Giant-cell granulomatous hypophysitis: a distinct clinicopathological entity

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Giant-cell granulomatous hypophysitis is a chronic inflammatory disorder of the pituitary gland. It presents clinically as a sellar mass lesion with pituitary insufficiency and/or hyperprolactinemia, and is radiologically indistinguishable from a pituitary tumor. In most of the previously reported cases the documentation of the disorder has been limited to autopsy tissue. Only a few cases documented by biopsy have been recorded. Four cases are presented here with radiological, endocrinological, and surgical findings. The appropriately documented cases collected from the literature and the present series are reviewed and the incidence, patterns of clinical and radiological presentation, and operative management of this disorder are discussed. This entity should be considered when evaluating patients with a pituitary mass and evidence of hypopituitarism and hyperprolactinemia.

KEY WORDS • granuloma • hypophysitis • transsphenoidal surgery • pituitary gland
FIG. 1. Case 1. Computerized tomography scan after intravenous administration of contrast medium showing a low-density intrasellar lesion with marked ring enhancement.

levels decreased to normal. The patient’s need for vasopressin diminished gradually and she required no hormonal replacement at the time of discharge from the hospital. The pathological diagnosis was giant-cell granulomatous hypophysitis (Fig. 2).

Case 2

This 19-year-old woman presented in March, 1985, with an 8-month history of galactorrhea and amenorrhea. She had no signs of thyromegaly or lymphadenopathy and her neurological examination was normal. She was referred to our institution on the basis of a CT scan showing a low-density intrasellar lesion with a slight ring enhancement after administration of contrast material. Preoperative endocrinological examinations revealed hyperprolactinemia (70 ng/ml) with reduced response to TRH. Basal and poststimulation values of TSH, LH, and FSH were normal. Plasma cortisol responded minimally to insulin-induced hypoglycemia. The preoperative impression was of a prolactinoma.

The patient underwent a transsphenoidal microsurgical procedure. Opening the floor of the sella turcica and incision of the dura mater (both of which were intact) disclosed within the adenohypophysis an abundant collection of creamy, grayish-yellow fluid, which was completely evacuated. The postoperative course was uneventful. At follow-up examination the patient was well and leading a normal life. Galactorrhea had ceased and menses had resumed. The pathological diagnosis was of giant-cell granulomatous hypophysitis (Fig. 3).

Case 3

This 57-year-old man was referred to our institution in November, 1985, for evaluation of opthalmoplegia of the right eye. He complained of long-lasting impotence. Three days before admission he experienced severe headache, ptosis of the right eyelid, and diplopia. At admission general and neurological examinations were normal except for a partial right third nerve palsy. A CT scan revealed a slightly contrast-enhancing isodense intrasellar mass expanding into the right parasellar area and into the sphenoid sinus. Hormonal studies yielded results consistent with severe hypopituitarism: the prolactin level was normal, but thyroid hormones, TSH, and gonadotropin values were below the normal range with minimal response to stimulation tests. Angiography demonstrated no vascular abnormalities. The preoperative impression was of a rapidly enlarging, nonsecreting pituitary adenoma.

At transsphenoidal surgery an intrasellar solid mass with a firm capsule extending into the sphenoid sinus

FIG. 2. Photomicrographs of the surgical specimen in Case 1. Left: Granulomatous area with multinucleated giant cells (arrows) and histiocytes. Van Gieson, × 220. Right: Higher magnification of the multinucleated giant cells showing intracytoplasmic inclusions (arrows). Van Gieson, × 550.
Giant-cell granulomatous hypophysitis

and the right parasellar area was totally resected. The immediate postoperative course was uneventful, with slow steady improvement in ocular motion. During the subsequent 2 years the patient has continued to receive hormonal replacement. Repeat CT has shown no recurrence of the mass. Pathological diagnosis was giant-cell granulomatous hypophysitis (Fig. 4).

Case 4
This 58-year-old man presented in January, 1988, with a long-standing history of panhypopituitarism for which he had been treated with hormonal replacement medication. General and neurological examination were normal. He had been referred to our institution on the basis of a CT scan demonstrating a uniformly enhancing, isodense mass lesion in an enlarged sella. Preoperative endocrinological evaluation confirmed hypothyroidism, hypoadrenalism, and hypogonadism. His prolactin level was in the normal range.

