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Case Report

Atypical Manifestation of Pituitary Crooke's Cell Tumor: A Case Report and Literature Review

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ABSTRACT

Background: Crooke's cell adenoma (CCA) is an unusual and aggressive subtype of corticotroph pituitary adenoma. It accounts for 0.03% of all pituitary adenomas.

Case Presentation: A 29-year-old female patient, with background history of hypertension and hypothyroidism, presented with 14 days history of generalized fatigue and left sided abdominal pain that were recently worsened with headache. The physical examination was unremarkable. Laboratory investigations showed elevated Adrenocorticotropic hormone (ACTH) levels. Despite normal head CT, MRI pituitary showed pituitary macroadenoma. Then, endoscopic trans nasal surgical resection of ACTH-producing pituitary macroadenoma was performed. Diagnosis of Crooke's cell adenoma was confirmed with histopathology studies. The postoperative course was uneventful.

Discussion: Crooke's cell adenomas are an uncommon form of pituitary tumor. They either produce adrenocorticotropic hormone, which causes Cushing's disease, or they remain unfunctional. These lesions are typically invasive, demonstrating tumors aggressive behavior, and can recur with a low cure rate following reoperation and/or radiotherapy. Rarity of CCA makes determining clinical prognosis and treatment challenging. The novelty of the current case lies in young age of presentation, shirt symptomatic duration, and initially unremarkable CT findings despite biochemical hypercortisolism and elevated ACTH levels.

Conclusion: Due to the rare entity of Crooke's cell adenoma, we report a 29-year-old female, with Cushing disease, who presented with generalized fatigue and left sided abdominal pain, found to be Crooke's cell adenoma. This case highlight the importance of maintaining a high index of suspension for functioning pituitary adenoma in patient with non-specific symptoms and normal initial imaging.

Introduction

Crooke's cell adenoma (CCA) is a rare and aggressive subtype of corticotroph pituitary adenoma, accounting for 0.03% of all pituitary adenomas [1]. It was first described by Arthur Crooke in 1935, as a tumor that is identified histologically by extensive Crooke's hyaline change [2, 3]. According to the WHO classification, more than 50% of the tumor cells must have this histologic alteration for the diagnosis of CCA [2]. These tumors tend to be large, invasive macroadenomas (77.2%) and are often accompanied by features of hypercortisolism, as in case of overt Cushing's disease [2]. However, silent variants have been reported, posing a diagnostic challenge [3]. They commonly present in middle aged women (Mean age 42.4) [2, 4].

The malignant potential of Crooke's cell tumors is controversial, but corticotroph pituitary carcinomas have been reported in patients with histologically proven CCA. Holthouse *et al.* (2001) reported such a change in the setting of recurrent Cushing's disease and metastasis, emphasizing the necessity of long-term follow-up even after apparent

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surgical cure [5]. Herein, we highlight an unusual case of Crooke's cell adenoma, with emphasis on clinical, radiological and histopathological aspects, highlighting the importance of recognizing this aggressive adenoma subtype for appropriate diagnosis, timely treatment and the need for long-term follow-up.

Case Presentation

A 29-year-old female patient, with a background history of hypertension and hypothyroidism, presented to the emergency department with 14-day-history of generalized fatigue and left sided abdominal pain, presenting a unique clinical manifestation. There was no nausea, vomiting, or urinary symptoms. A 6-months-history of easy fatigability with minimal exertion also was reported. The physical examination on admission was unremarkable. The patient's complaint resulted in multiple presentations for the emergency room, during which chest and abdominal X-rays were done. Further investigations revealed hypokalemia, and the status of hypertension and hypothyroidism were secondary to Cushing syndrome, high Adrenocorticotropic hormone (ACTH) levels.

Head CT showed no brain abnormalities.

