SUBMITTED 16 AUG 23
REVISION REQ. 22 OCT 23; REVISION RECD. 30 OCT 23
ACCEPTED 21 NOV 23
ONLINE-FIRST: DECEMBER 2023
DOI: https://doi.org/10.18295/squmj.12.2023.091

ACTH Secreting Pituitary Microadenoma Presenting with Acute Psychosis, Delirium and Paroxysmal Sympathetic Hyperactivity

Neeraja Rajeev,[1] Abdullah M. Al- Fataisi,[1] *Rajeev Kariyattil[2]

Departments of [1]Internal Medicine and [2]Surgery, Sultan Qaboos University, Muscat, Oman.
**Corresponding Author's e-mail: rajeevkariyattil@gmail.com*

Abstract

ACTH secreting pituitary adenomas are known to be associated with behavioral changes but acute presentation including psychosis and delirium are less common. We report the case of a 42-year-old lady with a known medical history of hypertension and diabetes mellitus, presenting with acute onset behavioral changes suggestive of psychosis. Further evaluation revealed an ACTH dependent Cushing's disease with a pituitary microadenoma. The patient was admitted for endoscopic resection of the adenoma. During the peri-operative period, she experienced worsening of psychosis along with delirium. She also developed episodes of unresponsiveness, posturing, severe diaphoresis and dyspnea accompanied by tachycardia and hypertension which were managed with Midazolam and Levetiracetam. A seizure work-up and CT brain were unremarkable. At follow-up, she showed full resolution of symptoms with good blood pressure and glycemic control. ACTH secreting pituitary microadenoma presenting with acute psychosis, delirium and paroxysmal sympathetic hyperactivity.

Keywords: Cushing's disease, neuropsychiatric, dysautonomia.

Introduction

Cushing's disease (CD), caused by an ACTH secreting pituitary adenoma is one of the commonest causes for Cushing's syndrome (CS)[1]. Though neuropsychiatric manifestations are seen in about 70% of patients with CS, only 8% presented with psychosis and agitation.[2,3]

Case Report

A 42-year-old lady with a known medical history of diabetes, hypertension and hypothyroidism presented to another medical facility with acute onset behavioral changes including irrelevant talk and agitation, suggestive of psychosis, which responded partially to anti-psychotic medication. She had no past history of behavioral changes. Further questioning revealed a history of recent weight gain and menstrual irregularity. Clinical examination revealed abdominal striae and cervico-thoracic fat deposition. Hormonal evaluation revealed serum cortisol level of 1159 nmol/L (reference range: 133-537 nmol/L) and ACTH levels of 97.9ng/L (reference range: 7.2-63.3 ng/L) and a 24 hour urinary cortisol level of 3063nmol/L (reference range: 58-807nmol/L). An MRI of the brain revealed a cup shaped hyperintensity on T1WI and T2WI along the floor of the sella. The left half of the sella was occupied by a hypointense non enhancing nodule with a thin normally enhancing rim of pituitary gland seen on right side. There was no suprasellar extension of this pituitary nodule. The findings were suggestive of a pituitary microadenoma with hemorrhagic changes (fig.1).

She was referred to the authors' institution for further management. An endocrine evaluation with overnight dexamethasone suppression test showed a basal midnight cortisol level of 1078 nmol/L and 833 nmol/L after 1mg of dexamethasone, confirming an ACTH dependent Cushing's disease. All laboratory investigations to rule out other metabolic causes of delirium were within normal limits. She was evaluated by psychiatry following worsening of her symptoms and a diagnosis of psychosis with delirium secondary to Cushing's disease was made. She was managed with the anti-psychotic Quetiapine along with intermittent Haloperidol. Subsequently, she developed episodes of unresponsiveness, posturing, severe diaphoresis and dyspnea accompanied by tachycardia (90-105 bpm), hypertension (200/110 mmHg) and oxygen desaturation which was treated with Midazolam and Levetiracetam for suspected seizures. The

possibility of a diagnosis of Paroxysmal sympathetic hyperactivity (PSH) was not considered at this time.

The following day, she underwent an endoscopic trans-nasal transphenoidal excision of the adenoma. Her immediate post-operative period continued to be stormy. The episodes of tachypnea, hypertension and fall in oxygen saturation also prompted a CT Pulmonary Angiography for pulmonary embolism which was negative. CT brain and seizure evaluation were carried out which were also unremarkable. A serum creatinine kinase level was sent to rule out neuroleptic malignant syndrome and which was within normal limits. However, by the third day, the paroxysmal episodes subsided and she had become calm and coherent. She was discharged on the 5th post-operative day on Quetiapine and Levetiracetam. The post operative serum cortisol level was 121nmol/L in the immediate post operative period and was 236 nmol/L after one month.