At transphenoidal surgery a very fibrous, encapsulated intrasellar lesion was partially resected. The postoperative course was uneventful. During the subsequent 11 months the patient continued to receive hormonal replacement. Repeat magnetic resonance imaging showed no increase in size of the remaining pituitary lesion (Fig. 5). Pathological diagnosis was giant-cell granulomatous hypophysitis (Fig. 6).

Summary of Cases
As soon as the histological diagnosis was known, the four patients were tested for cutaneous, skeletal, visceral, or laboratory evidence of systemic granulomatous
disease such as tuberculosis, syphilis, sarcoidosis, brucellosis, and histiocytosis X, as recommended by Taylor and Duft. No such process could be demonstrated on the basis of these studies.

Light microscopy was performed on the permanent biopsy sections, utilizing routine hematoxylin and eosin and van Gieson stain. Immunoperoxidase staining for immunoreactive adenylohyphosphysis hormones and neurophysines was also performed. Microscopic examination of the tissue disclosed characteristic features, all of which were identified in all four cases. These included preserved acini of anterior pituitary cells and islands of neurohypophysis, separated by large numbers of inflammatory cells with both lymphocytes and plasma cells predominating. Nodular aggregates interspersed between necrotic hemorraghic areas featured granular or vacuolated epithelioid histiocytes and multinucleated giant cells, many of which contained intracytoplasmic inclusions frequently disposed around an amorphous eosinophilic material, presenting a granulomatous appearance. Special staining for tubercle acid-fast bacilli, bacteria, and fungi was negative. The immunoperoxidase studies revealed areas of reactivity corresponding to the preserved normal pituitary tissue, whereas the inflammatory cells were nonreactive.

Discussion

Recent advances in endocrinological and neuroradiological expertise have greatly facilitated the early detection of pituitary tumors. Technical refinements of transsphenoidal microsurgery have also provided a safe, accurate, and beneficial approach to the sellar region, broadening the indications and increasing the number of such operations. As a consequence, rare pathological processes which have previously been identified only on autopsy material, such as inflammatory granulomas involving the intrasellar cavity and the pituitary gland, are now delineated in the clinical setting and emerge as a distinct pathological entity to be included in the differential diagnosis of sellar lesions.

Two main types of inflammatory lesions of the pituitary gland have been described: one such lesion, called "lymphocytic hypophysitis," is characterized by diffuse infiltration of the pituitary with lymphocytes and plasma cells. It is typically seen in females in the puerperium or during pregnancy and is suspected of being an autoimmune disorder. The other chronic inflammatory lesion of the pituitary gland is a giant-cell granulomatous process, termed "giant-cell granuloma" or "granulomatous hypophysitis," histologically characterized by nodular aggregates of multinucleated giant cells, histiocytes, and extensive lymphocytic and plasmacellular infiltration. Tuberculosis, syphilis, sarcoidosis, and other systemic granulomatous diseases also have been considered etiological factors in pituitary granulomas. After excluding these etiologies, the present cases should be included in the group of giant-cell granulomas of unknown origin.

Idiopathic granulomatous inflammation of the pituitary gland is thought to be an extremely rare event. The disorder was originally reported only as a postmortem finding. In 1980, Del Pozo, et al. reported that only 20 cases of giant-cell granuloma of unknown origin invading the pituitary had been described in the medical or pathological literature as necropsy observations. Previous descriptions of granulomatous hypophysitis documented by surgical biopsy are exceptional, amounting, as far as we can ascertain, to only four cases. Four additional instances are reported in the present study. Table 1 summarizes the clinical presentation, CT and operative findings, and follow-up course of all eight cases.

Granulomatous hypophysitis represents about 1% of the sellar pathology approached via the transsphenoidal route during the last 6 years at our institution. Although these may be merely chance findings, the possibility that nonspecific inflammatory granulomas of the pituitary are more frequent than generally thought should be considered. It may well be, as recently reported anecdotally by Ciric, that many patients with large surgical series of pituitary lesions have treated patients with intrasellar granulomas of undetermined cause.