MRI pituitary performed, with the following findings, showing left-sided focal lesion of pituitary gland that is highly suggestive of pituitary adenoma (Figure 1):

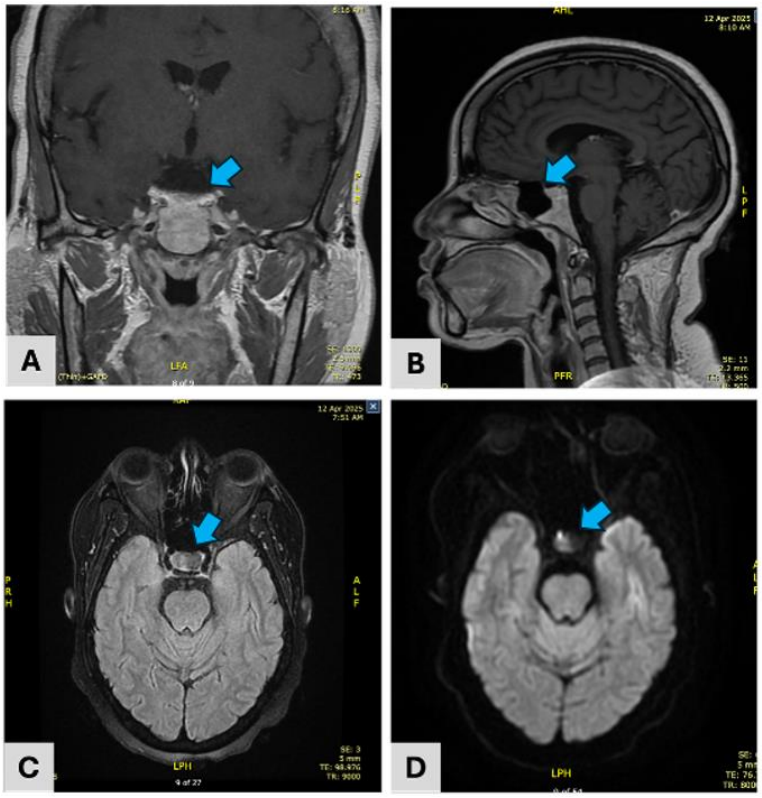

Figure 1: Preoperative MRI brain showing focal pituitary lesion. **A)** MRI T1 coronal view (FSE) + GAFD. **B)** MRI T1 sagittal view. **C)** MRI axial T2 FLAIR. DWI. Blue arrow pointing to the pathology.

- Well defined T2 hypointense hypoenhancing lesion relative to the background pituitary gland is seen on the left side of the pituitary measuring 1 × 0.6 × 0.9 cm indenting the left ICA and causing asymmetrical bulge of the gland contour with deviation of the infundibulum to the right likely suggesting adenoma.
- Non-specific bilateral periventricular/subcortical white matter tiny sub-centimetric focal T2/FLAIR hyperintensities are seen with no evidence of post contrast enhancement or diffusion restriction.
- Both cavernous sinuses are normal.
- The visualized parts of ventricular system are normal.

Table 1: Laboratory investigations on admission.

Test name	Result value	Reference range	Test name	Result value	Reference range
Calc osmolality	287	275-300 mosmo/kg	**Anion gap**	12 mmol/L	
Sodium	142	136-146 mmol/L	**Calcium**	2.4	2.2-2.65 mmol/L
Potassium	2.1	3.5-5.1 mmol/L	**Magnesium**	0.89	0.77-1.03 mmol/L
Chloride	97	98-107 mmol/L	**Phosphorous**	0.80	0.81-1.45 mmol/L
Bicarbonate	35	21-31 mmol/L	**RFT**	Normal	
WBC	9.3	3.9-11.1 × 10^9	**LFT**	Normal	

TSH	0.30	0.38-5.33 ulu/mL	**ACTH**	141	5-46 pg/ml
Free T4	11.0	7.9-16 pmol/L	**Urine R/M**	Normal	
FSH	9.70	IU/L	**Iron profile**	Normal	
LH	3.76	IU/L	**Cortisol**	249	
Estradiol	71	Pmol/L			
Prolactin	148	71-568 mIU/L			

Table 2: Postoperative laboratory investigations.

