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ORIGINAL ARTICLE

Primary pituitary abscess case series and a review of the literature

Burak Cabuk [1], Melih Caklili [1], Ihsan Anik [1], Savas Ceylan [1], Ozlem Celik [2], Cemal Ustün [3]

1 Department of Neurosurgery, Kocaeli University School of Medicine, Pituitary Research Center, Kocaeli, Turkey.
2 Division of Endocrinology and Metabolism, Department of Internal Medicine, Acibadem University School of Medicine, Istanbul, Turkey.
3 Department of Infectious Diseases and Clinical Microbiology, Acibadem University School of Medicine, Istanbul, Turkey.

Correspondence to: Prof. Savaş Ceylan (MD)
Kocaeli Üniversitesi, Umuttepe Yerleşkesi, Eski İstanbul Yolu 41380 Umuttepe, Kocaeli, Turkey
TEL.: +902623038614; E-MAIL: ssceylan@yahoo.com

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Abstract

OBJECTIVE: Pituitary abscess is a rare condition, with approximately 300 cases reported in the literature. Primary pituitary abscess, the most common type, occurs in previously healthy normal glands. Secondary pituitary abscess is secondary to pre-existing lesions in the pituitary region, such as pituitary adenoma, Rathke's cleft cysts, or craniopharyngioma and infections.
MATERIAL AND METHODS: A total of 2281 patients underwent pituitary surgery via endoscopic transsphenoidal approach in Kocaeli University Pituitary Gland Research Center between 1997 and 2018. Among this cohort 9 patients (4 female and 5 male) were diagnosed with primary pituitary abscess based on both intraoperative findings and postoperative histopathological evidence.
RESULTS: Primary pituitary abscess incidence was obtained 0.39% in our center. Mean age of the patients was 50 years old. There was no history of pituitary surgery, radiotherapy and infection diseases in our patients. Visual symptoms were prominent in two patients, hypopituitarism was found in 5 out of the 9 patients. All patients have typical pituitary lesion on pituitary magnetic resonance imaging. Staphylococcus species were the most commonly isolated organisms in the culture. A few weeks of antibiotic therapy were administered after surgery.
CONCLUSION: Presentation of fever, headache, diabetes insipidus, hypopituitarism and a sellar cystic mass with an enhanced rim after gadolinium contrast on pituitary magnetic resonance imaging may be suggestive of a pituitary abscess. Transsphenoidal endoscopic surgery, proper antibiotics and appropriate hormone replacement therapy when necessary are the keys of pituitary abscess treatment.

Abbreviations:
PA - Pituitary abscess
TSE - Transsphenoidal endoscopic
MRI - Magnetic resonance imaging
GH - Growth hormone
IGH-1 - Insulin-like growth factor 1
ACTH - Adrenocorticotropic hormone
TSH - Thyroid-stimulating hormone
T3 - Free triiodothyronine
T4 - Thyroxine
FSH - Follicle-stimulating hormone
LH - Luteinizing hormone
T - Testosterone
E2 - Estradiol
PRL - Prolactin
DI - Diabetes insipidus

INTRODUCTION

Pituitary abscess (PA) is a rare disease with an incidence of 0.2% and 1.1% of operative pituitary lesions (Dutta *et al.* 2006; Dalan & Leow, 2008; Jain *et al.* 1997; Vates *et al.* 2001; Liu *et al.* 2011; Agyei *et al.* 2017). The diagnosis is delayed due to non-specific symptoms and indistinguishable radiological findings. The diagnosis is usually made intraoperatively or postoperatively and intravenous antibiotics are administered empirically (Dalan & Leow 2008; Agyei *et al.* 2017). Primary PA occurs in previously healthy normal glands. One third of all PA are secondary, arising from preexisting lesions such as pituitary adenomas, Rathke cleft cysts, and craniopharyngiomas. Pituitary abscess can be caused by haematogenous seeding or by the direct extension of an adjacent infection such as sepsis, meningitis, cavernous sinus thrombosis, and recurrent sinusitis (Agyei *et al.* 2017). Transsphenoidal endoscopic (TSE) surgery, proper antibiotics, appropriate hormone replacement therapy when necessary are components of the treatment of PA (Gao *et al.* 2017; Jadhav *et al.* 1998; Wang *et al.* 2014). Herein, we present 9 patients with primary PA in the context of the review of the literature.