By two weeks she had recovered significantly except for occasional involuntary facial twitching. An EEG done at follow-up was normal and so the anti-epileptic medication was discontinued. By one month she was asymptomatic and by 3 months she was off anti-psychotic medication. At 6 months follow-up, she was back to her normal employment with good glycemic and blood pressure control. Histopathology report revealed a corticotropin variant of pituitary adenoma (fig.2). An MRI of pituitary on follow up showed no obvious residual lesion (fig 3).
This patient has given informed consent for the submission of this case report to the journal.

Discussion

Neuropsychiatric manifestations are seen in about 70% of patients with CS at presentation and may be the presenting feature in 12% of patients[2]. The most common symptom reported is depression which could not only be due to the hypercortisolism but also secondary to the other metabolic, skin and musculoskeletal effects and body image issues[2]. Less commonly, about 8% presented with psychosis and agitation.[2,3] In this case, the patient initially presented with sudden onset psychosis which progressed to delirium over a period of 1 week. However, the emergence of frequent episodes of hypertension, tachycardia and tachypnea along with unresponsiveness and dystonic posturing was extremely unusual and prompted a differential diagnosis including

seizures, pulmonary embolism and drug induced neuroleptic malignant syndrome. However, when reviewed retrospectively, these episodes were very similar to the paroxysmal sympathetic hyperactivity (PSH) episodes seen in severe head injury.[4,5] When the PSH diagnostic assessment tool was applied to this patient, a score of 18 was obtained which indicated a high probability of PSH.[5]

Though associated with severe head trauma in 80% of patients, PSH is rarely known to occur secondary to tumors especially with hypothalamic involvement.[6] This patient however had a microadenoma with no supra-sellar extension and the post-operative imaging did not reveal any insult to the supra-sellar region, either. Investigations into the pathophysiology of PSH have shown a significant surge in levels of ACTH, epinephrine, norepinephrine and dopamine during the paroxysms.[4] The patient's symptoms are also similar to the Type A phaeochromocytoma crisis secondary to catecholamine release.[7] In animal and human studies, ACTH has indeed been shown to influence adrenal medullary secretion either directly or indirectly through glucocorticoid stimulation[8–10]. It could therefore, be hypothesized that the elevated ACTH levels resulted in a catecholamine surge which possibly led to these PSH like episodes preceding and immediately following surgery, with rapid resolution thereafter. Confirmatory tests like plasma catecholamines and urinary metanephrine and normetanephrine could not be done as the diagnosis of PSH in this setting, was never under consideration, having never been reported previously.

Though medical management of neuropsychiatric symptoms especially with cortisol lowering agents like Metyrapone and receptor blockers like Mifepristone, have been successfully used as an adjunct, definitive management remains to be surgery with very good response seen, especially for psychosis.[3] Adjunctive management of the PSH like symptoms include opiates, benzodiazepines, β- antagonists and bromocriptine.(4) Could the pre-operative medical management with cortisol lowering or receptor blocking agents have reduced the severity of psychosis, delirium and possibly even the PSH like symptoms in this patient is difficult to ascertain but seems plausible.

Though surgery provides a resolution of acute neuropsychiatric manifestations, more chronic symptoms like depression could persist in many patients[2], suggesting the need for long term follow-up.

Conclusion

The diagnostic work-up of new onset behavioral disturbance especially psychosis should involve a good metabolic and hormonal screening. Though medical management can reduce the symptoms of psychosis in Cushing's disease, early surgery offers rapid and lasting resolution of symptoms. The features suggestive of sympathetic hyperactivity is an extremely unusual presentation for Cushing's disease, requiring exclusion of other serious causes before attributing an association.

Authors' Contribution

NR drafted the manuscript. AF and RK contributed intellectual content and edited the manuscript. All authors approved the final version of the manuscript.

Acknowledgement

We would like to thank Dr. Mohammed Arafa from the Department of Pathology at Sultan Qaboos University for providing us with the histopathology microphotographs.

