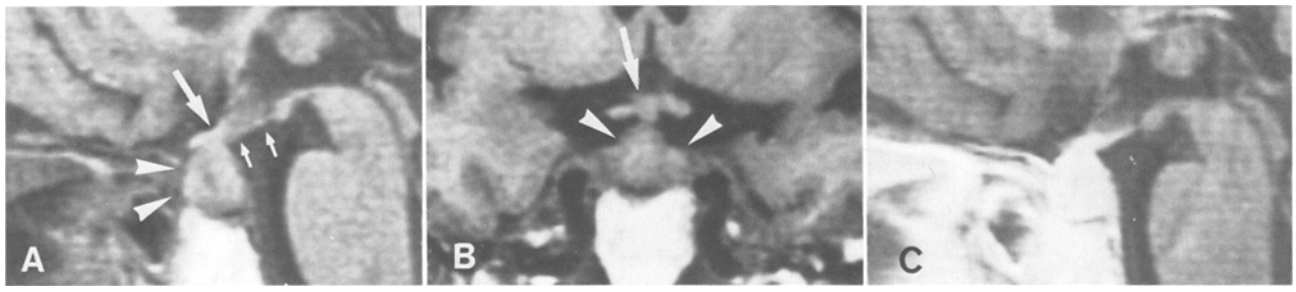

Fig. 1. Case 4. Sagittal (A) and coronal (B) T1-weighted MR images reveal an iso-intense mass in the sell turcica (arrow-heads) associated with a thickened pituitary stalk (large arrow) and infundibulum (small arrows). These lesions were homogeneously enhanced with Gd-DTPA (C)

