



Case Report

Radiographic pituitary stalk disruption: A rare sequela of secondary empty sella syndrome

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ABSTRACT

Background: This two-patient case series describes a rare sequela of postoperative empty sella syndrome (ESS) following transphenoidal resection of pituitary macroadenomas. This is characterized by progressive hormone dysfunction, diabetes insipidus (DI), and associated MRI evidence of pituitary stalk disruption.

Case Description: This phenomenon was retrospectively evaluated in a review of 2000 pituitary tumor resections performed by a single neurosurgeon (KOL). Chart review was retrospectively conducted to gather data on demographics, pituitary hormone status, tumor characteristics, and management. We identified 2 (0.1%) cases of progressive pituitary endocrine dysfunction occurring in the postoperative period associated with MRI evidence of pituitary stalk disruption within 6 weeks of discharge from the hospital. This was felt to be caused by the rapid descent of the residual normal pituitary gland down to the floor of the postoperative empty sella, causing relatively swift stalk stretching. Both patients developed DI, and one patient demonstrated increased pituitary hormone dysfunction.

Conclusion: This phenomenon is a rare manifestation of postoperative ESS, secondary to surgical resection of a pituitary macroadenoma. We discuss the associated potential risk factors and strategies for avoidance in these two cases. Routine instillation of intrasellar fat in patients at risk is felt to be protective.

Keywords: Empty sella syndrome, Endocrine dysfunction, Pituitary adenoma, Pituitary stalk disruption, Transphenoidal resection

INTRODUCTION

Empty sella syndrome (ESS) is a condition in which the sella turcica is partially or filled with cerebrospinal fluid (CSF) resulting in downward displacement of the normal pituitary gland.^[1,3] ESS can be primary, due to an inherent weakness of the diaphragma sellae and downward herniation of arachnoid into the sella, or secondary, following surgical or medical management of a pituitary macroadenoma. The incidence of ESS is thought to be more common than is reported in the literature, given that most cases are asymptomatic.^[8,14] A well-described complication of secondary ESS is the downward migration of the optic chiasm, resulting in progressive visual acuity and visual field deterioration.^[2,4] Although downward displacement of the residual normal pituitary gland is often seen on postoperative imaging, corresponding hormone dysfunction is rarely noted.^[1,3]

We describe two cases of secondary ESS associated with downward displacement of the residual normal pituitary gland, with MRI evidence of pituitary stalk disruption. Both cases were without

optic chiasm involvement. In the postoperative period, these two patients exhibited progressive endocrine dysfunction along with the delayed onset of diabetes insipidus (DI). The finding of progressing endocrine dysfunction in the weeks following surgery, with MRI evidence of pituitary stalk disruption is rare, seen in two cases to date at our institution in review of 2000 transsphenoidal tumor resections.

MATERIALS AND METHODS

Study design and eligibility criteria

Patients aged 18 years or older who underwent transsphenoidal surgery (TSS) for a pituitary tumor at our institution from July 2000 to January 2020 were retrospectively identified. In our review, 2000 patients underwent TSS at our institution in the study period. Of this cohort, only 2 (0.10%) demonstrated rapid short-term pituitary endocrinopathy and DI with MRI evidence of pituitary stalk disruption. Case presentations are described below. Data were then retrospectively gathered through electronic health record review, including demographics, laboratory values, radiographs, and operative management. Per independent Colorado Multiple Institutional Review Board guidelines, this study was determined to be exempt.

Pituitary adenoma clinical protocol

At our institution, surgical management for patients with pituitary adenomas is recommended for those presenting with symptoms of mass effect (headache, visual compromise, or endocrinopathy), growth hormone, adrenocorticotropic hormone, or thyroid-stimulating hormone (TSH) hypersecretion, or hyperprolactinemia refractory to medical management. The choice of microscopic or endoscopic TSS depends on surgeon preference, patient anatomy, and tumor characteristics (i.e. cavernous sinus involvement or suprasellar extension). Hormone dysfunction in the postoperative period is managed with the corresponding agent until there is evidence of resolution. Routine follow-up consists of an MRI of the pituitary 3 months postoperatively and then at various intervals thereafter depending on resection rate and the patient's symptoms.