The reviewed cases are equally divided between the two sexes, ranging in age from 19 to 58 years. The mean age of the female patients was 21.5 years, while all the male patients were aged over 50 years. In our series, the preoperative diagnosis was "prolactinoma" in Cases 1 and 2 and "nonsecreting adenoma" in Cases 3 and 4. Histological examination of the involved gland, however, revealed the lesions to be granulomatous hypophysitis. We did not consider the possibility of a granulomatous process before operation, since cutaneous, skeletal, visceral, or other laboratory manifestations which would suggest a granulomatous systemic disease were absent. Evidence of pituitary dysfunction was the most relevant feature of the clinical manifestations, ranging from panhypopituitarism to single hormonal abnormalities such as hyperprolactinemia or diabetes insipidus. At least partial laboratory investigation of pituitary function was performed in seven patients. Endocrine testing showed various degrees of hypopituitarism in six patients, as evidenced by TSH, adrenocorticotropic, and gonadotropic deficiencies or blunted response of TSH and prolactin to exogenous TRH administration. In addition to depressed pituitary function, two patients had evidence of moderate prolactin hypersecretion (< 100 ng/ml), manifested clinically by amenorrhea or amenorrhea/galactorrhea. One further patient exhibited markedly elevated levels of prolactin (> 1700 ng/ml). Except for the latter patient, these elevated serum prolactin levels could be the result of inhibition of prolactin-inhibiting factor by compression of the hypothalamic connection to the pituitary gland.

In one of our cases laboratory investigations gave results interpreted as being compatible with diabetes insipidus of central origin. This condition could have been caused by pressure on the hypothalamic-pituitary axis by the.
## TABLE 1

Summary of clinical data in eight reported patients

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Sex, Age (yrs)</th>
<th>Neurological &amp; Clinical Complaints</th>
<th>Endocrinological Findings</th>
<th>Computerized Tomography Findings</th>
<th>Operative Findings</th>
<th>Follow-Up Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del Pozo, et al., 1980</td>
<td>F, 28</td>
<td>headache, amenorrhea</td>
<td>hypopituitarism</td>
<td>intrasellar hypertrophy, intrasellar enhancing mass</td>
<td>firm mass, total removal</td>
<td>persistent hypopituitarism</td>
</tr>
<tr>
<td>Taylor &amp; Duff, 1980</td>
<td>M, 50</td>
<td>3rd nerve palsy</td>
<td>not reported</td>
<td>intrasellar hypertrophy, involvement of rt cavernous sinus</td>
<td>diffuse edema of the gland, biopsy</td>
<td>return to work</td>
</tr>
<tr>
<td>Holck &amp; Laursen, 1983</td>
<td>M, 54</td>
<td>headache</td>
<td>hyperprolactinemia</td>
<td>granuloma &amp; large chromophobe tumor with extensive suprasellar growth</td>
<td>total removal of firm hormonal mass</td>
<td>hormonal replacement medication</td>
</tr>
<tr>
<td>Albini, et al., 1987</td>
<td>F, 19</td>
<td>headache, hemianopsia</td>
<td>hypopituitarism</td>
<td>intrasellar hypertrophy, coexistence with Rathke’s cleft cyst</td>
<td>total removal of firm hormonal mass</td>
<td>hormonal replacement medication</td>
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<tr>
<td>Scarnarini, et al., 1989</td>
<td></td>
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<tr>
<td>Case 1</td>
<td>F, 20</td>
<td>headache, amenorrhea</td>
<td>hypopituitarism, diabetes insipidus, hyperprolactinemia</td>
<td>intrasellar hypertrophy, hypodense mass with ring enhancement</td>
<td>resection of sphenoidal mucocele; evacuation of creamy fluid collection</td>
<td>normal</td>
</tr>
<tr>
<td>Case 2</td>
<td>F, 19</td>
<td>amenorrhea, galactorrhea</td>
<td>hyperprolactinemia, diabetes insipidus, hypopituitarism</td>
<td>intrasellar hypertrophy, hypodense mass with ring enhancement</td>
<td>evacuation of creamy fluid collection</td>
<td>normal</td>
</tr>
<tr>
<td>Case 3</td>
<td>M, 57</td>
<td>3rd nerve palsy, long-standing impotence</td>
<td>hypopituitarism</td>
<td>isodense intrasellar enhancing mass extending into rt cavernous &amp; sphenoid sinuses</td>
<td>total removal of firm capsulated mass</td>
<td>hormonal replacement medication</td>
</tr>
<tr>
<td>Case 4</td>
<td>M, 58</td>
<td>long-standing panhypopituitarism</td>
<td>hypopituitarism</td>
<td>isodense intrasellar enhancing mass</td>
<td>partial removal of fibrous capsulated mass</td>
<td>hormonal replacement medication</td>
</tr>
</tbody>
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Granuloma is a type of mass effect including headaches in four cases, partial third nerve palsy in two cases, and visual field defects in one case. All eight reported patients demonstrated radiological findings consistent with a sellar mass causing intrasellar hypertension. The CT scan in five cases showed a uniformly or ring-like contrast-enhancing hypo- or isodense intrasellar mass; in two cases CT revealed extension of the process into the cavernous sinus and sphenoidal sinus. In one case the granuloma coexisted with a large chromophobe pituitary tumor with extensive suprasellar growth, in another case with an intra- and suprasellar Rathke’s cleft cyst, and in our Case 1 with a sphenoidal mucocele. The operative procedures performed in the eight patients identified by surgical biopsy (transsphenoidal approach in six cases, craniotomy in two) allowed total resection of the lesion in five cases, while in three instances only a subtotal removal of the mass could be accomplished.

