



Primary Non-Necrotizing Granulomatous Hypophysitis Mimicking Pituitary Adenomas

Hipofiz Adenomlarını Taklit Eden Primer Non-Nekrotizan Granülomatöz Hipofizitler

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ABSTRACT

AIM: The authors review their experience in the endoscopic endonasal transsphenoidal treatment of 5 patients, finally diagnosed as primary hypophysitis but initially assumed to be pituitary adenomas.

MATERIAL and METHODS: A retrospective study was undertaken to review 5 cases of primary non-necrotizing granulomatous hypophysitis (1.61%) through 310 endoscopic transsphenoidally operated cases with the diagnosis of pituitary adenoma between 2009 and 2013. All 5 cases were female without any background of autoimmunity or recent pregnancy. The initial presumptive diagnosis was pituitary adenoma for all patients. The endocrinological diagnoses of the patients were suspected Cushing's Disease, anterior pituitary deficiency with hyponatremia, hyperprolactinemia, and acromegaly. One of the patients had normal hormonal levels. All patients had macroadenomas including one invasive adenoma with skull base involvement. One of the patients (20%) had visual field defects. All patients underwent endoscopic endonasal transsphenoidal surgery (EETS).

RESULTS: All patients had improvement of hormonal levels postoperatively except the one with anterior pituitary deficiency who required long term hormone replacement after the surgery. Mean follow-up duration was 14.8 months.

CONCLUSION: Primary granulomatous hypophysitis without any known etiological factors is very rare in the literature. It can mimic pituitary adenomas in radiological and endocrinological aspects. EETS is an effective and safe treatment especially for visual and compression symptoms.

KEYWORDS: Primary hypophysitis, Non-necrotizing, Granulomatous, Endoscopic, Secretory adenoma

ÖZ

AMAÇ: Hipofiz adenomu ön tanısı ile endoskopik endonazal transsfenoidal (EETS) yöntemle tedavi edilen ve patoloji tanısı primer hipofizit olan 5 olguluk deneyim sunulmaktadır.

YÖNTEM ve GEREÇLER: Çalışmada 2009 ile 2013 yılları arasında endoskopik endonazal yolla opere edilen 310 hipofiz adenomu olgusu içerisinde patoloji tanısı primer nonnekrotizan granülomatöz hipofizit olan 5 olgu (%1,61) geriye dönük olarak incelendi. Hastaların hepsi kadın cinsiyette olup, hiçbirinde gebelik ya da altta yatan otoimmün hastalık gibi bir neden yok idi. Tüm hastaların ön tanısı hipofiz adenomu idi. Hastalarda endokrinolojik olarak sırasıyla şüpheli Cushing Hastalığı, hiponatremi ile birlikte hipofizer yetmezlik, hiperprolaktinemi, normal hormonal tablo ve akromegali ile uyumlu laboratuvar değerleri saptandı. Bir tanesi kafa kaidesi tutulumu ile birlikte invaziv adenom olmak üzere tüm olgular makroadenomdu. Bir hastada görme alanı defisiti saptandı. Tüm hastalara EETS cerrahi uygulandı.

BULGULAR: Preoperatif yetmezlik bulguları olan hasta hariç tüm hastalarda postoperatif normal hormonal değerler sağlandı. Hastalar ortalama 14,8 ay takip edildi.

SONUÇ: Primer non-nekrotizan hipofizitler nedeni bilinmeyen ve nadir görülen hastalıklar olup radyolojik ve endokrinolojik olarak hipofiz adenomlarını taklit edebilirler. EETS yol ise görme ile ilgili ve baskı semptomlarının kaldırılmasında güvenli ve etkili bir yöntemdir.