CASE DESCRIPTION

Case 1

A 54-year-old male presented to his primary care physician 5 years before neurosurgical evaluation with progressive fatigue. Laboratory testing was significant for a low free testosterone of 6.4 ng/mL (normal: 247–827 ng/mL), an luteinizing hormone (LH) of <0.2 mIU/mL (normal: 1.24–7.8 mIU/mL), follicular-stimulating hormone (FSH) <0.7 mIU/mL (normal: 1–18 mIU/mL), and a borderline

high prolactin of 15.6 ng/mL (normal: 3–13 ng/mL). Laboratories 1 month later were remarkable for an elevated alpha subunit of 1.4 c (normal: <0.05 µg/L), low free T3 of 3.3 ng/dL (normal: 80–180 ng/dL), and an elevated prolactin of 28.38 ng/mL (normal: 3–13 ng/mL) [Table 1]. The patient was initially managed conservatively with monthly intramuscular testosterone injections. However, his serum testosterone remained subtherapeutic and his fatigue continued to progress. An MRI of the pituitary was subsequently performed and showed a large sellar and suprasellar mass displacing the optic chiasm upwards, consistent with a pituitary macroadenoma [Figure 1]. The normal pituitary gland was seen to be draped centrally over the superior aspect of the mass. Subsequent ophthalmologic evaluation revealed evidence of a bitemporal hemianopsia.

One month later, he underwent TSS. The surgery was uneventful and achieved gross total resection of the tumor and good visualization of the diaphragma sellae. The diaphragma was noted to descend into the sella turcica at the time of surgery, partially obliterating the resection cavity. The normal gland was observed layered over the diaphragma superiorly and the resection was felt to be atraumatic to the gland. There was no intraoperative evidence of a CSF leak, and no packing was placed into the sella. The sellar floor was reconstructed using a layer of Gelfoam and a horizontal bone strut harvested from the anterior sphenoid during the initial exposure. Over the first 24 h, the patient had 15 L of urine output, with an upward trending sodium from 131 mEq/L to 141 mEq/L (normal: 135–145 mEq/L). The urine output subsequently stabilized with the serum sodium remaining in the ~140 mEq/L range after serial testing. Specific gravity was 1.002 and the patient was tolerating output by matching with oral fluid intake. His urine output subsequently diminished, and he was discharged home on the 3rd postoperative day with an as-needed prescription for desmopressin (DDAVP) if increased urine output recurred. Final surgical pathology was consistent with a chromophobic pituitary adenoma.

Follow-up with his endocrinologist 2 weeks postoperatively revealed serologic evidence of panhypopituitarism, including

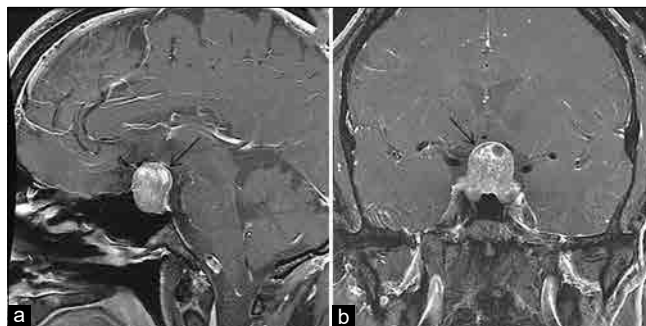


Figure 1: Case 1 preoperative contrast-enhanced T1-weighted MRI scan: (a) sagittal; (b) coronal. Arrows delineate the thin rim of normal pituitary gland draped superiorly over the tumor.

Table 1: Case 1 laboratory testing.

