This is a repository copy of *Simultaneous presentation of parathyroid carcinoma, papillary thyroid cancer and ACTH-independent hypercortisolism due to benign cortical adenoma*.

White Rose Research Online URL for this paper:
https://eprints.whiterose.ac.uk/196997/

Version: Accepted Version

Article:
Edafe, O., Debono, M. orcid.org/0000-0002-1059-9702, Tahir, F. et al. (1 more author) (2019) Simultaneous presentation of parathyroid carcinoma, papillary thyroid cancer and ACTH-independent hypercortisolism due to benign cortical adenoma. BMJ Case Reports, 12 (9). e230438. ISSN 1757-790X

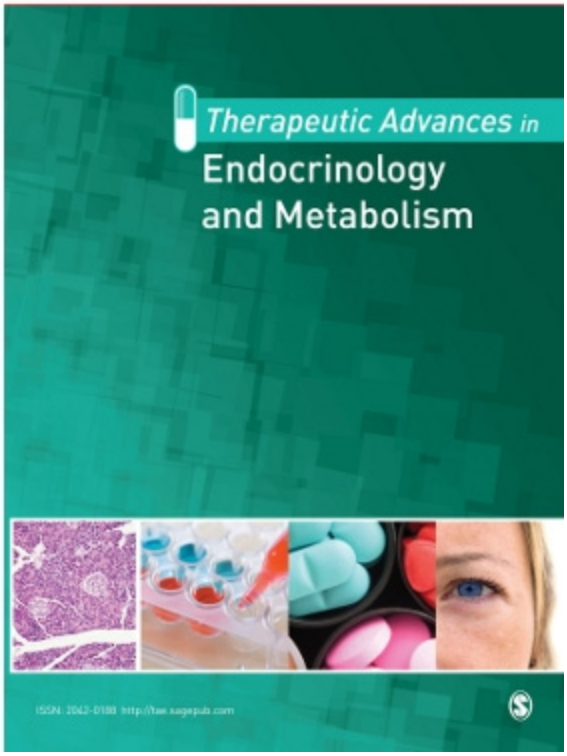
https://doi.org/10.1136/bcr-2019-230438

This article has been accepted for publication in BMJ Case Reports 2019 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/bcr-2019-230438.

Reuse
Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

eprints@whiterose.ac.uk
https://eprints.whiterose.ac.uk/



A case of adrenal Cushing's syndrome and Primary Hyperparathyroidism due to an atypical parathyroid adenoma.

Journal:	*Therapeutic Advances in Endocrinology and Metabolism*
Manuscript ID	TAE-21-04-047
Manuscript Type:	Case Report
Date Submitted by the Author:	10-Apr-2021
Complete List of Authors:	Newman, Christine; National University of Ireland Galway College of Medicine Nursing and Health Sciences, College of Nursing, Medicine, Midwifery and Health Science Costello, Maria; National University of Ireland Galway College of Medicine Nursing and Health Sciences, College of Medicine, Nursing and health sciences Casey, Mary; University Hospital Galway, Department of Pathology DAvern, Recie; Galway University Hospital, Department of Endocrinology Dinneen, Kate; Galway University Hospitals, Department of Pathology Lowery, Aoife; Galway University Hospitals, Department of Endocrine Surgery McHale, Teresa; Galway University Hospitals, Department of Pathology O'Shea, Paula; Galway University Hospitals, Department of Clinical Biochemistry

	Quinn, Anne; Galway University Hospitals, Department of Pathology Bell, Marcia; Galway University Hospitals, Department of Endocrinology
Keywords:	
Abstract:	Cushing's syndrome is a rare disorder of cortisol excess and is associated with significant morbidity and mortality. Hypercalcaemia due to hyperparathyroidism is a common condition, however in 10% of young patients it is associated with other endocrinopathies and occurs due to a genetic variant (e.g. Multiple Endocrine Neoplasia (MEN) 1, 2 and 4). We report the case of a 31-year-old woman who was referred to the Endocrinology out-patient service with an eight-month history of hirsutism, amenorrhoea and weight gain. Her biochemical work up was significant for adrenocorticotropic hormone (ACTH)-independent Cushing's syndrome. Radiological investigations revealed an adrenal adenoma. During investigation she was also found to have primary hyperparathyroidism due to a parathyroid adenoma. Pre-operatively the patient was commenced on metyrapone and both her adrenal and parathyroid lesions were successfully resected. There were several concerning findings on initial examination of the parathyroid tumour including possible extension of the tumour through the capsule and vascular invasion, however, following extensive review it was ultimately defined as an adenoma. Given the unusual presence of two endocrinopathies in a young patient, she subsequently underwent genetic testing. Analysis of multiple genes did not reveal any pathogenic variants. The patient is currently clinically well, with a normal adjusted calcium and no clinical features of cortisol excess. She will require long term follow up for recurrence of both hypercalcaemia and hypercortisolaemia.