ANAHTAR SÖZCÜKLER: Primer hipofizit, Non-nekrotizan, Granülomatöz, Endoskopik, Sekretuar adenom

INTRODUCTION

Inflammation of the pituitary gland is a rare condition characterized by infiltration and destruction of the gland (7, 38). The incidence is unclear and little is known, mostly from case reports in the literature (15, 20, 24, 30, 35). Inflammatory hypophysitis is classified into five sub-types: lymphocytic, granulomatous, xanthomatous, xanthogranulomatous and

necrotizing (21). Lymphocytic and granulomatous hypophysitis are the most common types (5). Hypophysitis can also be classified as primary (idiopathic) hypophysitis and secondary hypophysitis. It may develop due to systemic inflammatory disorders such as tuberculosis, Wegener's granulomatosis and sarcoidosis (12, 39, 42). The majority of inflammatory pituitary lesions occur in women, are related with the postpartum

period and most of them are in the form of lymphocytic hypophysitis (8, 41). Symptoms such as headache, visual disruption and involvement of pituitary gland and stalk, which may result in endocrine dysfunction, usually occur due to the influence of a sellar mass lesion (5).

Hypophysitis cases are generally misinterpreted as pituitary adenomas because of nonspecific radiological features (37). Therefore these lesions are usually diagnosed postoperatively by histological evaluation (13, 18). The treatment protocol remains for primary hypophysitis controversial because of the difficulties in the treatment. Medical treatment with high doses of corticosteroid agents has led to inconsistent results (6, 9). Nevertheless, surgical intervention has been associated with definitive diagnosis and satisfactory outcome (3, 14, 34).

We present 5 primary non-necrotizing granulomatous hypophysitis cases with hormonal disorder and mass effect symptoms such as headache and visual impairment in this study. All the patients underwent surgical treatment with an endoscopic endonasal transsphenoidal approach, misdiagnosed preoperatively as a pituitary adenoma.

MATERIAL and METHODS

A retrospective study was undertaken to review 5 cases of primary non-necrotizing granulomatous hypophysitis (1.61%) through 310 endoscopic transsphenoidally operated cases with the diagnosis of pituitary adenoma between 2009 and 2013. All 5 cases were female and the mean age was 47,6 years. The patients had no history of recent pregnancy or underlying autoimmune disease. Headache, hormonal elevation, hormonal deficiency and vision loss were the most common presenting features. The initial presumptive diagnosis was pituitary adenoma in all patients. Endocrinological evaluation of the patients led to one case of suspected Cushing's Disease, one anterior pituitary deficiency with hyponatremia, one hyperprolactinemia, one normal hormonal level and one acromegaly. All patients had macroadenomas including one invasive adenoma with skull base and cavernous sinus involvement. One patient (20%) had a visual field defect. Although they were initially diagnosed as pituitary adenomas with pre-operative radiological imaging and endocrinological evaluation, postoperative histological assessment with hematoxylin eosin (H&E) staining showed dense inflammatory cell and multinuclear giant cell infiltration inside a fibrotic stroma. Immunohistochemical staining revealed scattered CD68 positive histiocytes. These histopathological findings led to a diagnosis of non-necrotizing granulomatous hypophysitis (Figure 1A-D). The patients were investigated for granulomatous systemic disease after the postoperative pathological diagnosis of non-necrotizing granulomatous hypophysitis, but did not show any evidence of such disease.

Patient 1

A 40-year-old woman presented with a 3-month history of headache and weight gain. Neurological evaluation and fundoscopic examinations were normal. Pituitary Magnetic resonance imaging (MRI) revealed a 20x12x10 mm lesion with

a diffuse homogenous enhancement following gadolinium administration, considered to be a macroadenoma (Figure 2A). The endocrinological evaluation revealed that serum cortisol and ACTH levels were higher than normal and the cortisol and ACTH levels were suppressed with 8 mg dexamethazone. The patient was diagnosed as suspected Cushing's Disease. She was operated with endoscopic endonasal transsphenoidal approach and the tumor was removed totally. Surgery was uncomplicated. The postoperative period was uneventful. Postoperative serum cortisol and ACTH levels were within the normal range. There were no complaints or tumor recurrence within 14 months of follow-up.