MATERIAL AND METHODS

A total of 2281 TSE surgery was performed for sellar pathologies in Kocaeli University Pituitary Gland Research Center between August 1997 and January 2018. Nine patients were diagnosed with primary PA. Most studies use the following triad for the diagnosis of PA: 1) pituitary lesion with mass effect on pituitary magnetic resonance imaging (MRI) and the MRI findings described earlier, 2) pus observed intraoperatively, 3) histopathology showing acute or chronic inflammation containing polymorphonuclear cells or macrophages (Agyei *et al.* 2017). Gender, age, clinical presentation, endocrine examination findings, imaging results, culture results for pathogenic microorganisms, postoperative hormone replacement therapy and follow-up data were recorded for each included patient. This study was approved by the Ethics Committee of Kocaeli University Medical School and written informed consent was obtained from all patients.

Physical examination and a complete history were obtained. Evaluations of biochemical pituitary function, pituitary MRI and ophthalmologic evaluations were conducted preoperatively, postoperatively and during follow-up. Endocrine examinations included measurements of growth hormone (GH), insulin-like growth factor 1 (IGF-1), plasma cortisol, adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), free triiodothyronine (T3), thyroxine (T4), follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone (T), estradiol (E2), and prolactin (PRL) levels. Serum GH and IGF-1 levels were measured using chemiluminescent immunomet-

Tab. 1. Demographic, clinical characteristics, pathologies, microbiological cultures and follow-up periods of 9 patients with primary pituitary abscess

Age	Sex	Complaints	Pathology	Cultures	Endocrine Findings	Follow-up (months)
46	F	Headache, visual impairment	Abscess formation	S.Aureus	No	35
56	F	Visual impairment	Abscess formation	No organism	No	20
33	M	Headache, fever	Abscess formation	S.Aureus Klebsiella Ozaenae	No	24
43	M	Headache, polyuria	Insufficient	S.Aureus	DI, hypogonadism	16
67	M	Headache, nausea	Abscess formation	No organism	No	24
64	M	Nausea, vomiting	Insufficient	S.Aureus	Hypothyroidism Hypocortisolism	36
58	F	Headache, weakness, fever	Abscess formation	No organism	Hypothyroidism Hypocortisolism Hypogonadism	15
27	F	Headache	Abscess formation	S.Aureus	Hypogonadism	5
58	M	Headache, weakness	Abscess formation	S.Aureus	Hypocortisolism Hypogonadism	3

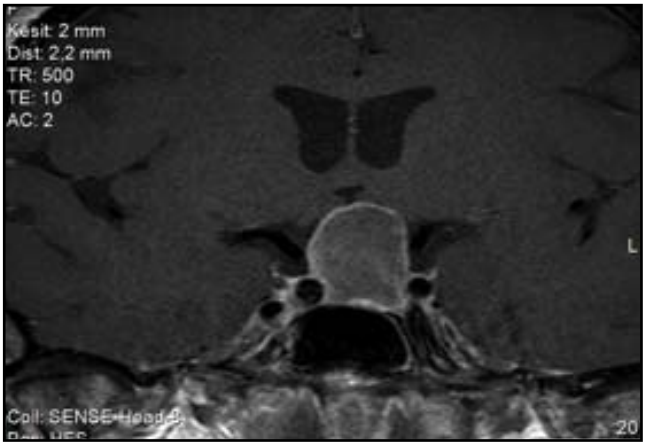

Fig. 1A. A sellar mass measuring 24x17 mm, hypointense on MRI T1-weighted coronal image with peripheral enhancement after gadolinium injection.