Test name	Result value	Reference range	Test name	Result value	Reference range
PCT	0.06	Ng/mL	**Phosphorus**	0.69	0.81-1.45 mmol/L
CRP	3	0-8 mg/L	**U. osmolality**	288	300-1300 mosmo/kg
Calc osmolality	322	275-300 mosmo/kg	**Urine Na**	180	20-110 mmol/L
Sodium	164	136-146 mmol/L	**WBC**	10.3	3.9-11.1 × 10^9
Potassium	3.2 L	3.5- 5.1 mmol/L	**RFT**	Normal	
Chloride	115	98-107 mmol/L	**LFT**	Normal	
Bicarbonate	30	21-31 mmol/L	**ACTH**	Less than 5	5-46.0 pg/mL
Anion gap	22	Mmol/L			
Calcium	2.2	2.2-2.65 mmol/L			
Magnesium	0.86	0.77-1.03 mmol/L			

The patient was evaluated by endocrinologist with impression of Cushing's disease with pituitary macroadenoma, measuring 1.1 cm. Endoscopic trans-nasal surgical resection of ACTH-producing pituitary macroadenoma was performed and pituitary tumor, measuring 1.2 × 0.5 × 0.3 cm, was resected. Histopathologically, the tumor grows as sheets and rosettes, with plasmacytoid-like appearance (Figure 2). The tumor cells show chromophobe cytoplasm. Mitosis is present as 1/10hpf, and Ki67 proliferation index is elevated to 7%. The tumor cells express Tpit transcription factor, along with ACTH -juxtanuclear, however, negative for other transcription factors, as Pit1 and SF1, and to other pituitary hormones, as GH, PRL, TSH, LH and FSH. CAM5.2 is expressed strongly as concentric perinuclear positivity. The findings are of Crooke's cell adenoma.

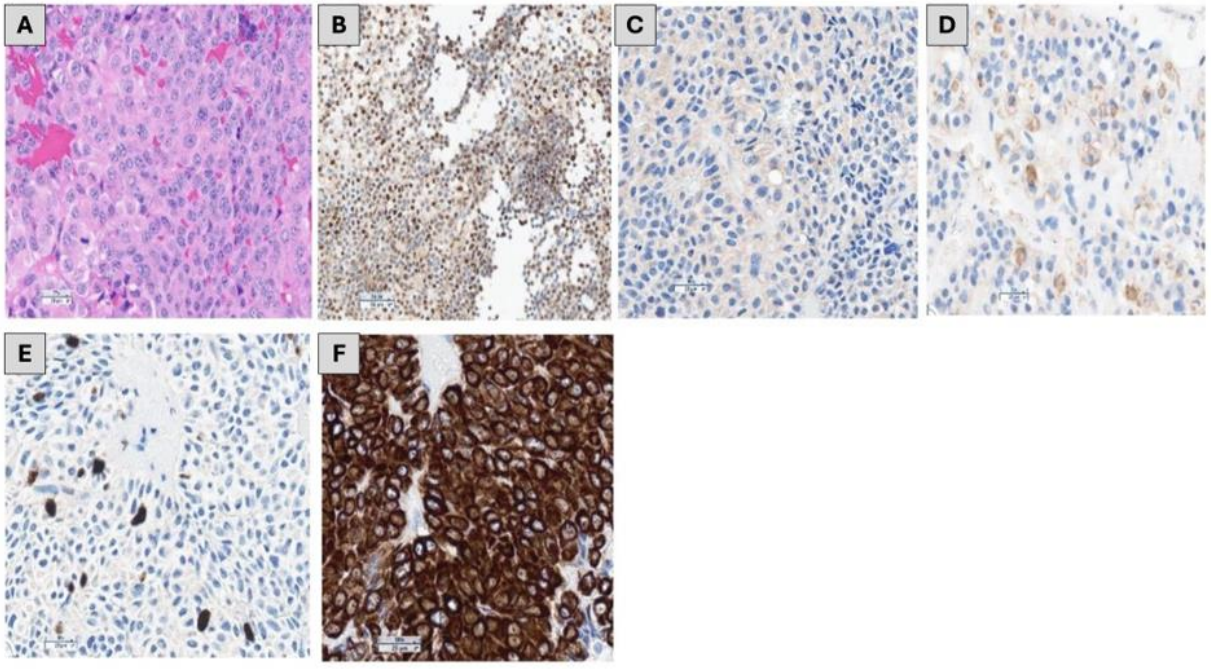

Figure 2: A) H&E stained slides show tumor growing as sheets. The tumor cells has a chromophobe cytoplasmic appearance. **B)** The tumor is diffusely positive for Tpit transcription factor. **C & D)** The tumor expresses ACTH in variable in strength and location, juxtanuclear or diffuse. **E)** Ki67 proliferation index is elevated reaching around 7%. **F)** CAM5..2 is expressed as ring-like concentric cytoplasmic positivity.