Patient 2

A 49-year-old woman presented with a 1-month history of nausea and vomiting. Neurological evaluation and fundoscopic examinations were normal. Endocrinological and laboratory evaluations showed severe hyponatremia with a need for sodium replacement therapy due to hypopituitarism. Pituitary MR imaging revealed an 11x10x9 mm lesion considered to be macroadenoma, with heterogeneous enhancement following gadolinium administration (Figure 2B). The patient was operated with endoscopic endonasal transsphenoidal approach and the tumor was removed totally. Surgery was uncomplicated. The postoperative period was uneventful. There was no complaint or tumor recurrence within 16 months of follow-up under hormonal replacement therapy.

Patient 3

A 63-year-old woman presented with a 6-month history of headache and amenorrhea. Neurological evaluation and fundoscopic examination was normal. Endocrinological and laboratory assessments showed a high prolactin level that was considered to be stalk effect. Pituitary MR imaging revealed a 14x16x14 mm lesion with diffuse homogenous enhancement following gadolinium administration, considered to be a macroadenoma with pituitary stalk compression (Figure 2C). The patient was operated with the endoscopic endonasal transsphenoidal approach and the tumor was removed totally. Surgery was uncomplicated. The postoperative period was uneventful. Postoperative prolactin levels were within the normal range. There was no complaint or tumor recurrence within 16 months of follow up.

Patient 4

A 38-year-old Sudanese woman presented with a severe headache and visual loss for the last year. Neurological examination was remarkable for quadrantsopia. The patient had been treated with radiotherapy for nasopharynx carcinoma in Sudan. Pituitary MRI revealed a 28x35x59 mm macroadenoma, with heterogeneous contrast enhancement, that invaded the right cavernous sinus, Meckel's cave, skull base and clivus with slight optical chiasm compression (Figure 2D). Endocrine and laboratory assessments were normal. The patient was operated with the endoscopic endonasal transsphenoidal approach and peroperative histological