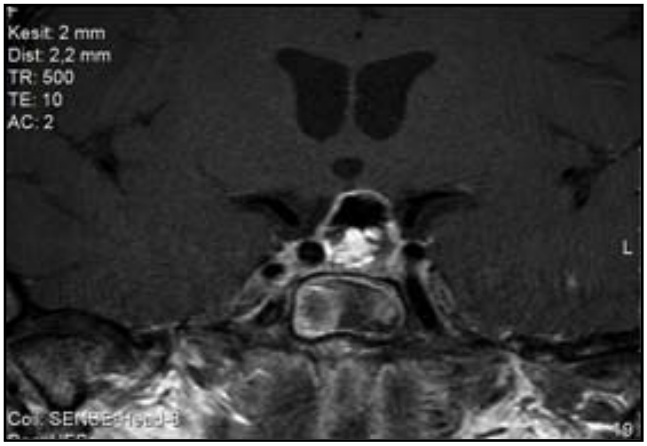

Fig. 1B. Post-operative pituitary MRI was clear of residual lesions.

ric assays (Immulite 2000; Siemens), Other biochemical parameters were measured locally using standard commercial assays. Diabetes insipidus (DI) was confirmed according to general criteria.

RESULTS

The 9 patients with primary PA including 5 males and 4 females with a mean age of 50 years. (range 27–67 years). The average follow-up duration was 7.2 years (range 1.5–22.6 years).

Table 1 shows demographic, clinical characteristics, pathologies, microbiological cultures, endocrine evaluation and follow-up periods of 9 patients with primary PA. Five patients were diagnosed with hypopituitarism based on clinical signs and symptoms, including findings from biochemical tests. Two patient were diagnosed secondary hypothyroidism (fT4 levels : 7 and 6.2 pmol/L, respectively). Two male and two female patients were diagnosed secondary hypogonadism according to low T and E2 levels. Three patient have central hypocortisolism (Cortisol levels were 3, 0.67, 1.67 μg/dL respectively). A patient was diagnosed with central DI. Headache (7/9 patients) was the most common complaint. Two patients have visual disturbances, including decreased visual acuity and visual field impairment. Although PA is considered an infectious disease, only 2 patients presented with fever.

All patients showed the typical features of abscesses, including hypointensity or isointensity on T1-weighted imaging (T1WI), hyperintensity or isointensity on T2-weighted imaging (T2WI), and rim enhancement after gadolinium injection (Figure 1A, 2A, 3). The patients were followed up with clinic, laboratory results and pituitary MRI 3 months after surgery (Figure 1B, 2B).

There was no history of pituitary surgery and any infectious diseases in our patients. All patients underwent pituitary surgery via endoscopic transsphenoidal approach. Specimens for the culture and histopathol-

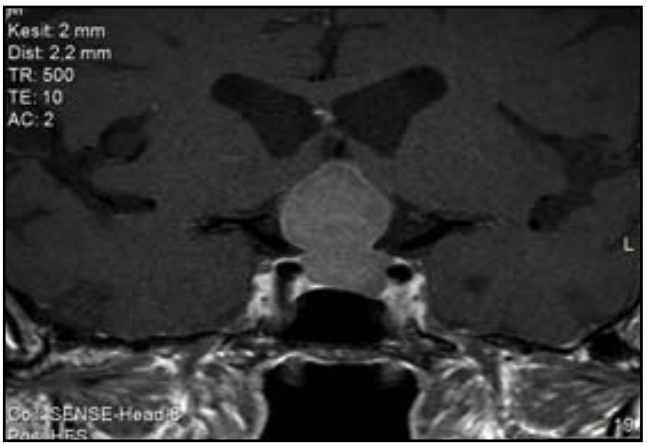

Fig. 2A. Pituitary MRI coronal image shows a 30x20 mm dense, cystic, hypointense lesion on T1-weighted image that has reached to suprasellar cisterna and third ventricle, elevating optic chiasma

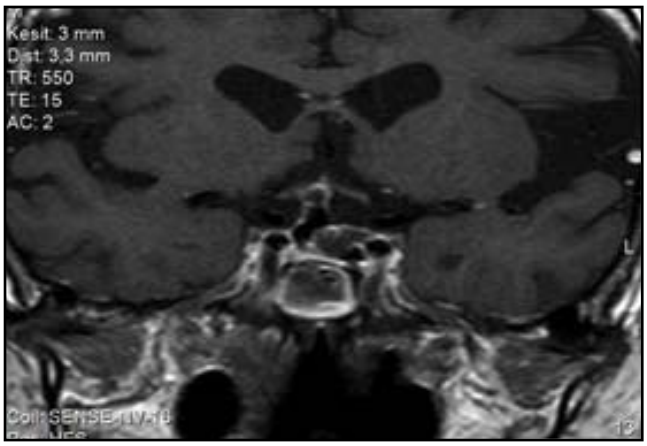

Fig. 2B. Post –operative MRI revealed complete resolution of the abscess.

