CASE REPORT

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Cushing Disease in a Patient with Double Pituitary Adenomas Complicated with Diabetes Insipidus: A Case Report

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Abstract

Managing a patient with both pituitary hypersecretory and hyposecretory manifestations may be perplexing. We report a 14-year-old female who presented with weight gain, polyuria and polydipsia. Biochemical results were consistent with Cushing disease with central diabetes insipidus. Pituitary magnetic resonance imaging showed a right adenoma with stalk thickening. The immunohistochemistry staining of both adenomas was positive for adrenocorticotropic hormone, thyroid stimulating hormone, growth hormone and luteinizing hormone. Postoperatively, the patient developed panhypopituitarism with persistent diabetes insipidus. The coexistence of double adenomas can pose diagnostic and management challenges and is a common cause of surgical failure. Intraoperative evaluation is important in the identification of double or multiple pituitary adenomas in a patient presenting with multiple secretory manifestations.

Key words: double pituitary adenoma, Cushing disease, diabetes insipidus, adrenocorticotropic hormone-secreting pituitary adenoma

INTRODUCTION

Double or multiple pituitary adenomas are rare and are defined as two or more concurrent adenomas in the pituitary gland that differ morphologically or immunocytochemically.[1] The diagnosis of double or pituitary adenomas is based on histopathologic examination (HPE), surgical specimen (0.4-1.3%) and autopsy series (0.9 – 2%) because identification by magnetic resonance imaging (MRI) or during surgery is difficult.[1-4] The tumours are usually microadenomas with an average size of 3 mm, or one is overshadowed by a co-existing but larger pituitary adenoma and is clinically silent.[5]

Presentations can be either non-functioning or functioning and rarely present with more than one hypersecretory syndrome due to pluri-hormonal adenomas (production of two or more hormones). We report a case of clearly separated adenomas presenting with Cushing syndrome (CS) with diabetes insipidus (DI). To the best of our knowledge, this is the youngest case in the recent literature of Cushing disease due to double pituitary adenomas (DPA), located within the anterior pituitary and infundibulum.

CASE

A 14-year-old female presented with a 10-month history of weight gain of 15 kg associated with hirsutism, polyuria, polydipsia and secondary amenorrhea of 9 months duration. Menarche occurred at twelve years of age. Signs of Cushing syndrome were present such as moon-like facies with mild plethora, truncal obesity, thin skin with easy bruising, purplish abdominal striae, proximal myopathy and hyperpigmentation over the creases. Her blood pressure was 158/89 mmHg and her pulse rate was 96 beats per minute. Height was 153 cm, weight was 78.8 kg with body mass index of 33.6 kg/m^2 and waist circumference of 104 cm. Breast development and pubic hair distribution corresponded to Tanner stage 2. All other systems were unremarkable.

Her 24-hour urinary free cortisol was 512 nmol/24h (normal range: 57.7 – 806.6) and serum cortisol post low dose dexamethasone suppression test was 149 nmol/L. The diagnosis of adrenocorticotropic hormone (ACTH)-dependent CS was confirmed with ACTH level of 45.82 pg/ml (normal range: 7.2 – 63). The rest of the hormonal work-up is shown in Table 1. We suspected that the patient may have DI as shown by serum sodium of 151 mmol/L, serum osmolarity of 314 mOsm/kg, urine osmolarity of

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Table 1. Baseline (pre-operative) hormonal levels

Parameters	Results	Normal range
24 hours urinary free cortisol	512.2 (3.6 L of urine)	57.7-806.8 nmol/d
Overnight 1 mg dexamethasone suppression test	149	<50 nmol/L
ACTH	45.82	7.2-63 pg/ml
DHEAS	7.97	0.01-7.6 umol/L
Plasma Renin Activity	7.364	0.3-1.9 mg/ml/hr
Serum aldosterone	441.5	41.71-208.9 pg/ml (supine)
FSH	<0.3 IU/L	
LH	<0.1 IU/L	
Estradiol	133 pmol/L	
Testosterone	1.17	0.101-1.67 nmol/L
Cortisol	730	101-535.7 nmol/L
Prolactin	<0.3	1.4-24.2 ug/L
FT4	15.57	9-19.05 pmol/L
TSH	1.46	0.35-4.94 uIU/ml