SCHOLARONE™
Manuscripts

A case of adrenal Cushing's syndrome and Primary Hyperparathyroidism due to an atypical parathyroid adenoma

C Newman[1,2], M Costello[1, 2] , M Casey[3], R Davern[2], K Dinneen[3], A Lowery[4], T McHale[3], PM O'Shea[5], AM Quinn[3], M Bell[2]

[1] College of Nursing, Midwiferey, Medicine and Health Science, National University of Ireland, Galway

[2]Department of Endocrinology, Galway University Hospital

[3]Department of Pathology, Galway University Hospital

[4]Department of Endocrine Surgery, Galway University Hospital

[5]Department of Clinical Biochemistry, Galway University Hospital

Emails

christine.newman@nuigalway.ie

Maria.costello@hse.ie

Maryb.casey@hse.ie

reciedavern@rcsi.ie

katea.dinneen@hse.ie

aoife.lowery@hse.ie

Teresa.mchale@hse.ie

paulam.oshea@hse.ie

annema.quinn@hse.ie

marcia.bell@hse.ie

For Peer Review

Summary

Cushing's syndrome is a rare disorder of cortisol excess and is associated with significant morbidity and mortality. Hypercalcaemia due to hyperparathyroidism is a common condition, however in 10% of young patients it is associated with other endocrinopathies and occurs due to a genetic variant (e.g. Multiple Endocrine Neoplasia (MEN) 1, 2 and 4). We report the case of a 31-year-old woman who was referred to the Endocrinology out-patient service with an eight-month history of hirsutism, amenorrhoea and weight gain. Her biochemical work up was significant for adrenocorticotropic hormone (ACTH)-independent Cushing's syndrome. Radiological investigations revealed an adrenal adenoma. During

investigation she was also found to have primary hyperparathyroidism due to a parathyroid adenoma. Pre-operatively the patient was commenced on metyrapone and both her adrenal and parathyroid lesions were successfully resected. There were several concerning findings on initial examination of the parathyroid tumour including possible extension of the tumour through the capsule and vascular invasion, however, following extensive review it was ultimately defined as an adenoma. Given the unusual presence of two endocrinopathies in a young patient, she subsequently underwent genetic testing. Analysis of multiple genes did not reveal any pathogenic variants. The patient is currently clinically well, with a normal adjusted calcium and no clinical features of cortisol excess. She will require long term follow up for recurrence of both hypercalcaemia and hypercortisolaemia.

Learning Points

- 10% of young patients (<45 years) with hypercalcaemia will have a genetic variant
- Atypical adenomas are an uncommon cause of hypercalcaemia and account for the minority of parathyroid adenomas
- Metyrapone can be used to improve symptoms of hypercortisolaemia pre-operatively even in those with mild-moderate Cushing's syndrome

Background

Hypercalcaemia and Cushing's syndrome are both important health conditions which cause disabling symptoms. They can occur together in the setting of MEN but rarely co-exist outside of these conditions. Atypical parathyroid adenomas are rare, benign lesions which share overlapping features with parathyroid carcinoma.

We report the unique case of a 31-year-old woman who was diagnosed with both conditions in the absence of a known genetic condition. To our knowledge this is the first reported case of an atypical parathyroid adenoma and adrenal adenoma occurring in the same patient.

Case Presentation

A 31-year-old Caucasian woman was referred to the Endocrinology service with an eight-month history of secondary amenorrhea, fatigue, hirsutism and a 13kg weight gain. She

For Peer Review

denied easy bruising and proximal myopathy and had no past medical history. On examination the patient was hypertensive and had a body mass index of 26.2kg/m^2. She exhibited marked clinical features of cortisol excess including dorsal skin thinning, hirsutism, facial flushing, characteristic moon facies, interscapular fat pad, central adiposity and purple abdominal striae.