References

1. Santos A, Resmini E, Pascual JC, Crespo I, Webb SM. Psychiatric Symptoms in Patients with Cushing's Syndrome: Prevalence, Diagnosis and Management. *Drugs*. 2017;77(8):829-842. doi:10.1007/s40265-017-0735-z
2. Lin TY, Hanna J, Ishak WW. Psychiatric Symptoms in Cushing's Syndrome: A Systematic Review. *Innov Clin Neurosci*. 2020;17(1-3):30-35.
3. Mubarak Mohamed AS, Iqbal A, Prasad S, Hoggard N, Blackburn D. Cushing's disease presenting with psychosis. *Pract Neurol*. 2021;21(4):351-353. doi:10.1136/practneurol-2021-002974

4. Zheng RZ, Lei ZQ, Yang RZ, Huang GH, Zhang GM. Identification and Management of Paroxysmal Sympathetic Hyperactivity After Traumatic Brain Injury. *Front Neurol*. 2020;11. doi:10.3389/fneur.2020.00081
5. Baguley IJ, Perkes IE, Fernandez-Ortega JF, Rabinstein AA, Dolce G, Hendricks HT. Paroxysmal Sympathetic Hyperactivity after Acquired Brain Injury: Consensus on Conceptual Definition, Nomenclature, and Diagnostic Criteria. *J Neurotrauma*. 2014;31(17):1515-1520. doi:10.1089/neu.2013.3301
6. Perkes I, Baguley IJ, Nott MT, Menon DK. A review of paroxysmal sympathetic hyperactivity after acquired brain injury. *Ann Neurol*. 2010;68(2):126-135. doi:10.1002/ana.22066
7. Meijs AC, Snel M, Corssmit EPM. TEACHING CASE PRESENTATIONS Pheochromocytoma/paraganglioma crisis: case series from a tertiary referral center for pheochromocytomas and paragangliomas. Published online 2000. doi:10.1007/s42000-021-00274-6/Published
8. Yoshida-Hiroi M, Tsuchida Y, Yoshino G, Hiroi N. Intranasal Administration of ACTH(1-24) Stimulates Catecholamine Secretion. *Hormone and Metabolic Research*. 2005;37(8):489-493. doi:10.1055/s-2005-870307
9. Wurtman RJ, Axelrod J. Adrenaline Synthesis: Control by the Pituitary Gland and Adrenal Glucocorticoids. *Science (1979)*. 1965;150(3702):1464-1465. doi:10.1126/science.150.3702.1464
10. Axelrod J. CATECHOLAMINES: EFFECTS OF ACTH AND ADRENAL CORTICOIDS. *Ann N Y Acad Sci*. 1977;297(1 ACTH and Rela):275-283. doi:10.1111/j.1749-6632.1977.tb41860.x

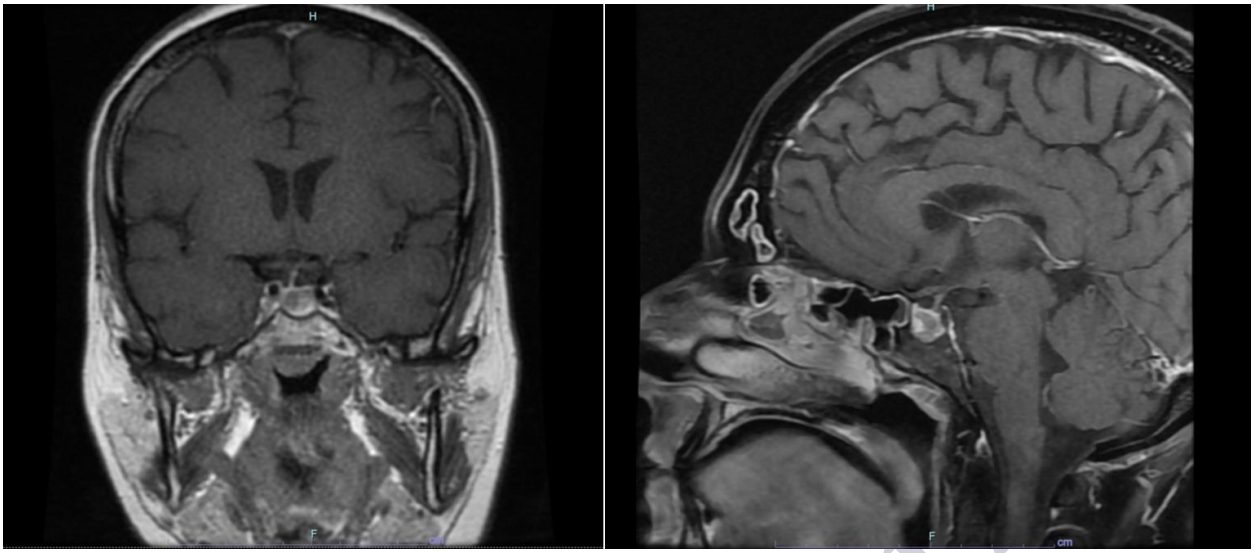

Figure 1: Pre-operative T1W coronal and sagittal MRI with contrast showing hemorrhagic pituitary microadenoma.