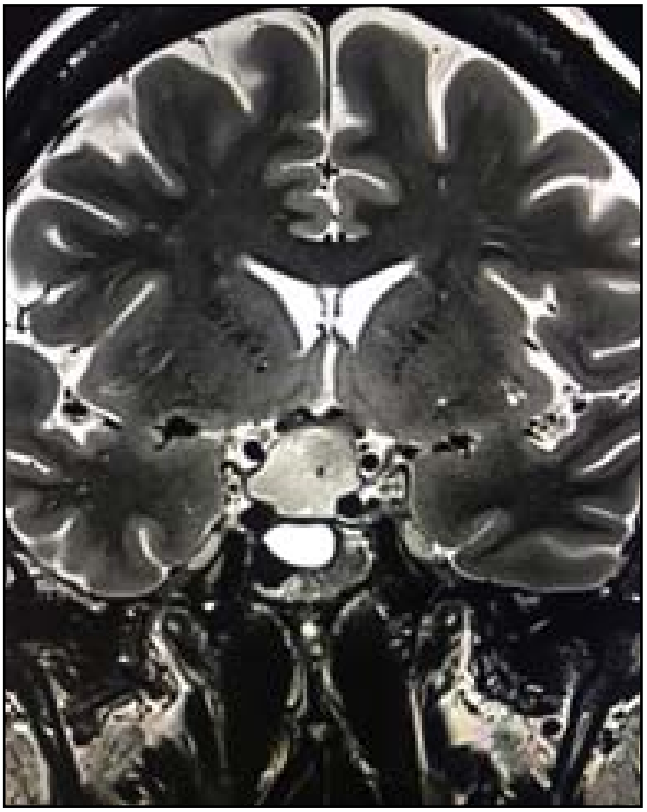

Fig. 3. T2 weighted MRI coronal view shows a mass 20x16 mm dense, hyperintense, cystic lesion.

ogy were collected with an injector from intrasellar space to prevent the contamination (Figure 4). Cultures were positive for Staphylococcus Aureus in 6 patients of 9 patients. Ceftriaxone and metronidazole treatments were administered to 8 patients. Vancomycin treatment was administered to one patient who had Methicillin Resistant Staphylococcus Aureus in culture. After surgery, hypopituitarism continued in patients and treated with oral prednisolone, L-thyroxine and sex steroid therapy properly. One patient with DI is still taking desmopressin.

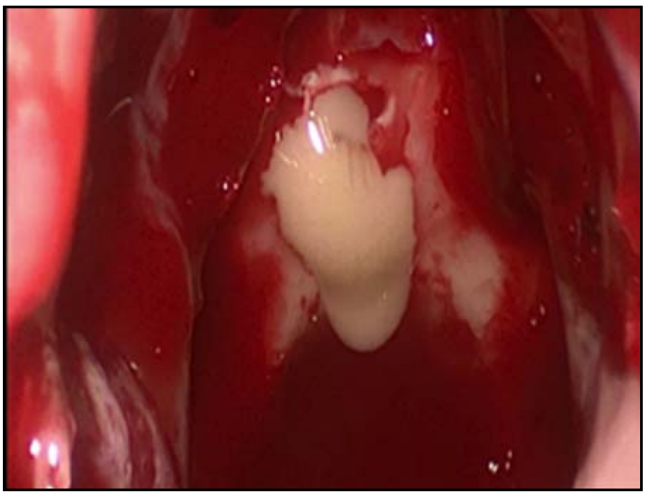

Fig. 4. Yellow purulent material drained during endoscopic transsphenoidal surgery.