ACTH: Adrenocorticotropic hormone; DHEAS: dehydroepiandrosterone sulfate; FSH: follicle-stimulating hormone; LH: luteinizing hormone; FT4: Free T4; TSH: thyroid stimulating hormone

83 mOsm/kg and urine sodium of 21 mmol/L. However, since there was no radiological evidence to suggest any stalk abnormalities, our team decided to proceed with both phase 1 and phase 2 of the water deprivation test. While preparing for the water deprivation test, the patient was advised to drink fluids whenever she felt thirsty, resulting in the normalization of the serum sodium on the day of the water deprivation test. The results of the water deprivation test were consistent with DI (Table 2). Pituitary MRI revealed a small focal area with delayed enhancement on dynamic sequence in the right pituitary gland measuring 3.0 x 2.0 mm (Figure. 1). On the mid-sagittal plane of the T1 post-contrast study, focal thickening of the pituitary stalk (3.9 mm) was suspicious of either an inflammatory cause or another mass lesion (Figure 2). The bilateral inferior petrosal sinus sampling with desmopressin stimulation demonstrated a right central to peripheral ACTH ratio of 7.42.

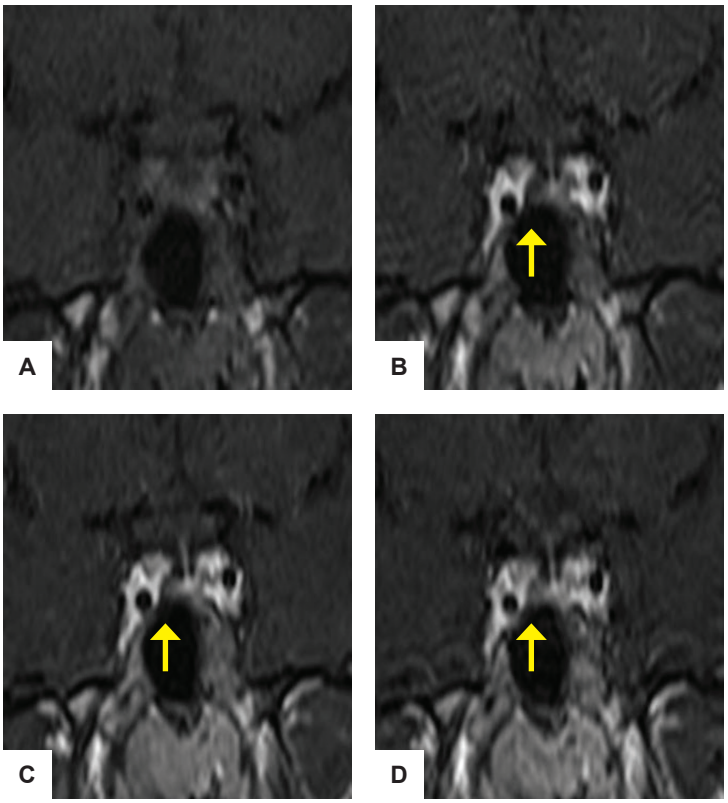

Figure 1. Pituitary MRI. High-resolution pre-contrast **(A)** and selected dynamic contrast enhance T1 **(B)**, **(C)**, and **(D)** at 39 seconds, 64 seconds and 89 seconds post-gadolinium respectively. The pituitary gland does not show any distinct lesion on the pre-contrast image. In the dynamic post-contrast sequence, a distinct area of delayed enhancement at the right side of the pituitary gland represents the microadenoma *(yellow arrow)*. A subtle displacement of the pituitary stalk to the left and mild inferior bulging of the sellar floor on the right side indicates the presence of a mass in the right pituitary gland.