Laboratory test	Preoperative evaluation	Two weeks postoperative	Three months postoperative	Normal range
LH	<0.2 mIU/mL	<0.2 mIU/mL	***	1.24–7.8 mIU/mL
FSH	<0.7 mIU/mL	<1.0 mIU/mL	***	1–18 mIU/mL
Prolactin	Initial: 15.6 ng/mL (1-month follow-up: 28.38 ng/mL)	9 ng/mL	***	3–13 ng/mL
Free testosterone	6.4 ng/mL	60 ng/mL	146 ng/mL	241–827 ng/dL
Alpha-subunit	1.4 µg/L	***	***	<0.5 µg/L
ACTH	39 pg/mL	***	<5 pg/mL	7–69 pg/mL
Cortisol	15.1 µg/dL	2.0 µg/dL	<1 µg/dL	AM cortisol: 4–22 µg/dL (7–9 AM) PM cortisol: 3–17 µg/dL (3–5 PM)
fT3	3.3 ng/dL	***	***	80–180 ng/dL
fT4	1.04 ng/dL	***	1.23 ng/dL	0.89–1.76 ng/dL
TSH	0.59 mIU/L	0.06 mIU/L	***	0.34–5.6 mIU/L

LH: Luteinizing hormone, FSH: Follicular-stimulating hormone, ACTH: Adrenocorticotrophic hormone, fT3: Free triiodothyronine, fT4: Free thyroxine, TSH: Thyroid-stimulating hormone

new hypoadrenalism [Table 1]. He was then started on adrenal supplementation, with thyroid replacement and testosterone initiated 2 weeks later. At this time, his initial postoperative symptoms of DI appeared to be reemerging and he was placed on daily DDAVP. His postoperative MRI taken 1 month following surgery revealed a marked descent of the residual pituitary gland to the floor of the sella, with either severe stretching or complete disruption of the pituitary stalk [Figure 2]. Overtime, the patient's DI resolved but he continues to suffer from panhypopituitarism.

Case 2

A 58-year-old male presented to the neurosurgery clinic with a 2-year history of progressive vision loss. Initial ophthalmologic evaluation revealed bilateral cataracts, for which he underwent surgery. While he initially noted improvement, he subsequently developed unexplained right-sided vision loss. Visual field testing revealed evidence of a right-sided temporal field loss. A pituitary MRI revealed a 2.2 cm × 2.4 cm × 4.0 cm cystic sellar mass, with suprasellar extension [Figure 3]. On review of systems, the patient noted decreased energy and symptoms suggestive of sleep apnea (without a formal diagnosis). Endocrine laboratory studies revealed an FSH of 4 mIU/mL (normal: 1–18 mIU/mL), LH of 1.6 mIU/mL (normal: 1.24–7.8 mIU/mL), random AM cortisol of 3.0 mg/dL (normal: 4–22 µg/L), free T3 of 64 ng/dL (normal: 80–180 ng/dL), TSH of 5.71 mIU/L (normal: 0.34–5.6 mIU/L), free T4 of 0.36 ng/dL (normal: 0.89–1.76 ng/dL), free testosterone of 181 ng/dL (normal: 241–827 ng/dL), and prolactin of 510.2 ng/mL (normal: 3–13 ng/mL) [Table 2].

The MRI revealed a substantial cyst within the sella and suprasellar region with a fluid-fluid level consistent with subacute hemorrhage. The patient was diagnosed with a

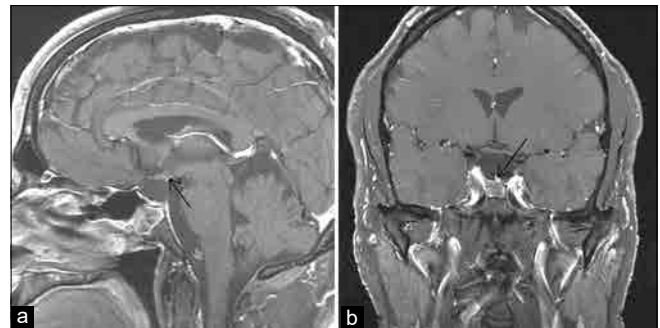


Figure 2: Case 1 2-month postoperative contrast-enhanced T1-weighted MRI scan: (a) sagittal; (b) coronal. Arrows delineate the proximal and distal aspect of the pituitary stalk.