The postoperative course was uneventful and the patient discharged on postoperative day 6. The patient is following both neurosurgery and endocrinology outpatient clinics regularly.

Discussion

Historically, Dr. Arthur Crooke reported, in 1935, patients with Cushing's syndrome had homogeneous hyaline material replace the cytoplasmic granules of the anterior pituitary's basophilic cells. This documented phenomenon is referred to as Crooke's changes [3, 6]. The Crooke's hyaline alteration only occurs in the human pituitary gland when elevated cortisol levels are present [3]. These morphological alterations seen in Cortocotroph cells due to the prolonged exposure to glucocorticoids, characterized by the deposition of perinuclear cytokeratin filaments producing a hyalinized appearance of the cytoplasm on hematoxylin and eosin staining [2, 7].

According to WHO new classification, pituitary adenomas are classified as densely granulated, sparsely granulated, or Crooke's cell adenomas. Crooke's cell adenoma is a unique type of ACTH immunoreactive adenoma during which the cells develop Crooke's hyaline transformation [2, 7]. This transformation is triggered by hypercortisolism. Studies reported that the Crooke's hyaline deposition consisted of intermediate filament keratin, as revealed by immunohistochemistry with unclear exact mechanism [7]. Keratin filaments that deposit in Crooke's-like ACTH cells include CK8, CK18 and CK20, according to researchers [7].

CCAs are typically invasive macroadenomas that trigger clinical features of Cushing disease or nonfunctional pituitary macroadenomas, with variable localizing features [2, 6]. These include headache, visual impairment, and ophthalmic manifestation [2, 4]. Also, focal mass effects were reported [1, 6]. In the current case, the main presenting complaint was recurrent attacks of abdominal pain that recently worsened and were associated with headache.

George *et al.* reported a case series of ACTH-producing pituitary tumors, identifying its aggression and recurrence probabilities [1, 8]. In the study, tumor aggressiveness indicators such MIB-1, topoisomerase-2 alpha, and p53 were expressed inconsistently throughout the tumor, indicating that these markers might not always reflect the innately aggressive character of CCAs [8, 9]. Further studies documented the malignant transformation of Crooke's cell tumors [4, 10]. The definitive diagnosis of Crooke's cell adenoma (CCA) can be established only by histopathological results, despite certain clinical and radiological findings that support the diagnosis [2, 6]. In the presented case, CCA diagnosis was achieved through histopathology.

Radiologically, image typical findings include suprasellar or parasellar cistern extension, as well as invasion to the cavernous sinus, sphenoid sinus and posterior fossa, leading to visual disturbances, headaches and cranial nerve palsies [2, 11]. These tumors have also been associated with a high rate of recurrence and resistance to therapy: nearly 39% of patients require additional treatment within the first year post-operatively, 60% recur after the first year, and 24% have multiple recurrences [11].

Although CCAs may appear similar to other corticotroph macroadenomas on radiological studies, their aggressive nature and high recurrence rate following complete surgical resection should prompt histopathological and immunohistochemical examination. These tumors usually demonstrate intense expression of ACTH, cytokeratin (CK8/18), and T-PIT, a corticotroph lineage-specific transcription factor [4, 7, 12]. CCAs also show a high proliferation index, as reflected by Ki-67 expression, which indicates tendency for aggressive behavior and progression into carcinoma [2].

Crooke's tumor cell adenoma can be managed by surgical excision, followed by pharmacological agents and/or radiotherapy. Pharmacologically, alkylating agents, as Temozolomide, are the used in central nervous system malignancies treatment [4, 10]. Endoscopic endonasal transsphenoidal excision of pituitary adenoma was performed to our patient.