DISCUSSION

We present 9 patients with primary PA as a case series among 2281 operated cases (our incidence 0.39 %). The rarity of PA is also evidenced by the reporting of only a few hundred cases in the literature, most of which were case reports (Dutta *et al.* 2006; Dalan & Leow 2008; Jain *et al.* 1997; Vates *et al.* 2001; Liu *et al.* 2011; Agyei *et al.* 2017; Gao *et al.* 2017). Liu *et al.* (2011) and Gao *et al.* (2017) have reported the largest series in the literature, containing 33 and 66 patients with PA respectively. The incidence of PA was reported respectively 1.1% and 1.04% in patients who underwent surgery for various pituitary disorders at their institution. Vates *et al.* (2001) and Jain *et al.* (1997) each reported 0.6% incidence of PA among 3500 and 1000 patients with operated pituitary lesions, respectively.

There are two types of PA; primary and secondary. Primary PA, the most common type, occurs in previously healthy normal glands. Secondary PAs are secondary to pre-existing lesions in the pituitary region, such as pituitary adenoma, Rathke's cleft cysts, or craniopharyngioma (Agyei *et al.* 2017; Su *et al.* 2006; Hatipoglu *et al.* 2006; Jaiswall *et al.* 2004; Liu *et al.* 2010, Gonzales *et al.* 2012; Shuster *et al.* 2010). There was no history of pituitary surgery and any infectious diseases in our patients.

According to a review of literature, headache, hypopituitarism, and visual disturbance are the most common presenting symptoms of pituitary abscess. Visual deficits included photophobia, diplopia, and visual field defects. Endocrinopathies resulting from hypopituitarism usually include hypogonadism, DI, hypothyroidism, and hypocortisolemia (Agyei *et al.* 2017). Headache and DI were the most common presenting symptoms in the report by Liu *et al.* (2011). In our case series, headache was prominent in 7 patients and visual symptoms were found in 2 patients, hypopituitarism was found in 5 patients.

In the reported literature presenting fever ranges from 18%- 42% (Dutta *et al.* 2006; Dalan & Leow 2008; Vates *et al.* 2001; Liu *et al.* 2011; Wang *et al.* 2014; Liu *et al.* 2010). In the case series reported by Dutta *et al.* (2006) fever and headache were the predominant symptoms. Although fever is not always present, leukocytosis with neutrophil dominance is prevalent in cases with PA. Also increased ESR and CRP levels were reported both in case reports and case series (Agyei *et al.* 2017; Gonzales *et al.* 2012; Shuster *et al.* 2010). Two patiens have fever and increased ESR and CRP levels in our case series.

The pre-operative MRI diagnosis was mostly macroadenoma due to non-specific radiological findings of PA. Wolansky *et al.* (1997) reported that the typical presentation of primary PA gives the same or slightly

lower signal than brain on T1-weighted images and hyperintense or isointense on T2-weighted imaging with a rim enhancement on gadolinium injection. Because similar appearance might be seen most sellar lesions, it is difficult to distinguish an abscess from the lesions, such as Rathke's cleft cysts, cystic craniopharyngiomas, cystic adenoma. Therefore MRI findings are diagnostically valuable when combined with clinical presentation. In most case series authors report to identify the abscess in surgical operation with the observation of a purulent material. Preoperative diagnosis is difficult, and its success has been variable throughout the literature. Vates *et al.* (2001) were corrected in the diagnosis of 20.8% of their cases, whereas Wang *et al.* (2014) were accurated in 83% of theirs. Liu *et al.* (2011) and Bossard *et al.* (1992) made an accurate diagnosis of PA in 50% and 24% of their patients, respectively.