The histological features of giant-cell granulomatous hypophysitis were first described in detail by Gougerot and Gy on 3 in 1911 and by Simmonds on 6 in 1917. In 1949, Sheehan and Summers reviewed the literature, collecting 10 postmortem cases and characterizing the lesion by the presence within both the adeno- and neurohypophysis of multinucleated giant cells coexisting with histiocytes, lymphocytes, and plasma cells. The gross pathological picture appears to be related to the chronology of the pituitary lesion. In our Cases 1 and 2 (both young women with a brief history of menstrual disturbances) the operative management consisted of the evacuation of a collection of creamy fluid. In our Cases 3 and 4 (older men with a long history of hypopituitarism) as well as in the case reported by Del Pozo, et al., the consistency of the tissue was firmer and the appearance of the mass through the surgical microscope was that of a fibrous adenoma. This fibrous scar tissue is considered the end stage of the granulomatous process, although, according to Bleish and Robbins, it could result in an empty sella.

The agent responsible for the formation of granulomatous elements remains uncertain. Both infection and systemic interstitial inflammatory processes were ruled out in the reported cases. Therefore, in light of the relatively frequent association of giant-cell hypophysitis with other chronic pathological processes involving the parasellar region (such as adenomas, Rathke’s cleft cyst, or mucocele as in our Case 1), it is tempting to argue that the inflammatory cells might be seen as a manifestation of a granulomatous foreign-body type reaction. It has been suggested that immunological or mechanical factors play a key role in determining this sterile inflammatory reaction to substances elaborated by tumor cells or to colloid-like material produced by spilled cyst contents.

At the present time, the management of cases of giant-cell granulomatous hypophysitis presenting as an intrasellar expanding mass causing hypopituitarism...
should include an exploratory approach to the sellar region for both pathological identification and sellar as well as chiasmal decompression (if vision is compromised). When a granulomatous process is suspected, pathological analysis of a frozen section should be obtained at biopsy, because the early recognition of this disease and its differentiation from a tumor may avoid major resection of the remaining pituitary tissue, which in turn would cause worsening of preexisting hypopituitarism. Finally, as already emphasized by Albini, et al., the occurrence of clinicopathological entities such as giant-cell granulomatous hypophysitis stresses the need for establishing a precise pathological diagnosis before initiating medical treatment for a presumed pituitary tumor.

References

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