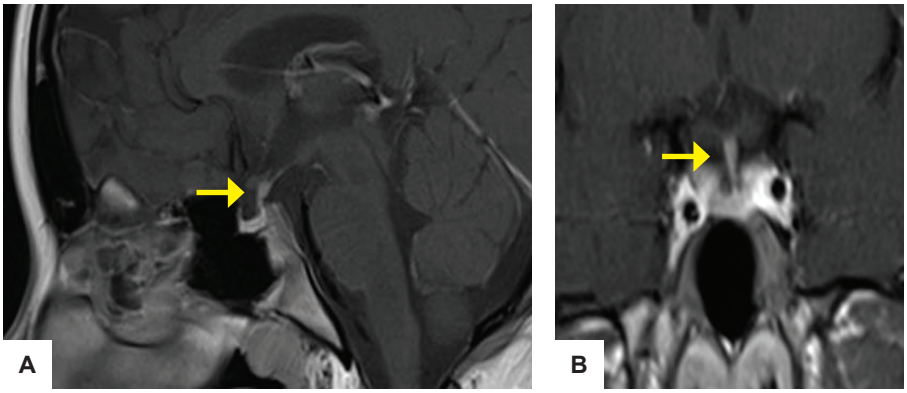

Figure 2. Pituitary MRI. T1 post-contrast in axial **(A)** and mid-sagittal **(B)** demonstrate homogeneous enhancement of the pituitary gland. On the mid-sagittal plane, at the optic chiasm level, a subtle enhancing pituitary stalk lesion, with focal thickening *(yellow arrow)* results in the loss of a normal tapering pituitary stalk.

Table 2. Water deprivation test results

Phase 1	10am	12pm	2pm
Weight (kg)	79.8	78.6	77.9
Serum Na (mmol/L)	138	138	144
Serum Osmol (mOsm/kg)	285	286	291
Urine Osmol (mOsm/kg)	60	60	74
Urine volume (ml)	200	250	300
*Subcutaneous desmopressin 2 ug administered at 4pm			
Phase 2	**4pm**	**6pm**	**8pm**
Weight (kg)	77.5	77.4	78.3
Serum Na (mmol/L)	141	138	137
Serum Osmol (mOsm/kg)	293	292	289
Urine Osmol (mOsm/kg)	76	100	221
Urine volume (ml)	310	200	150

She underwent transsphenoidal surgery (TSS) and intraoperatively, was noted to have two separate lesions containing cheesy material at the posterior aspect of the right pituitary lobe and the infundibulum. The right hypophysectomy resection extending to the midline with the infundibular mass removal was uneventful. Results of the HPE of both specimens were consistent with pituitary adenoma and both immunohistochemistry (IHC) stains were positive for ACTH, growth hormone (GH), *luteinizing hormone* (LH) and thyroid stimulating hormone (TSH), and weakly positive for prolactin (PRL) and *follicle-stimulating hormone* (FSH) (Figures 3 and 4). On the second postoperative day, her ACTH, cortisol and Free T4 levels