probable hemorrhagic macroprolactinoma with associated panhypopituitarism. There was no evidence of DI. Due to the sizable subacute hematoma and vision changes, TSS was recommended. Surgery was uneventful with evacuation of the hematoma and removal of a significant amount of soft tumor tissue lining the cavity. The diaphragma was noted to descend downward into the sella at the time of surgery, covered by a layer of normal appearing pituitary gland. Gross total tumor resection was felt to have been obtained with no evidence of a CSF leak. Postoperatively, he initially did well, and his vision improved, leading to discharge on postoperative day 3. The patient was discharged home on both thyroid and adrenal hormone replacement, based on his preoperative hormone levels.

At discharge, he had no evidence of polyuria with a stable serum sodium level. He subsequently returned several days later to the emergency department with weakness, myalgia, and nausea. Laboratory testing revealed hyponatremia with a serum sodium level of 118 mEq/L (normal: 135–145 mEq/L). He was admitted to the hospital with the diagnosis of

Table 2: Case 2 laboratory testing.

Laboratory test	Preoperative evaluation	Three weeks postoperative	One year postoperative	Two years postoperative	Normal range
LH	1.6 mIU/mL	***	***	<0.2 mIU/mL	1.24–7.8 mIU/mL
FSH	4.0 mIU/mL	***	***	***	1–18 mIU/mL
Cortisol	3 µg/dL	<1 µg/dL	3 µg/dL	<1 µg/dL	AM cortisol: 4–22 µg/dL (7–9 AM) PM cortisol: 3–17 µg/dL (3–5 PM)
Alpha-subunit	0.37 µg/dL	***	***	***	<1.37 µg/dL (for males 55–64 years old)
fT3	64 ng/dL	***	***	***	80–180 ng/dL
fT4	0.36 ng/dL	1.39 ng/dL	1.37 ng/dL	1.38 ng/dL	0.89–1.76 ng/dL
TSH	5.71 mIU/L	***	***	<0.01 mIU/L	0.34–5.6 mIU/L
Free testosterone	181 ng/dL	<20 ng/dL	***	***	241–827 ng/dL
ACTH	***	<5 pg/mL	<5 pg/mL	2.2 pg/mL	7–69 pg/mL
Prolactin	510 ng/mL	12.8 ng/mL	16.5 ng/mL	16.9 ng/mL	3–13 ng/mL

LH: Luteinizing hormone, FSH: Follicular-stimulating hormone, fT3: Free triiodothyronine, fT4: Free thyroxine, TSH: Thyroid-stimulating hormone, ACTH: Adrenocorticotropic hormone

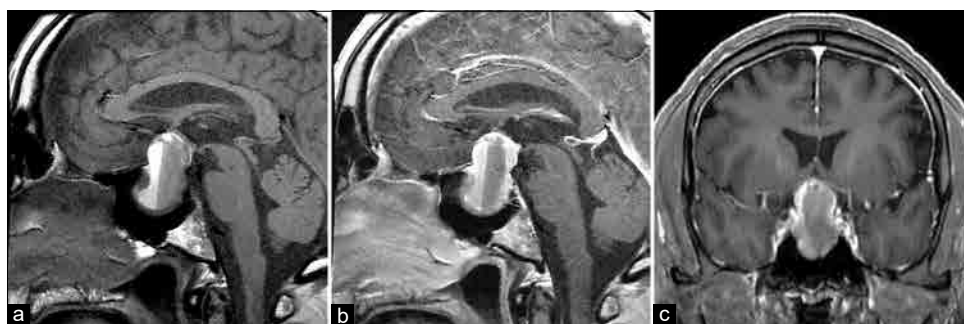


Figure 3: Case 2 pituitary MRI scan: (a) preoperative sagittal noncontrast-enhanced T1-weighted image, (b) preoperative sagittal contrast-enhanced T1-weighted image, (c) preoperative coronal noncontrast-enhanced T2-weighted image pituitary. Note the fluid-fluid level within the sella in each, consistent with subacute hemorrhage.