Pathological assessment is necessary to identify whether abscess has aroused on a pre-existing lesion such as adenoma, Rathke's cleft cyst or it is solely a primary abscess (Hatipoglu *et al.* 2006; Jaiswall *et al.* 2004; Thomas *et al.* 1998; Uchiyama *et al.* 2011). Seven patients had confirmative pathological abscess reports whereas other two had insufficient pathological material in our case series. Due to inconclusiveness of pathology, microbiological evaluation and cultures are important for the diagnosis of pituitary abscess. Gram-positive bacteria (Staphylococcus, Streptococcus, and Pneumococci) are the most commonly isolated organisms in cultures, but also other organisms such as gram-negative bacteria, fungal organisms can be positive (Dutta *et al.* 2006; Dalan & Leow; 2008; Vates *et al.* 2001; Agyei *et al.* 2017; Pepene *et al.* 2010). Staphylococcus species were the most common agent in the cultures in our case series. Antibiotic therapy should be started when suspicion for pituitary abscess is raised to prevent progression of disease and future sequelae. Four to 6 weeks of antibiotic therapy is typically reported in the literature (Vates *et al.* 2001; Agyei *et al.* 2017; Jadhav *et al.* 1998; Zegarra-Linares *et al.* 2015; Zhu *et al.* 2014).

Of the surgical approaches, the TSE approach is the most favored (Dutta *et al.* 2006; Dalan & Leow 2008; Vates *et al.* 2001; Agyei *et al.* 2017; Zhang 2012). It provides a wider view to the surgeon and facilitates excision of various sellar lesions including abscess. This wide angle and panoramic view also aid visualization of blind spots and reduce damage to the gland. Dalan *et al.* (2008) believe that TSE provides the best means of reversing visual deficits because it led to improvement of the visual fields in 80% of the patients in their analysis and it stabilized progressively deteriorating visual fields in another 16%. In the surgical closure of the pituitary abscess, foreign bodies – absorbable haemostat, collagen dura matrix etc.- are not left in the surgical field following hemostasis. In these cases, we did not perform the multilayer closure technique that we used in the standard TSE surgery.

In some cases, endocrinological disorders resolve after both surgical and medical intervention, but there are also cases with lifelong need of hormone replacement therapy. Agyei JO *et al.* (2017) reported that of the 151 patients who presented with endocrine abnormalities, 32.3% had complete recovery of endocrine function, 33.8% had partial recovery, and 22.5% had no recovery of pituitary function. In our series hypopituitarism was found in 5 patients. Central DI and hypopituitarism continued and they were receiving appropriate hormone therapies after surgery.

Postoperative pituitary abscess recurrence is uncommon. Liu *et al.* (2011) reported 4 of 33 patients with recurrence who had immunologic disorders or had undergone previous surgery. In report of Vates *et al.* (2001) one patient was found with recurrence of pituitary abscess (4%). Agyei JO *et al.* (2017) reported analysis of 200 cases, 20 patients had recurrence of pituitary abscess, for a recurrence rate of 10%. Of these patients, 5 had undergone craniotomy as primary treatment and the rest underwent the TSE approach. Fifteen of the patients (9.7%) who underwent TSE surgery had recurrence, whereas 5 out of 29 patients (17.2%) in the craniotomy group experienced recurrence, giving the craniotomy group a higher rate of recurrence. The most common complications of surgery for pituitary abscess include meningitis, cerebritis, infectious vascular injury,and cerebrospinal fluid leakage. Zhang X *et al.* (2012) reported no complication and recurrence postoperatively in 29 patients. Also we didn't see any complication and recurrence in our patients. Pituitary abscess was associated with a mortality of 4.5% in the last review of the literature. Pituitary apoplexy, hypothalamic dysfunction, sepsis, meningitis or systemic disease, and unknown etiologies caused to mortality (Agyei JO *et al.* 2017).

In conclusion PA are rare, life threatening disorders which mimic many other sellar mass lesions. Presentation of fever, headache, diabetes insipidus, hypopituitarism and a sellar cystic mass with an enhanced rim after gadolinium contrast on pituitary MRI may be suggestive of PA. TSE surgery is the best approach for evacuation of these sellar lesions. Proper antibiotics and appropriate hormonal replacement therapy when necessary are the keys to the treatment of PA.

lar, the group reported that the location of AVPV nuclei and SCN were determined in relation to white matter landmarks and the third ventricle. However, in humans there is no structural presence of the AVPV, hence these methodologies are restricted to rodent models.

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DECLARATION OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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