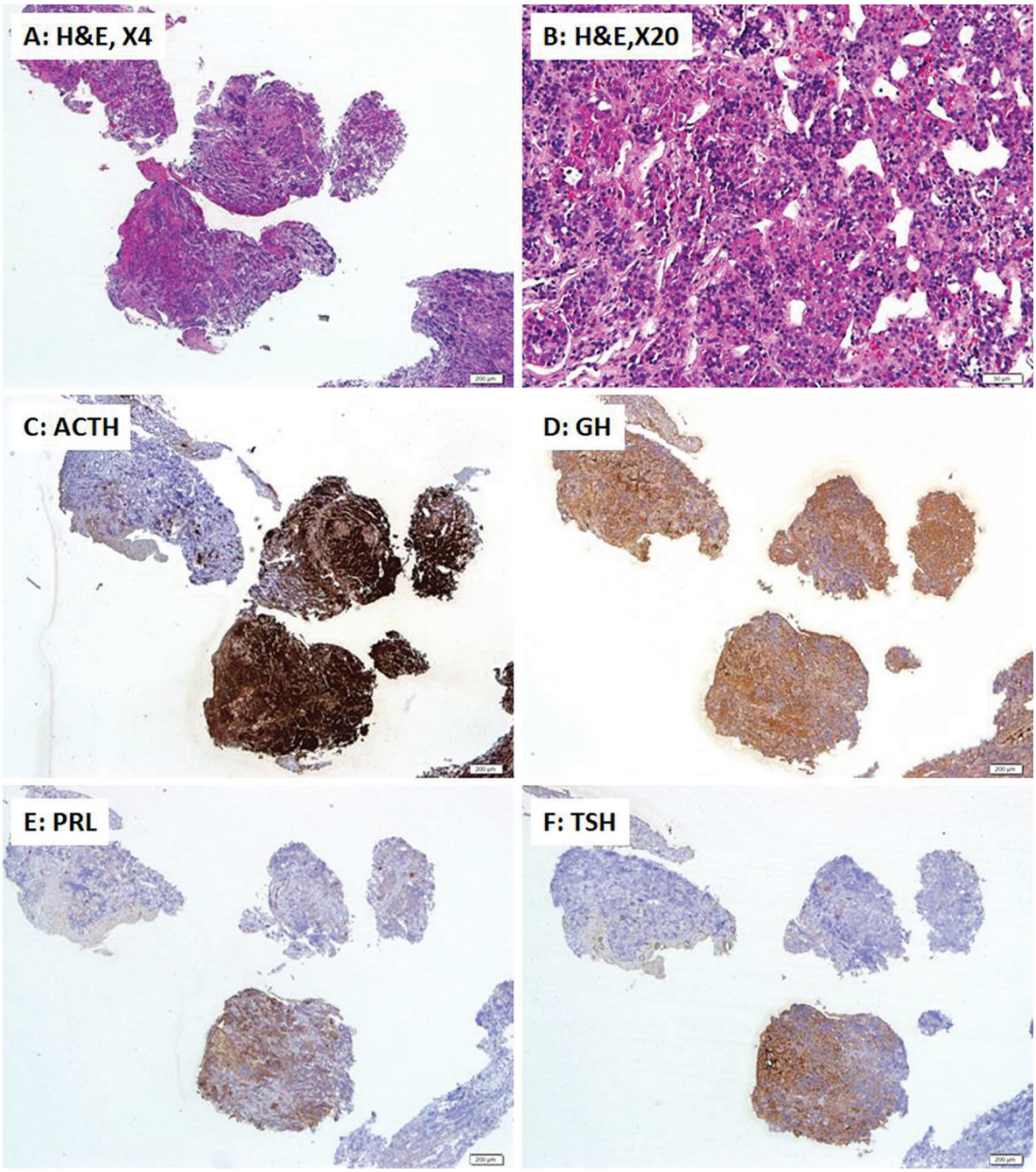

Figure 3. Pluri-hormonal pituitary adenoma located at the right lobe of pituitary. **(A)** (H&E, X4), **(B)** (H&E, X20) producing ACTH **(C)**, GH **(D)**, Prolactin **(E)** and TSH **(F)**.

were 4.2 pg/ml, <20 nmol/L and 7.36 pmol/L, respectively. Hence, anterior pituitary hormone replacement was initiated with oral hydrocortisone 10 mg and 5 mg at 8 am and 12 pm respectively, as well as oral levothyroxine 75 mcg daily. Her sublingual desmopressin was continued at 60 mcg *nocte* as her DI was persistent after TSS.

Six months after transsphenoidal surgery, the patient has shown clinical improvement with amelioration of her Cushingoid features and resumption of her menses by the 3rd month postoperatively. She has also managed to reduce her weight to 71.1 kg with exercise and diet modification.

DISCUSSION

Our case proved to be interesting as she presented features of CS and central DI which could not be attributed to any detectable stalk lesion on MRI. Most DPA were GH- or PRL-secreting or non-functioning adenomas.[1,6-8] Ogando-Rivas E *et al.* demonstrated a higher frequency of GH-secreting adenomas compared with ACTH-secreting adenomas in 17 cases of double or multiple pituitary adenomas identified preoperatively by MRI and confirmed by histology and immunohistochemistry. The age of the patients ranged from 22 to 67 years, and most were female.[9] Other studies also reported a higher frequency in patients with acromegaly, followed by those presenting with Cushing disease.[1,2]