Investigation

Laboratory studies revealed hypercortisolaemia. Her baseline morning cortisol level was 704 nmol/L. A 48h low dose dexamethasone suppression test was performed- cortisol values at 24h and 48h were 702 nmol/L and 703 nmol/L respectively (normal suppression <50nmol/L)(1).

Her baseline adrenocorticotrophic hormone (ACTH) level was appropriately suppressed at 1.4 ng/L (Reference Interval (RI): 7.2-63.3 ng/L) which was consistent with a diagnosis of ACTH-independent Cushing's syndrome. Concentrations of androstenedione and dehydroepiandrosteone sulphate were both less than the respective lower reference limits (1.3 nmol/L [2.0-5.4 nmol/L] and <0.4 umol/L [1.6-7.8 µmol/L] repectively) due to ACTH suppression.

Other relevant laboratory results including a pituitary profile and a biochemical work-up of amenorrhoea are depicted in table 1.

Table 1

Result	**Level**	**Reference interval**
Testosterone	<0.5	0.3-1.7 nmol/L
Androstenedione	1.3	2-5.4 nmol/l
DHEAS	<0.4	1.6-7.8 umol/L
17-hydroypreogesterone	<1.0	<18 nmol/L (adult female)
Oestrodiol	<100	Varies with cycle phase (pmol/L)
FSH	4.4	Varies with cycle phase (IU/L)
LH	3.0	Varies with cycle phase (IU/L)
Free T4	15.1	10.5-22 pmol/L
TSH	0.71	0.27-4.2 mIU/L
Prolactin	704	102-496 nmol/L
IGF-1	152	73-244 ug/L

For Peer Review

Normetanephrine	<300	0-1180 pmol/L
Metanephrine	<100	0-510 pmol/L
3-methoxytyramine	<100	0-180 pmol/L
Aldosterone	130	122-1179 pmol/L
Direct renin	25.8	6.1-62.7 mIU/L

DHEAS: dehydroepiandrosterone
TSH: thyroid stimulating hormone
IGF1: insulin like growth factor 1
FSH: follicle stimulating hormone
LH: luteinising hormone

A 24h urinary steroid profile (analysed at St Bartholomew's Hospital, London) demonstrated elevated 11-hydroxy cortisone and low concentrations of corticosterone:cortisol metabolites which further supported the diagnosis of autonomous cortisol secretion. A 24 hour urinary free cortisol was not performed.

With evidence of clinical and biochemical cortisol excess a dedicated adrenal computed tomography (CT) was performed to localise the site of disease and revealed a 3.3 x 2.2 cm lesion of the right adrenal gland. Hounsfield units were <10 and radiological features were consistent with an adrenal adenoma (Image A). The contralateral adrenal gland appeared normal on imaging.

During the course of her out-patient investigations the patient was also found to have an elevated adjusted calcium level of 2.7 mmol/L (RI: 2.17-2.51 mmol/L). This was accompanied by an elevated parathyroid hormone level of 113.5 ng/L (15-65 ng/L), a Vitamin D level of 27 nmol/L (>50 nmol/L considered sufficient), a reduced phosphate level of 1.06 mmol/L (RI: 1.12-1.45 mmol/L) and a normal renal profile. This biochemical profile was suggestive of a diagnosis of primary hyperparathyroidism. A 24h urinary calcium level of 6.45 mmol/day (RI: 2.5-7.5) excluded a diagnosis of benign familial hypocalciuric hypercalcemia.

For Peer Review

Other investigations including gastrin, vasoactive intestinal peptide and pancreatic polypeptide were not performed as the patient did not display any gastrointestinal symptoms at that time.
A parathyroid ultrasound and sestamibi scan (Image B) showed concordance identifying a 1cm right inferior parathyroid adenoma. Following

A specialist surgical opinion was sought for these two synchronous findings, and following multi-disciplinary team discussion, the decision was made to treat the patient's Cushing's syndrome with a laparoscopic adrenalectomy before preforming a parathyroidectomy to treat her primary hyperparathyroidism.
Prior to the adrenalectomy the patient was commenced on metyrapone to reduce serum cortisol levels and minimise peri-operative complications. She was commenced on metyrapone at a dose of 250mg three times daily (tds) which was gradually increased to 500mg tds. She was educated on potential side effects and the importance of use of effective contraception while using metyrapone. She was counselled regarding possible hypocortisolaemia and provided with hydrocortisone supplementation for emergency use.