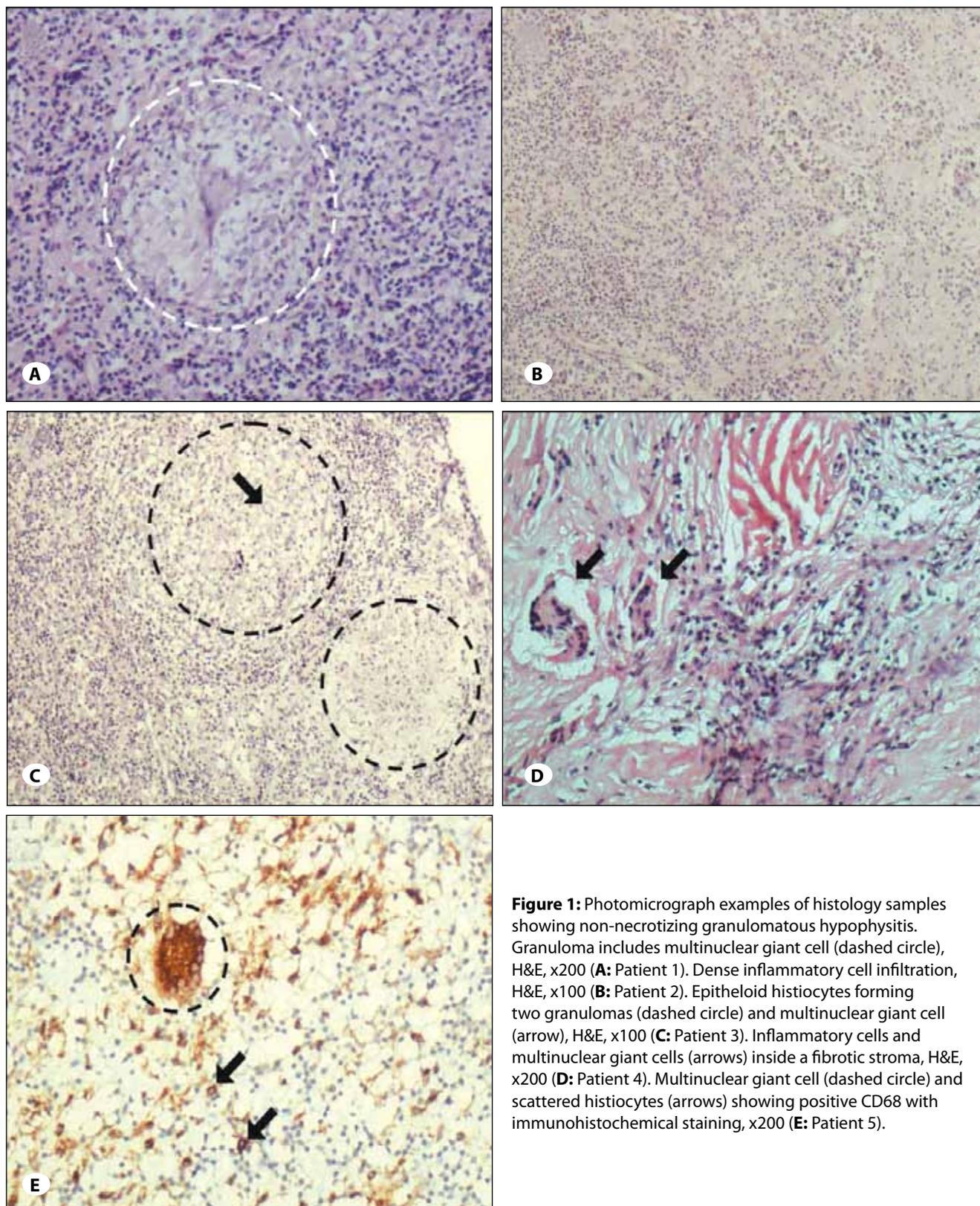


Figure 1: Photomicrograph examples of histology samples showing non-necrotizing granulomatous hypophysitis. Granuloma includes multinuclear giant cell (dashed circle), H&E, x200 (**A:** Patient 1). Dense inflammatory cell infiltration, H&E, x100 (**B:** Patient 2). Epithelioid histiocytes forming two granulomas (dashed circle) and multinuclear giant cell (arrow), H&E, x100 (**C:** Patient 3). Inflammatory cells and multinuclear giant cells (arrows) inside a fibrotic stroma, H&E, x200 (**D:** Patient 4). Multinuclear giant cell (dashed circle) and scattered histiocytes (arrows) showing positive CD68 with immunohistochemical staining, x200 (**E:** Patient 5).

evaluation of the patient was reported as non-necrotizing granulomatous hypophysitis. The operation was discontinued and steroid therapy was started.

Patient 5

A 48-year-old woman presented with a 6-month history of headache, enlargement of hands/feet and dyspnea. Neurological evaluation and fundoscopic examinations were normal. Pituitary MR imaging revealed a 15x10x10 mm lesion with heterogeneous enhancement following gadolinium administration and was considered as macroadenoma (Figure 2E). The endocrinological examinations revealed that serum growth hormone (GH) and insulin like growth factor (IGF-1) levels were higher than normal range. The patient was diagnosed as acromegaly. She was operated with endoscopic endonasal transsphenoidal approach and the tumor was removed totally. Surgery was uncomplicated. The postoperative period was uneventful. Postoperative serum GH and IGF-1 levels were within normal interval for her age and gender. There were no complaints or tumor recurrence within 8 months of follow up.

RESULTS

All patients had an excellent surgical outcome. Early postoperative MRI scans were excellent in all except patient 4. Total tumor excision was performed for 4 patients (Figure 3A-D). Only one patient (Patient 4) had subtotal tumor removal. Postoperative hormonal replacement therapy was needed only in patient 2. The other three patients had normal hormonal laboratory findings. There were no intraoperative or postoperative complications and all patients were discharged after a mean postoperative duration of 3 days. There was no detected recurrence in the 4 patients within a mean follow-up duration of 14.8 months. The patient data are summarized in the Table I.