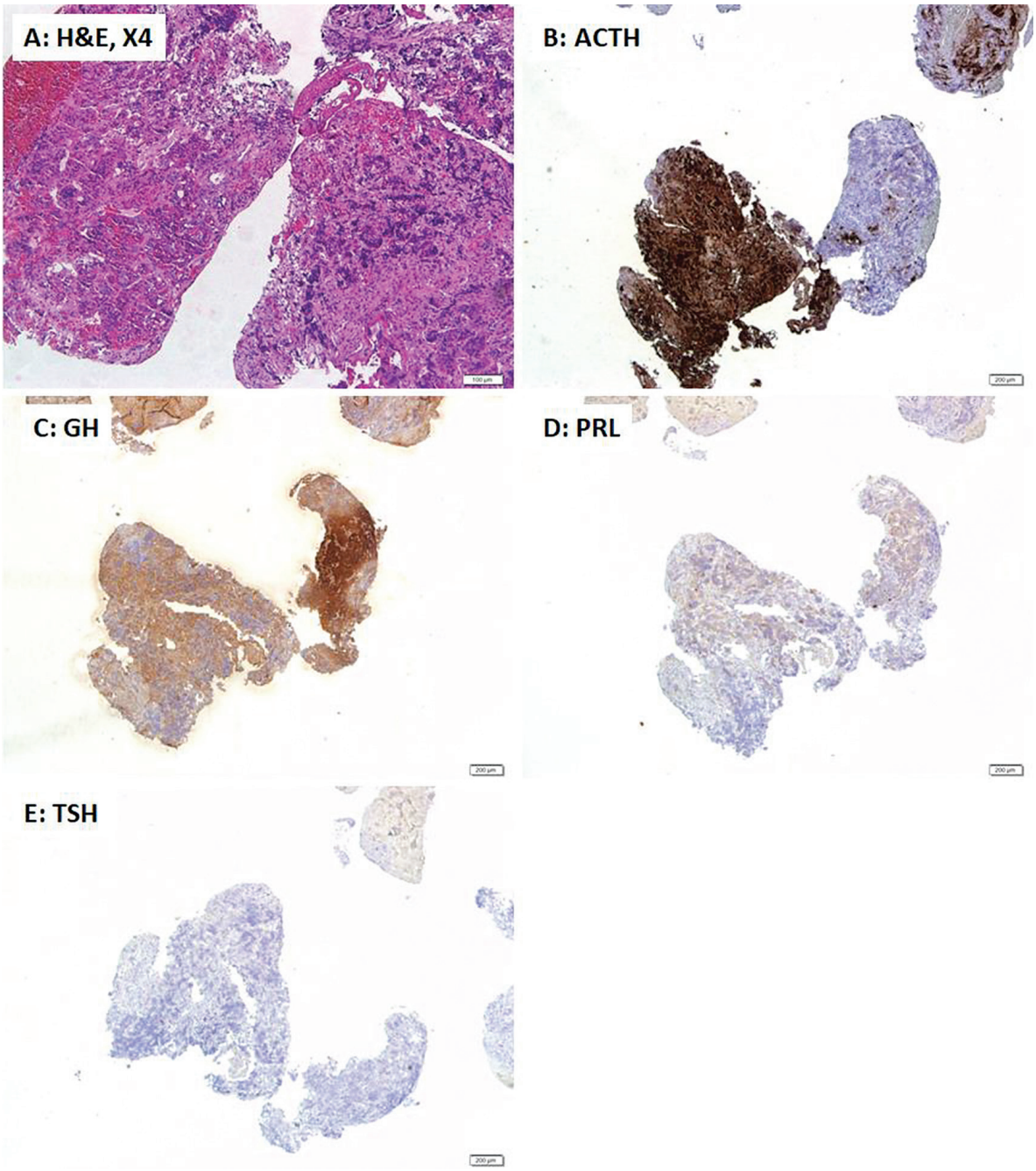

Figure 4. Pluri-hormonal pituitary adenoma located at the midline of pituitary **(A)** (H&E, X4), producing ACTH **(B)**, GH **(C)**, and focally Prolactin **(D)** and TSH **(E)**.