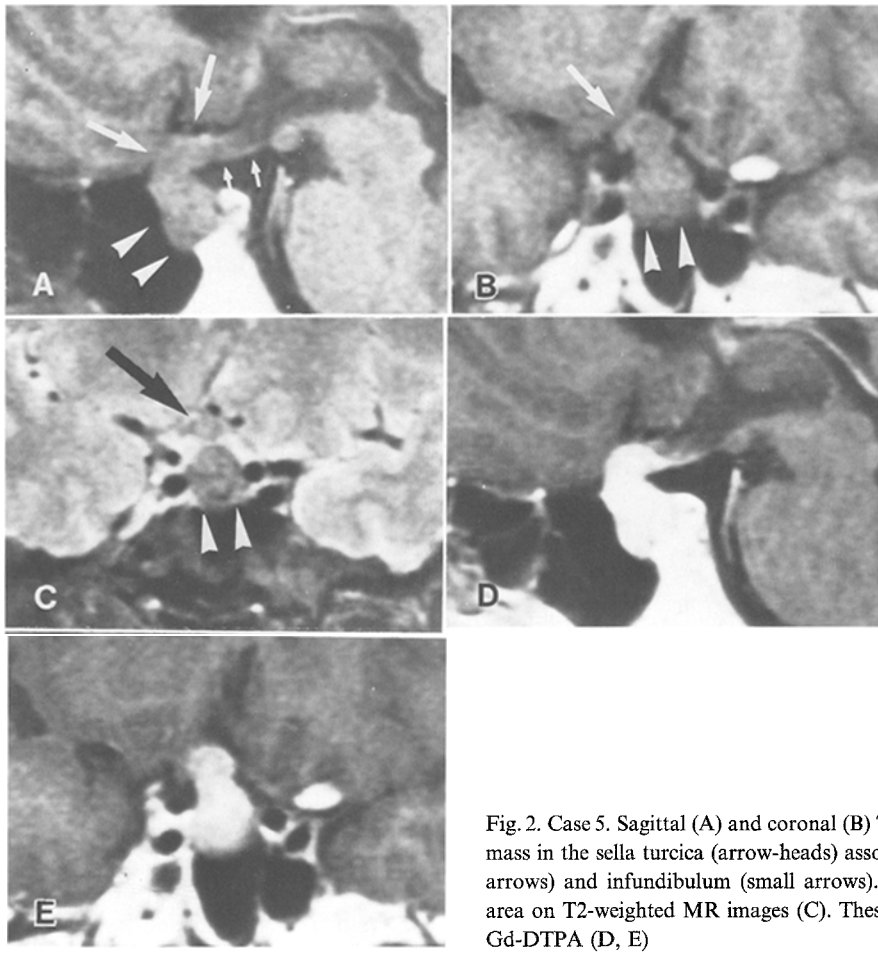

Fig. 2. Case 5. Sagittal (A) and coronal (B) T1-weighted MR images reveal an iso-intense mass in the sella turcica (arrow-heads) associated with a thickened pituitary stalk (large arrows) and infundibulum (small arrows). These findings appeared as a low-intensity area on T2-weighted MR images (C). These lesions were homogenously enhanced with Gd-DTPA (D, E)

bitemporal hemianopsia. An intradermal tuberculin test was strongly positive. Skull X-ray films disclosed slight enlargement of the sella turcica. T1-weighted MR images demonstrated an abnormally thickened pituitary stalk and infundibulum continuous with a sellar iso-intensity mass (Fig. 2 A, 2 B). These lesions were homogenously enhanced by the administration of Gd-DTPA (Fig. 2 D, 2 E), and appeared as a low-density area on T2-weighted MR images (Fig. 2 C). Endocrinological examination revealed panhypopituitarism with a lowered value of serum PRL (2.2 ng/ml). Water-deprivation test showed normal water metabolism.

The patient underwent a trans-sphenoidal procedure on October 10, 1990. The sella was filled with avascular, gray-reddish fibrous tissue, a biopsy of which was taken. No normal posterior lobe of the pituitary was evident. The intra-operative frozen section revealed nontumourous granulomatous tissue, and surgery was therefore terminated without further resection of the tissue. Light microscopic inspection demonstrated that the granulomas were composed of epithelioid histiocytes (Fig. 3 A) and Langhans' multinucleated giant cells (Fig. 3 D), which were positive for anti-macrophage antibody (Fig. 3 B, 3 C, 3 E). Fibrosis with infiltration by lymphocytes and