Conclusion

The current case reported the diagnostic value of dedicated pituitary MRI when biochemical markers suggest Cushing's disease, even if CT imaging is normal. Moreover, given the aggressive nature and higher recurrence rates associated with Crooke's cell adenoma, early identification has significant implications for surgical planning, postoperative surveillance, and long-term endocrine follow-up. Awareness of this rare pathological variant is essential for neurosurgeons and endocrinologists to optimize management strategies and anticipate potential recurrence.

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Ethical Approval

Ethical approval is exempt/waived at our institution.

Consent

Written informed consent obtained from the patient for publishing their medical history and a copy is available for review upon the request.

Research Registration

Not applicable.

Author Contributions

Athary Saleem: Literature review, manuscript drafting, paper writing and editing, image editing, and assisted in the endoscopic endonasal resection of pituitary lesion. Mariam Alsheikh: Paper editing. Abdullah Alsayedomar: Paper writing and editing. Mohamad Alkaak: Paper writing and editing. Maryam Almurshed: Histopathology slides preparation, paper writing and editing. Mohammed Ghorbani: Perform endoscopic endonasal pituitary lesion resection. Tarik Alsheikh: Paper editing, supervision, and final approval.

REFERENCES

1. Saege W, Ludecke DK, Buchfelder M, Fahlbusch R, Quabbe HJ et al. (2007) Pathohistological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry. *Eur J Endocrinol*, 156 (2): 203-216. [Crossref]
2. Di Ieva A, Davidson JM, Syro LV, Rotondo F, Montoya JF et al. (2015) "Crooke's cell tumors of the pituitary." *Neurosurgery*, 76 (5): 616-622. [Crossref]
3. Oldfield EH, Vance ML, Louis RG, Pledger CL, Jane Jr JA et al. (2015) Crooke's changes in Cushing's syndrome depend on the degree of hypercortisolism and individual susceptibility. *J Clin Endocrinol Metab*, 100 (8): 3165-3171. [Crossref]
4. Taiwo A, Kamalumpundi V, Becker N, Correia M (2023) Pituitary Crooke Cell Adenoma: Two Cases of an Aggressive Pituitary Adenoma. *JCEM Case Rep*, 1 (6): luad114. [Crossref]
5. Holthouse DJ, Robbins PD, Kahler R, Knuckey N, Pullan P (2001) Corticotroph pituitary carcinoma: case report and literature review. *Endocr Pathol*, 12 (3): 329-341. [Crossref]
6. Khatri KJ, Javanmard P, Pawha PS, Miller JD (2019) Clinically silent adrenocorticotropic hormone-secreting Crooke cell adenoma presenting as unilateral ear pain. *AACE Clin Case Rep*, 5 (2): e150-e153. [Crossref]
7. Zhu D, Wang Z, Tian T, Wu X, He D et al. (2022) Prevalence and clinical characteristics of Crooke's cell adenomas in 101 patients with T-PIT-positive Pituitary adenomas: Case series and literature review. *Front Endocrinol (Lausanne)*, 13: 947085. [Crossref]
8. Sathiyabama D, Asha U, Shwetha SD, Thakkar R, Dil JS et al. (2014) Crooke′ s cell adenoma of the pituitary: A histological, immunocytochemical, and electron microscopic study of a rare case. *Neurol India*, 62 (2): 216-217. [Crossref]
9. Todnem N, Ward A, Segar S, Rojiani AM, Rahimi SY (2018) Clinically Silent Adrenocorticotropic Hormone− Positive Crooke Cell Adenoma: Case Report and Review of Literature. *World Neurosurg*, 119: 197-200. [Crossref]
10. Kovács GL, Góth M, Rotondo F, Scheithauer BW, Carlsen E et al. (2013) ACTH-secreting Crooke cell carcinoma of the pituitary. *Eur J Clin Invest*, 43 (1): 20-26. [Crossref]
11. George DH, Scheithauer BW, Kovacs K, Horvath E, Young WF et al. (2003) Crooke's cell adenoma of the pituitary: an aggressive variant of corticotroph adenoma. *Am J Surg Pathol*, 27 (10): 1330-1336. [Crossref]
12. Sood R, Das L, Gupta K, Kumar A, Tripathi M et al. (2021) Crooke cell adenoma: Uncommon and aggressive variant of corticotroph adenoma. *Clin Neuropathol*, 40 (5): 295. [Crossref]