Table 3. Summary of double ACTH pituitary adenomas cases compared to our case

	Year	Age	Gender	Sites of lesion	Immunohistochemistry I & II	Clinical symptoms/ presentation
Case 1 [17]	2010	56	F	Right and left pituitary	ACTH strong & ACTH weak	Cushing disease
Case 2 [18]	2014	38	F	Infundibulum and anterior pituitary	ACTH strong & ACTH strong	Cushing disease
Case 3 [19]	2016	50	F	Right and left pituitary	ACTH strong & ACTH strong	Cushing disease
Case 4 [20]	2017	37	F	Left pituitary lobe	ACTH strong & ACTH strong	Cushing disease
Case 5 [21]	2021	36	F	Right anterior pituitary	ACTH strong & ACTH strong	Cushing disease
Our case	2019	14	F	Right lobe and infundibulum	ACTH strong & ACTH strong	Cushing disease & diabetes insipidus

The incidence of ACTH-secreting tumours with double or multiple pituitary adenomas ranged between 1.6–3.3%.[10-12] In the previous report, 60 cases of multiple pituitary adenomas were observed, of which 58 cases were double adenomas and were grouped according to immunohistochemical criteria. Among all combinations, ACTH- and PRL-secreting tumours seemed to be the most common (33%), followed by GH- and nonfunctional adenomas (24%) and GH-PRL adenomas (10%).[13] Double pituitary adenomas with ACTH hypersecretion have been reported with FSH-secreting lesions, GH-secreting and, most commonly, prolactin-secreting adenomas or silent PRL-immunoreactive adenomas.[1,6,10,14-16] There had been 5 reported cases of double ACTH-secreting pituitary tumours presenting with CS in female patients with an age range of 36-56 years old summarized in Table 3.[17-21] Our case is the youngest and the only patient who manifested Cushing disease with DI. She had two different lesions in the pituitary with strong positive staining for ACTH, GH, LH and TSH, and weakly positive for prolactin and FSH.

It has been reported that the ACTH-secreting adenomas may originate in or extend into the pituitary stalk. Previous literature also observed DPA in both the anterior pituitary gland and stalk. Hence, multiple adenomas should be identified before the operation to achieve curative surgical management.[22] The critical first step in managing double adenomas is their identification, which is based on MRI.[5,12,23] Preoperative MRI is an effective and sensitive method to determine the presence of multiple adenomas.[5,13,24] Pu et al., in their review of 42 patients with CS found that 22 (52.4%) were diagnosed from preoperative MRI, 2 (4.8%) from computerized tomography (CT) scan and the remaining 18 patients were diagnosed during surgery.[21] Previous literature reported MRI to be superior in detecting multiple pituitary adenomas; however, in our patient, the second adenoma could be missed radiologically due to its small size. Hence, intraoperative evaluation via surgical exploration may assist in diagnosing double or multiple pituitary adenomas.[1,9,15,19] Endoscopic TSS is used more often than the microscopic approach, particularly in cases of pituitary lesions.[24] Other literature reviews revealed similar findings with the majority of them being visible to the surgeon by the endoscopic approach.[1,9,15,19]

In our case, the patient underwent neuro-endoscopic TSS, which allowed for better visualization and enabled the detection of another microadenoma which prevented the requirement for a second surgery. Previous cases reported that patients had to undergo two surgeries to resect two pituitary adenomas. Following the first surgery, the disease manifestation and hormone levels revealed that the tumours were not in remission, indicating another microadenoma.[3,12,14] Therefore, distinguishing between a normal pituitary gland and a pituitary adenoma is crucial in surgery.

The only way to ensure that both adenomas are removed surgically is to look at the biochemical and HPE findings. If a single tumour is removed and repeated hormonal work-up shows no evidence of biochemical remission, reexamination is usually required in the early postoperative period. Unfortunately, poor surgical outcomes in patients with DPA have been reported.[7,25] Even if 100% biochemical cure can be achieved, patients are usually left with pituitary insufficiency as demonstrated in our patient who required hormone replacement.[26,27] In the presence of high-resolution MRI scanning and inferior petrosal sinus sampling, a hemi-hypophysectomy can be performed if the patient does not achieve biochemical remission after the surgery to preserve as much glandular tissue as possible. If the lesion is not visible on the pituitary gland surface, then the surgeon can make exploratory incisions into the gland to search for the primary or second tumour to avoid missing the causal adenoma.