DISCUSSION

The most common pituitary mass is adenoma while other mass lesions include metastases, cysts, hyperplasias, infections and inflammations (3). Inflammatory pituitary situations are very rare and there are few published cases. Inflammatory hypophysitis can be classified as primary or idiopathic hypophysitis and secondary hypophysitis may occur

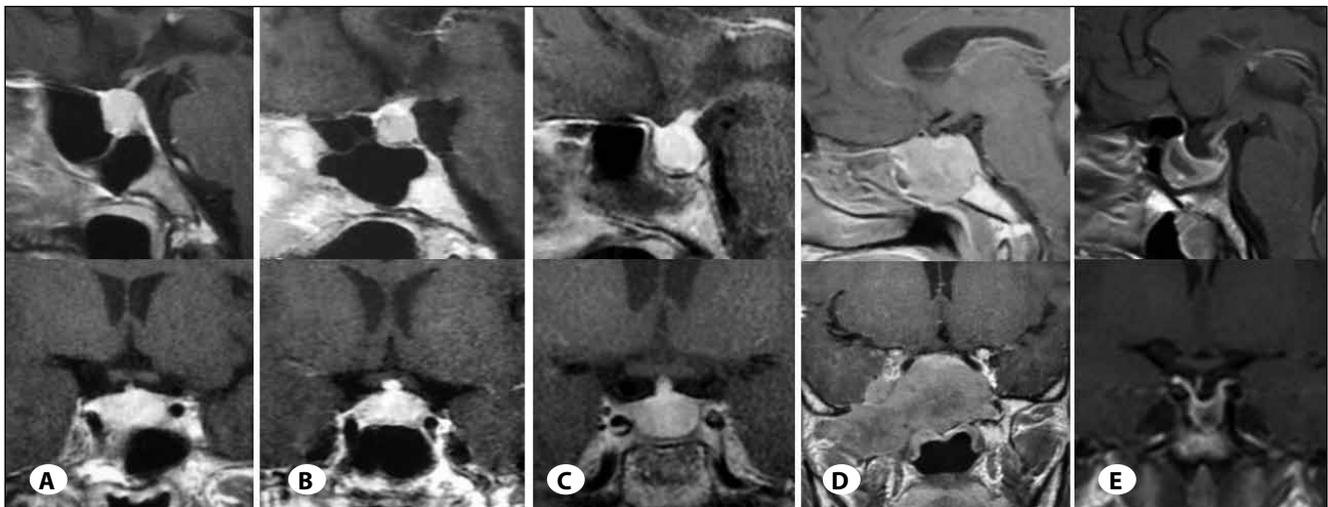


Figure 2: Preoperative sagittal and coronal contrast enhanced magnetic resonance images of patients (A: patient 1, B: patient 2, C: patient 3, D: patient 4, E: patient 5).