syndrome of inappropriate antidiuretic hormone secretion. This resolved over several days and he was discharged home on his previous adrenal and thyroid replacement. Over the next 4 weeks, he gradually developed symptoms consistent with DI and was started on DDAVP 5 weeks postoperatively. An MRI obtained at that time, due to the new symptoms, revealed a marked descent of the residual pituitary gland and diaphragma sellae down to the floor of the sella, with severe thinning and apparent discontinuity of the pituitary stalk [Figure 4]. A postoperative ophthalmologic examination revealed improvement in his right visual field deficit, with the left visual field remaining normal. His 1- and 2-year postoperative endocrine evaluations showed that he continues to suffer from panhypopituitarism, with resolution of his DI. He is on no treatment for his prolactinoma with the most recent prolactin level being 16.5, which has remained stable over serial evaluation [Table 2].

DISCUSSION

ESS was first described in 1951 after 788 human cadavers with no history of pituitary disease were examined.^[8] They noted a

finding of an incomplete diaphragma sellae with flattening of the normal pituitary gland at the bottom of the sella turcica in 40 (5.1%) of the 788 cases.^[8] Although the phenomenon is rare and is generally asymptomatic, both primary and secondary causes of ESS are well described. Primary ESS on neuroimaging is found incidentally in approximately 12% of cases, with a 5:1 female-to-male predominance.^[5,8] Symptoms associated with primary ESS include headache, menstrual irregularities, galactorrhea, hirsutism, and sterility. Being overweight and frank obesity are seen in 73% and 14% of patients, respectively.^[10] Endocrine abnormalities can be variable, with growth hormone deficiency and prolactin elevation being common. Secondary ESS is most seen following surgical removal of a pituitary macroadenoma, radiation therapy, or medical treatment of a macroprolactinoma with dopaminergic agonist therapy. The most common complication described in secondary ESS is the onset of gradual visual disturbance secondary to egress of the optic chiasm into the sella.^[6,7] Welch and Stears, in 1971, reported the first surgical treatment of this condition with a transcranial chiasmectomy.^[15] The first chiasmectomy

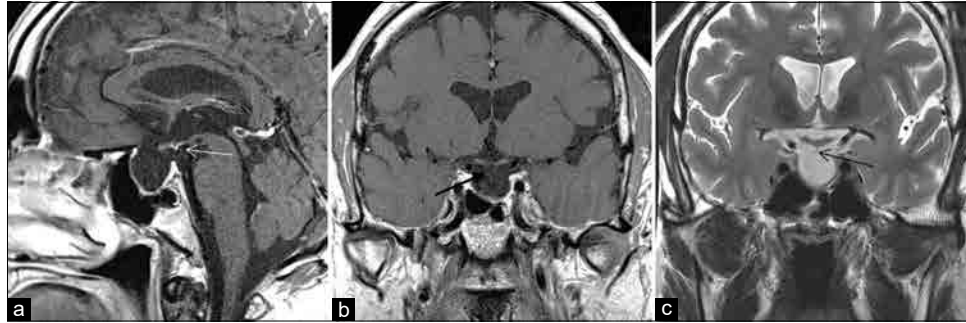


Figure 4: Case 2 postoperative pituitary MRI scan. (a) Contrast-enhanced T1-weighted sagittal image, (b) contrast-enhanced T1-weighted coronal image, (c) coronal noncontrast-enhanced T2-weighted image. Arrows delineate the proximal pituitary stalk, with no distal stalk remnant seen.