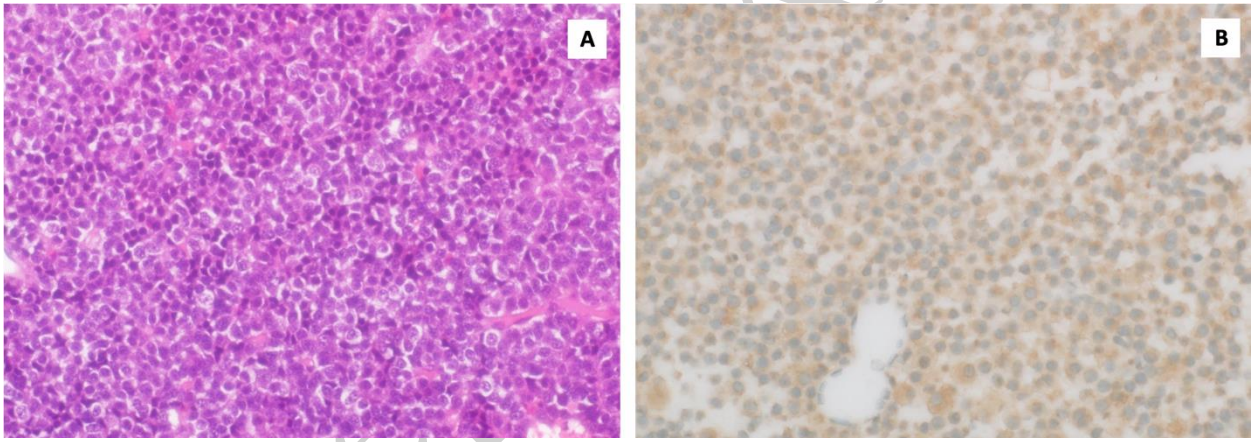

Figure 2: Tumour tissue formed of groups and trabeculae of uniform cells with nuclear stippled chromatin, inconspicuous nucleoli and moderately abundant acidophilic cytoplasm **(A)** (H&E, 200x). The cells show diffuse weak to moderate staining for ACTH **(B)** (Immunohistochemistry, 200x).

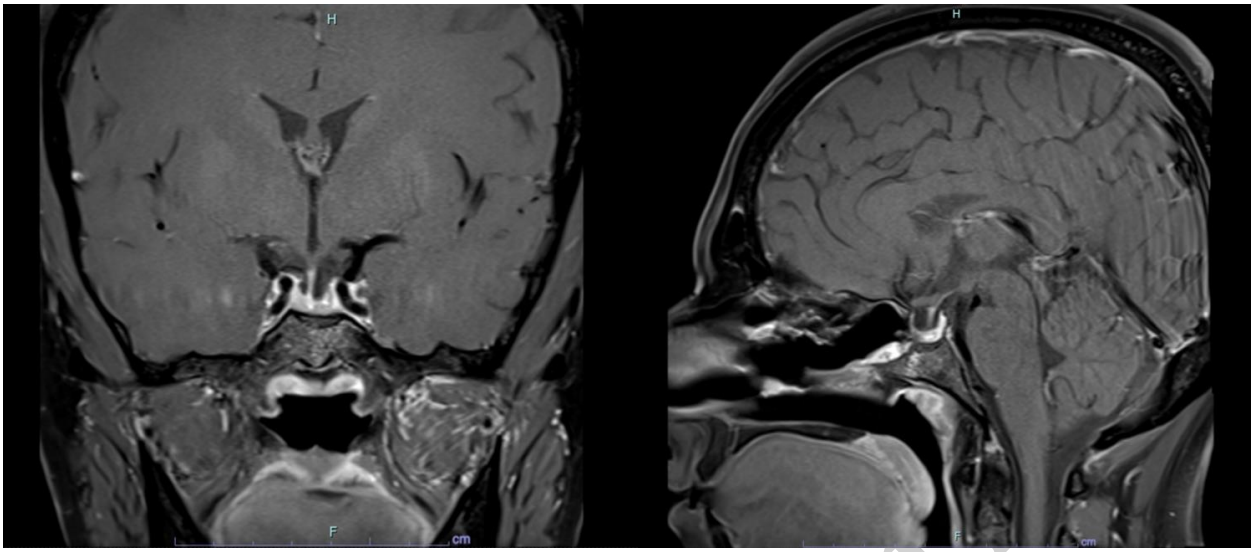

Figure 3: Post-operative T1W coronal and sagittal MRI with contrast showing no obvious residual.