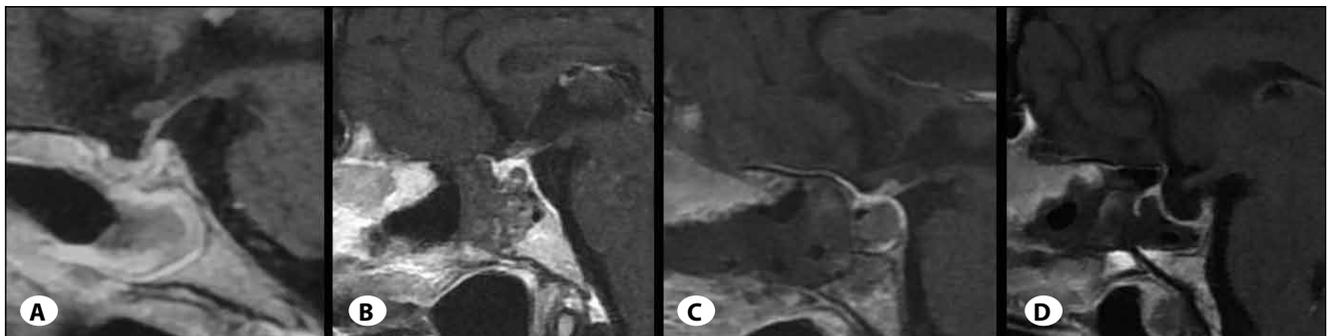


Figure 3: Postoperative sagittal contrast-enhanced magnetic resonance images of patients (A: patient 1, B: patient 2, C: patient 3, D: patient 5).

Table I: Summary of the Patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age	40	49	63	38	48
Gender	Female	Female	Female	Female	Female
Signs&Symptoms	Headache, weight gain for 3 months	Nausea and vomiting for 1 month	Headache and amenorrhea for 6 months	Headache, visual loss for 1 year	Headache, growth of hands/feet, dyspnea for 6 months
Neurological Exam & Fundoscopy	Normal	Normal	Normal	Quadrantopsia	Normal
Radiology	Homogenous macroadenoma	Heterogenous macroadenoma with chiasm compression	Homogenous macroadenoma with chiasm and stalk compression	Heterogenous macroadenoma with skull base invasion and chiasm compression	Heterogenous macroadenoma
Endocrinology & Laboratory	High cortisol and ACTH	Hypopituitarism, Hyponatremia	High prolactin (stalk effect)	Normal	High GH and IGF-1
Initial Diagnosis	Pituitary Adenoma (Cushing's Disease)	Pituitary Adenoma (Non-secretory)	Pituitary Adenoma (Non-secretory)	Pituitary Adenoma (Non-secretory)	Pituitary Adenoma (Somatotropinoma)
Tumor Removal	Total	Total	Total	Subtotal	Total
Histological Diagnosis	Non-necrotising granulomatous hypophysitis	Non-necrotising granulomatous hypophysitis	Non-necrotising granulomatous hypophysitis	Non-necrotising granulomatous hypophysitis	Non-necrotising granulomatous hypophysitis
Follow-up	14 months	16 months	16 months	20 months	8 months

due to systemic inflammatory disorders (5, 7, 12). Primary hypophysitis is classified into five sub-types: lymphocytic, granulomatous, xanthomatous, xanthogranulomatous and necrotizing (38). Currently, it is unclear whether these entities are truly distinct or they are just different manifestations of the same disease. They have same clinical and radiological features, and there is no safe way to distinguish these entities from each other without histological examination (7). Granulomatous hypophysitis is a less commonly described entity in the literature, with a rather unclear pathogenesis. It was first described by Simmonds in 1917 (34). Granulomatous hypophysitis has an annual incidence of 1 in 10 million and accounts for less than 1% of all pituitary disorders (31). In contrast to lymphocytic hypophysitis, there is no gender predominance (7). In this study, we presented five primary granulomatous hypophysitis cases mimicking secretory, non-secretory and invasive pituitary adenomas to illustrate the clinical spectrum of this entity. All patients were female and the mean age was 47.6 years. Recent pregnancy and underlying autoimmunity were not noted.

Clinical presentation of both hypophysitis and pituitary adenomas is with headache, visual disturbances caused by optic chiasm compression, pituitary dysfunctions, hyperprolactinoma, diabetes insipidus (DI), fatigue and lethargy (6, 11,