performed through the transsphenoidal route was reported by Olson *et al.* in 1972.^[12]

To the best of our knowledge, the phenomenon of rapid postoperative descent of the residual pituitary gland and diaphragma into the sella with MRI evidence of pituitary stalk disruption has not been previously described. Historically, sustained postoperative pituitary endocrine dysfunction has been noted to occur in <2% of patients.^[1,3,4,11] Postoperative DI can occur transiently in about 12% of patients, based on one review, with Black *et al.* noting an incidence of near 1% for microadenomas and up to 9.5% for macroadenomas.^[3] Ciric *et al.* described an overall rate of prolonged DI of 3.4%, with Barker *et al.* noting a range from 8.7% to 12.6% in their series.^[4]

In the two cases described in this report, the rapid descent of the residual pituitary gland into the sella turcica was felt to contribute to severe stretching of the pituitary stalk. This led to an associated increase in pituitary hormone dysfunction with the need for additional adrenal hormone replacement in one patient and the onset of delayed DI in both cases. On review of the patients' preoperative imaging, factors that may have predisposed our two cases to this phenomenon are large tumor volume, a deep sella extending into the inferior sphenoid region and a residual normal pituitary gland centered superiorly along the diaphragma. This, therefore, allowed the descent of the entire residual pituitary gland down to the floor of the sella turcica, bringing the diaphragma and pituitary stalk down with it. A protective variable may be a gland offset to the lateral side of the sella, allowing adherence of the gland laterally and theoretically preventing this degree of descent.

As a result of this experience, we have changed the operative technique at our institution. In our current practice, we do not routinely place fat into the sella turcica during routine macroadenoma resection, unless there is evidence of an intraoperative CSF leak. However, based on these two cases and recognition of the risk factors mentioned above, we now place intrasellar fat after tumor resection to bolster the gland superiorly in those patients felt at risk. Overtime, as the fat

is reabsorbed, this may promote a gentler and more gradual descent of the residual gland, allowing the pituitary stalk to elongate slowly overtime, without disruption.^[9]

Although a rare occurrence, since adopting this practice, we have seen no further instances of this phenomenon of "pituitary ptosis," a syndrome of postoperative ESS with MRI evidence of pituitary stalk disruption, increasing pituitary hormone dysfunction, and delayed-onset DI.

Limitations

This study is limited by its design (retrospective two-patient case series), which hinders our ability to predict the risk or severity of this phenomenon. Similarly, because routine postoperative care at our institution involves routine MRI at 3 months after surgery, we cannot comment on the exact rate of diaphragmatic descent before that time. No other cases of pituitary stalk disruption at 3 months postoperatively have been observed at our institution, but our investigation is thus at risk of bias and results may thus not be generalizable to the greater population.

Future directions

This phenomenon of postsurgical pituitary stalk disruption is important for neurosurgeons and endocrinologists to be aware of, given the potential ability to prevent subsequent postoperative pituitary endocrinopathy, a significant source of quality-of-life morbidity for pituitary adenoma patients. The rarity of symptomatic secondary ESS represents an opportunity to conduct a larger investigation to query the true prevalence of this disorder. It may be that other variables, such as obesity, may independently predict a patient's risk. In addition, serial radiographic and laboratory examinations could better characterize the rate and degree of diaphragma descent and stalk disruption, in correspondence with panhypopituitarism. Finally, our technique of preemptive sellar packing warrants further investigation as it relates to the risk of this phenomenon.

CONCLUSION

We describe two cases of “pituitary ptosis” endocrinopathy at our institution, demonstrated by MRI evidence of pituitary stalk elongation and disruption after TSS. This is a rare syndrome of panhypopituitarism associated with DI, manifesting as progressive endocrine dysfunction in the perioperative period following macroadenoma resection. In patients at risk of this complication, placement of intrasellar fat can potentially prevent rapid descent of the gland into the sella turcica and is a rational preventative measure.

Declaration of patient consent

Patient’s consent not required as patients identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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