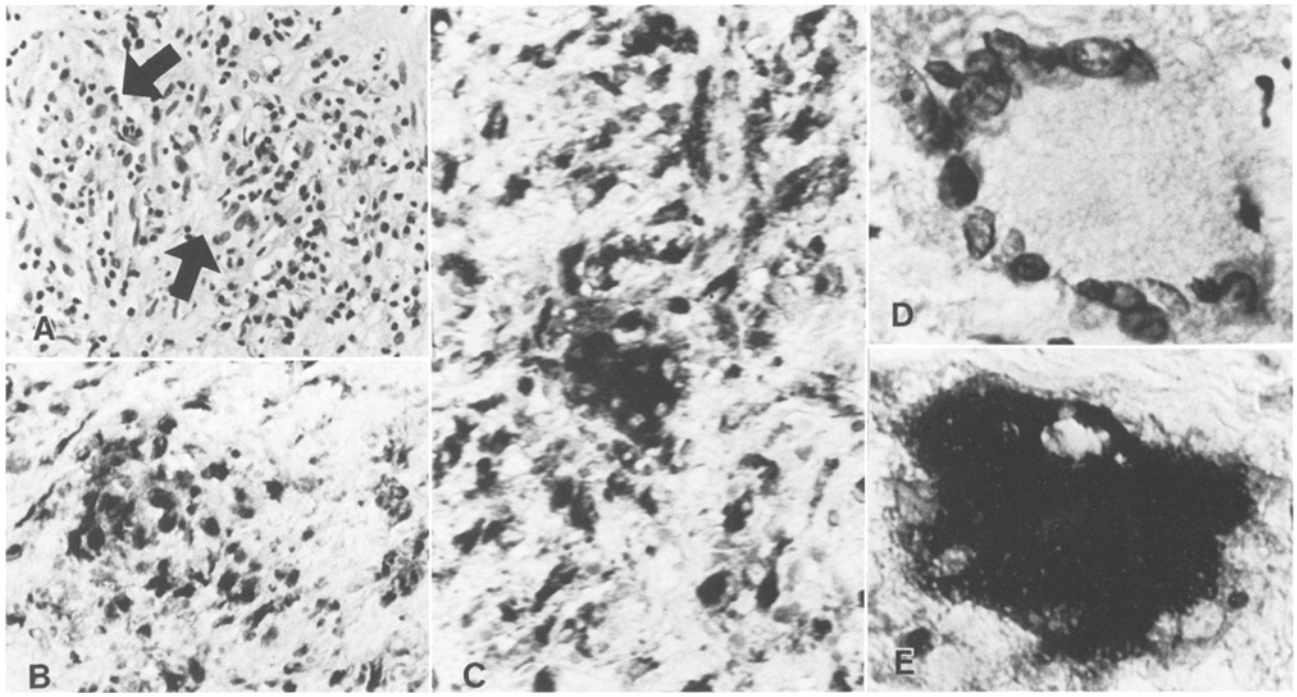

Fig. 3. Case 5. Photomicrograph of the surgical specimen showing granulomatous areas composed of epithelioid histiocytes (arrows) with infiltration of lymphocytes and neutrophils (A: × 100). The epithelioid histiocytes are positive for anti-macrophage antibody (B: × 100). At higher magnification, the granulomatous area reveal Langhans' mutlinucleated giant-cells, which were positive for anti-macrophage antibody (C: immunohistochemical stain with anti-macrophage antibody × 200, D: H&E stain × 400, E: immunohistochemical stain with anti-macrophage antibody × 400)

neutrophils was also present. The normal architecture of the adeno- and neurohypophysis was not identified, and immunostain for anterior pituitary hormones was negative. There was no caseous necrosis, acid-resistant bacteria, or fungi. These clinical and pathological findings led to the diagnosis of giant cell granulomatous hypophysitis of unknown aetiology.

The immediate postoperative course was uneventful, with improvement in both visual fields. During the subsequent year, the patient has received replacement of corticosteroid and thyroid hormones. The remaining pituitary lesion did not increase in size on repeated follow-up MR images.

Discussion

Granulomatous inflammation is characterized by the presence of granulomas composed of nodular collections of epithelioid cells, which are derived from macrophages[5]. Typical multinucleated Langhans' giant cells were present in the surgical specimen from Case 5. Although multinucleated giant cells are an additional freature of granulomas[5], no specific aetiology can be determined by their presence. We found that these giant cells, as well as the epithelioid histiocytes, were immunohistochemically positive for anti-macrophage antibody. The origin of the giant cells is controversial. It has been suggested that the giant cells were syncytial cells derived from the remaining epithelial cells[14]. However, in agreement with our immunohistochemical findings, current evidence suggests that the giant cells are coalesced macrophages or epithelioid histiocytes[5, 14].

Case 4 with concurrent Hashimoto's thyroiditis presented positive serum antibodies to the pituitary gland. This suggests an auto-immune process as a factor in the pathogenesis of this patient's pituitary lesion. This has also been suggested in lymphocytic hypophysitis[14]. Lymphocytic hypophysitis is distinguished from granulomatous hypophysitis by the absence of nodular aggregates of epithelioid histiocytes and multinucleated giant cells[7, 15, 18]. However, McKeel[9] suggested that these two entities represented different phases of the same disease, listing the ultrastructural similarities between lymphocytic and idiopathic granulomatous hypophysitis; e.g., the presence of degranulated, inactive secretory cells, focal oncocytic changes in the secretory cells, and inflammatory cells within the peri-acinar basement membrane. Miyamaoto *et al.*[10] supported this proposal by documenting a case of lymphocytic

Table 3. *Several Factors in Granulomatous Formation Involving the Hypophysis*

Tuberculosis
Sarcoidosis
Histiocytosis X
Moniliasis
Syphilis
Foreign body (including adenoma and Rathke's cleft cyst)

hypophysitis presenting with remarkable granulomatous changes.