15, 16, 17, 32, 43). Headache is the first and most common symptom (16). Pituitary function is commonly affected in inflammatory hypophysitis, where ACTH and TSH deficiencies are the most frequently reported anomalies (6, 15, 18, 38). Hyperprolactinemia may develop as a result of stalk compression, presenting with amenorrhea/galactorrhea in females and decreased libido in males (1). DI may result from inflammatory destruction and/or compression of the posterior pituitary or stalk (38). All our patients had macroadenomas and headache was the most common symptom, similar to the literature. Three of the five patients had visual disruption (60%). The endocrinological evaluation of our 3 patients revealed one anterior pituitary deficiency and hyponatremia, one hyperprolactinemia and one normal hormonal level. In contrast to previously published cases, two of our patients had an uncommon endocrinological finding: serum cortisol and ACTH levels were higher than normal and were suppressed with 8 mg dexamethasone, as is seen in Cushing's Disease (patient 1), and serum GH and IGF-1 levels were higher than normal as seen in acromegaly (patient 5). These cases are uncommon and important as they represent a hypophysitis case mimicking a secretory pituitary adenoma, in contrast to previously published hypophysitis cases, which were initially diagnosed as non-secretory adenomas.

An inflammatory lesion is difficult to differentiate from a pituitary adenoma both clinically and radiologically. MRI plays a crucial role in the diagnosis of inflammatory hypophysitis. Characteristic MRI findings are thickening of the parasellar duramater and pituitary stalk with a contrast-enhancing sellar mass (9, 18, 20). A triangular-shaped sellar mass, an enlarged pituitary and thickened sphenoidal mucosa are the other MRI findings that can be visualized in hypophysitis cases (9, 14). Pituitary stalk thickening was the most common finding and seen in 66% of granulomatous hypophysitis cases (11, 8, 32). All these radiological features are non-specific, which is why hypophysitis cases are generally misinterpreted as pituitary adenoma and the diagnosis is usually made postoperatively by histological examination (8, 37, 41). The initial presumptive diagnosis was pituitary adenoma in our patients and all patients underwent EETH.

The natural history of inflammatory hypophysitis is incompletely understood and its treatment is controversial (25, 26, 38). Satisfactory responses to high-dose steroid therapy and administration of methotrexate have been reported (2, 13, 39, 40, 44). Spontaneous resolution of the lesion on MRI following steroid therapy has been described, but endocrine improvement is rare (21). Insufficient treatment has been associated with granuloma formation and sudden death in hypophysitis cases (4, 10). Considerable side effects of long-term steroid therapy and recurrence of lesions following steroid withdrawal have been identified (19, 21, 22, 26, 28, 33). Transsphenoidal surgery is performed for both diagnosis and therapy. Surgery should be performed in cases with progressive compression or those in whom radiological and/or clinical progression occurs during conservative medical management (7). The hyperprolactinemia and mass effect such as visual disruption and stalk compression (DI) resolves after surgery in most cases (23, 27, 29). On the other hand, definitive histological diagnosis of hypophysitis may obviate the unnecessary use of high-dose steroid therapy and facilitate the treatment of other conditions such as infection or neoplasm (21). Surgical intervention has resulted in further deterioration of visual field deficits and/or hypopituitarism in rare instances (22, 29, 36). We operated on all our patients via the endoscopic endonasal transsphenoidal approach with the diagnosis of pituitary adenoma. The high hormonal levels (cortisol/ACTH, prolactin and GH/IGF-1) of Patient 1, 3 and 5 returned to normal and visual field defects of Patient 2, Patient 3 and Patient 4 totally recovered after the surgery. Patient 2 needed to use hormonal replacement therapy postoperatively and had no complaints within the follow-up period. Steroid therapy for hypophysitis was not begun for any of the patients before or after the surgery. There were no surgical complications during or after the operation.

CONCLUSION

Granulomatous hypophysitis is a heterogeneous group of inflammatory pituitary gland lesions. Secondary hypophysitis is more easily diagnosed as patients are likely to have other systemic manifestations of their underlying disorder. Most

primary hypophysitis cases are diagnosed postoperatively and can have a variety of clinical, endocrinological and radiological presentations. Even if radiological findings do not support the diagnosis of hypophysitis, it should be kept in mind that primary hypophysitis can mimic non-secretory and invasive pituitary adenomas with mass effect or secretory adenomas with its clinical and laboratory findings.

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