CONCLUSION

This is the youngest patient with double ACTH-secreting pituitary adenoma and diabetes insipidus. The coexistence of double adenomas can be challenging to diagnose with poor surgical outcomes. Intraoperative evaluation is important in the identification of double or multiple pituitary adenomas in a patient presenting with multiple secretory manifestations. Post-operative biochemical cure can be achieved but usually ends up with pituitary insufficiency.

Ethical Considerations

The patient's mother has given her consent for the publication of this article.

Statement of Authorship

The authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement

WHK: Conception, Curation, Investigation, Writing – original draft preparation; **IIA:** Conception, Curation, Investigation, Writing – original draft preparation; **NAW:** Writing – review and editing.

Author Disclosure
The authors declared no conflict of interest.

Data Availability Statement
No datasets were generated or analyzed for this study.

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References
1. Kontogeorgos G, Scheithauer BW, Horvath E, et al. Double adenomas of the pituitary: a clinicopathological study of 11 tumors. Neurosurgery. 1992;31(5):840-9. PMID: 1331847. DOI: 10.1227/00006123-199211000-00003.
2. Sano T, Horiguchi H, Xu B, et al. Double pituitary adenomas: six surgical cases. Pituitary. 1999;1(3-4):243-50. PMID: 11081204 DOI: 10.1023/a:1009994123582
3. Kontogeorgos G, Kovacs K, Horvath E, Scheithauer BW. Multiple adenomas of the human pituitary. A retrospective autopsy study with clinical implications. J Neurosurg. 1991;74(2):243-7. PMID: 1988594 DOI: 10.3171/jns.1991.74.2.0243.
4. Tomita T, Gates E. Pituitary adenomas and granular cell tumors. Incidence, cell type, and location of tumor in 100 pituitary glands at autopsy. Am J Clin Pathol. 1999;111(6):817-25. PMID: 10361519 DOI: 10.1093/ajcp/111.6.817.
5. Budan RM, Georgescu CE. Multiple pituitary adenomas: a systematic review. Front Endocrinol (Lausanne). 2016; 7: 1. PMID: 26869991. PMCID: PMC4740733 DOI: 10.3389/fendo.2016.00001.
6. Eytan S, Kim KY, Bleich D, Raghuwanshi M, Eloy JA, Liu JK. Isolated double pituitary adenomas: A silent corticotroph adenoma and a microprolactinoma. J Clin Neurosci. 2015;22(10):1676-8. PMID: 26067545 DOI: 10.1016/j.jocn.2015.03.040.
7. Kim K, Yamada S, Usui M, Sano T. Preoperative identification of clearly separated double pituitary adenomas. Clin Endocrinol (Oxf). 2004;61(1):26-30. PMID: 15212641 DOI: 10.1111/j.1365-2265.2004.02055.x.
8. Syro LV, Horvath E, Kovacs K. Double adenoma of the pituitary: a somatotroph adenoma colliding with a gonadotroph adenoma. J Endocrinol Invest. 2000;23(1):37-41. PMID: 10698050. DOI: 10.1007/BF03343674.
9. Ogando-Rivas E, Alalade AF, Boatey J, Schwartz TH. Double pituitary adenomas are most commonly associated with GH- and ACTH-secreting tumors: systematic review of the literature. Pituitary. 2017; 20(6):702-8. PMID: 28766078 DOI: 10.1007/s11102-017-0826-6.
10. Ratliff JK, Oldfield EH. Multiple pituitary adenomas in Cushing's disease. J Neurosurg. 2000;93(5):753-61. PMID: 11059654 DOI: 10.3171/jns.2000.93.5.0753.
11. Kannuki S, Matsumoto K, Sano T, Shintani Y, Bando H, Saito S. Double pituitary adenoma--two case reports. Neurol Med Chir (Tokyo). 1996;36(11):818-21. PMID: 9420436 DOI: 10.2176/nmc.36.818.