Different from lymphocytic hypophysitis and typical granuloma, the histological findings in Cases 3 and 4 were non-specific chronic inflammation consisting of granulation with lymphocytic infiltration. Roth[14] suggested that in the healing state, the granulomas are fibrous with only a few residual multinucleated giant cells. He also indicated that, when accompanied by Hashimoto's disease, lymphocytes are often the only inflammatory cells in granulomatous hypophysitis. Therefore, the pituitary lesions in Case 4, and possibly in Case 3, may represent the terminal stage of granulomatous or lymphocytic hypophysitis with a mild clinical course[18].

It is noteworthy that all of our patients developed polyuria and polydipsia early in the clinical course, and that 3 patients had diabetes insipidus of central origin on water-deprivation tests. Although the endocrinological investigation demonstrated anterior pituitary dysfunction in three patients, only one reported decreased libido, which is symptomatic of hypopituitarism. These endocrinological features conflict with those reported in the literature in that idiopathic granulomatous hypophysitis and lymphocytic hypophysitis affect primarily the anterior pituitary[12, 13, 14, 15]. The posterior pituitary and infundibulum are frequently impaired in cases of sarcoidosis, tuberculoma, and histiocytosis X, often resulting in diabetes insipidus[2, 4, 6, 11, 13, 14].

Our radiological findings point to predominance of posterior pituitary or hypothalamic impairment in that the abnormally thickened pituitary stalk and infundibulum were enhanced homogeneously by the contrast material, as was the concurrent sellar lesion. Minimal sellar enlargement despite the existence of an intrasellar mass contrasts strikingly with the dilated sella due to an expanding mass such as a pituitary adenoma.

Granulomatous inflammation is typical of the tissue response elicited by tuberculosis, fungal infection, and the presence of a foreign material[5]. Table 3 lists several factors in granulomatous formation involving the hypophysis[1, 2, 3, 7, 8, 9, 14, 15]. Sarcoidosis was not considered as an aetiological factor in any of our patients, because no manifestation of this disorder was detected by appropriate examinations: There was no bilateral hilar lymphadenopathy or lung fibrosis on chest radiograms, there were no lesions of the skin, eye or other organs, abnormal electrocardiograms, or elevated serum ACE (angiotensin converting enzyme) levels[2, 14]. Moniliasis was ruled out by the absence of fungi on H & E and PAS stain in all cases. Foreign bodies, such as adenomas[8] or Rathke's cleft cyst[1], were not identified in any of the surgical specimens. There was also no direct evidence for tuberculoma in that histopathological findings revealed neither caseous necrosis by H & E stain, nor acid resistant organisms by Ziehl-Neelsen stain. However, the intradermal tuberculin test was strongly positive in three patients, including one with a history of pulmonary tuberculosis. Therefore, tuberculosis cannot be ruled out as a pathogenetic factor in the pituitary lesions of these three cases.

Regarding the long-term prognosis, endocrinological dysfunction was prolonged in all of our cases. Replacement of both corticosteroid and thyroid hormones was required in 3 cases, and three patients needed vasopressin therapy. No additional therapeutic modality for the residual pituitary lesions, such as irradiation or administration of high-dose corticosteroid, was used. Radiologically, the size of the residual pituitary lesion in all patients remained unchanged.

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Correspondence and Reprints: Dr. M. Higuchi, Department of Neurosurgery, Osaka University Medical School, 1-1-50, Fukushima, Osaka 553, Japan.