12. McKelvie PA, McNeill P. Double pituitary adenomas: a series of three patients. Pathology. 2022;34(1):57-60. PMID: 11902447 DOI: 10.1080/00313020120105651
13. Iacovazzo D, Bianchi A, Lugli F, et al. Double pituitary adenomas. Endocrine. 2013 Apr;43(2):452-7. PMID: 23325364 DOI: 10.1007/s12020-013-9876-3
14. Oyama K, Yamada S, Hukuhara N, et al. FSH-producing macroadenoma associated in a patient with Cushing's disease. Neuro Endocrinol Lett. 2006;27(6):733-6. PMID: 17187002
15. Kontogeorgos G, Thodou E. Double adenomas of the pituitary: an imaging, pathological, and clinical diagnostic challenge. Hormones (Athens). 2019;18(3):251-4. PMID: 31388898 DOI: 10.1007/s42000-019-00126-4
16. Meij BP, Lopes MB, Vance ML, Thorner MO, Laws ER Jr. Double pituitary lesions in three patients with Cushing's disease. Pituitary. 2000;3(3):159-68. PMID: 11383480 DOI: 10.1023/a:1011499609096
17. Andrioli M, Pecori Giraldi F, Losa M, Terreni M, Invitti C, Cavagnini F. Cushing's disease due to double pituitary ACTH-secreting adenomas: the first case report. Endocr J. 2010;57(9):833-7. PMID: 20595779 DOI: 10.1507/endocrj.k10e-140
18. Mendola M, Dolci A, Piscopello L, et al. Rare case of Cushing's disease due to double ACTH-producing adenomas, one located in the pituitary gland and one into the stalk. Hormones (Athens). 2014;13(4): 574-8. PMID: 25402386 DOI: 10.14310/horm.2002.1503
19. Pu J, Wang Z, Zhou H, et al. Isolated double adrenocorticotropic hormone-secreting pituitary adenomas: a case report and review of the literature. Oncol Lett. 2016;12(1):585-90. PMID: 27347184 PMCID: PMC4907318 DOI: 10.3892/ol.2016.4673
20. Reddy Pa, Harisha P, Reddy Vu, Agrawal A. Adrenocorticotropic hormone secreting monohormonal double pituitary microadenomas causing Cushing's disease. J Mahatma Gandhi Inst Med Sci. 2017;22:113-5.
21. Mathai C, Anolik J. Cushing's Disease as a result of two ACTH-secreting pituitary tumors. AACE Clin Case Rep. 2020;7(2):149-52. PMID: 34095475 PMCID: PMC8053624 DOI: 10.1016/j.aace.2020.12.002
22. Mason RB, Nieman LK, Doppman JL, Oldfield EH. Selective excision of adenomas originating in or extending into the pituitary stalk with preservation of pituitary function. J Neurosurg. 1997;87(3):343-51. PMID: 9285597 DOI: 10.3171/jns.1997.87.3.0343
23. Bader LJ, Carter KD, Latchaw RE, Ellis WG, Wexler JA, Watson JC. Simultaneous symptomatic Rathke's cleft cyst and GH secreting pituitary adenoma: a case report. Pituitary. 2004;7(1):39-44. PMID: 15638297 DOI: 10.1023/b:pitu.0000044632.15978.44
24. Yadav Y, Sachdev S, Parihar V, Namdev H, Bhatele P. Endoscopic endonasal trans-sphenoid surgery of pituitary adenoma. J Neurosci Rural Pract. 2012;3(3):328-37. PMID: 23188987 PMCID: PMC3505326 DOI: 10.4103/0976-3147.102615
25. Cannavò S, Curtò L, Lania A, Saccomanno K, Salpietro FM, Trimarchi F. Unusual MRI finding of multiple adenomas in the pituitary gland: a case report and review of the literature. Magn Reson Imaging. 1999;17(4):633-6. PMID: 10231191 DOI: 10.1016/s0730-725x(98)00214-8
26. Pantelia E, Kontogeorgos G, Piaditis G, Rologis D. Triple pituitary adenoma in Cushing's disease: case report. Acta Neurochir (Wien). 1998;140(2):190-3. PMID: 10399001 DOI: 10.1007/s007010050083
27. Woosley RE. Multiple secreting microadenomas as a possible cause of selective transsphenoidal adenomectomy failure. Case report. J Neurosurg. 1983;58(2):267-9. PMID: 6848686 DOI: 10.3171/jns.1983.58.2.0267