Treatment

The patient's hirsutism, hypertension and facial swelling improved significantly with a combination of metyrapone and anti-hypertensive medications.
She underwent successful adrenalectomy from a retroperitoneal laparoscopic approach after 4 weeks of metyrapone therapy.
She was able to discontinue anti-hypertensive medications and had spontaneous recovery of menstruation. She initially had symptoms of hypocortisolaemia and was treated with oral hydrocortisone however this was discontinued after 9 months as the patient's morning cortisol was 398 nnmol/L indicating contralateral adrenal gland recovery.

To treat her second endocrinopathy, the patient underwent a 4-gland neck exploration with intra-operative PTH. There was an interval of 5 months between surgeries and during this time the patient's serum corrected calcium fluctuated between 2.7-2.9 mmol/L. She denied symptoms of polydipsia, polyuria or constipation and maintained a fluid intake of 2.5-3

For Peer Review

litres of water per day. She did not require pharmacological therapy to reduce her serum calcium during this time.

During surgery the right lower parathyroid gland was excised and the intra-operative PTH reduced from a baseline of 193 ng/L to 55ng/L at ten minutes which satisfied the Miami Criterion for successful parathyroid gland resection. The patient's post-operative biochemistry was satisfactory with an adjusted calcium of 2.37 mmol/L, iPTH 19.6 ng/L and phosphate of 1.11 mmol/L.

Outcome and follow-up

Histology of the adrenal gland confirmed a 2.6cm encapsulated adenoma confined to an otherwise normal adrenal gland. A mixture of clear and compact cells was identified without capsular or vascular involvement and the Ki67 index was <5% (Image C-E).

Histology of the parathyroid gland showed an atypical parathyroid adenoma with a calcified capsule, partial extension of the tumour through the capsule and morphological changes raising the possibility of vascular invasion. The Ki67 proliferation index was <2% (Image F-I). The sample weighed 1.485 grams in total (including a portion of thymic tissue). Given the neoplastic features and the complexities of this case the specimen was sent to St. Guy's and Thomas' Hospital in London for a second pathological opinion. There was no necrosis or increased mitotic activity. The appearances of entrapped tumour cells within the capsule, without complete invasion, were considered in keeping with an atypical adenoma.

Given the atypical nature of the parathyroid adenoma, the presence of two endocrinopathies and her young age, the patient was genetically tested for the following panel of genes: *MEN1; Cyclin Dependent Kinase Inhibitor (CDKN) 1A, 1B , 2B* and *2C*; *RET; Cell Division Cycle 73 (CDC73)/*hyperparathyroid jaw-tumour syndrome and *Calcium sensing receptor (CASR).* No pathogenic variants were identified.

The patient is currently clinically well. She does not have any features of cortisol excess or hypertension and her adjusted calcium is in the normal range. The multidisciplinary team

For Peer Review

determined the patient will require long term follow up for recurrence of hypercalcaemia and hypercortisolaemia as atypical adenomas are associated with occasional recurrence.

Discussion

We present this interesting case of synchronous Cushing's syndrome and hypercalcemia secondary to an atypical parathyroid adenoma. We will discuss the interesting aspects of this case, namely the use of metyrapone pre-operatively in a patient with adrenal Cushing's; the occurrence of Cushing's syndrome and hyperparathyroidism together outside of a known genetic variant; and the presence of atypical parathyroid histology.

Cushing's syndrome is a rare disorder cause by excess cortisol secretion. Untreated Cushing's syndrome is associated with an increased risk of mortality and multiple significant co-morbidities including diabetes, hypertension and cardiovascular disease(2, 3).

Definitive treatment of Cushing's syndrome requires the excision of any causative lesion(4). Given the effects of hypercortisolaemia patients are often high-risk surgical candidates. In such cases adrenolytic agents or adrenal enzyme inhibitors (including metyrapone) can be used pre-operatively to normalise cortisol levels and reduce the operative risk.

Metyrapone is extremely effective at reducing cortisol levels and will reduce circulating cortisol in up to 90% of patients with hypercortisolaemia (5).

Despite its efficacy metyrapone can cause troubling side effects and not all patients receive metyrapone pre-operatively because of this reason. Metyrapone produces its side effects – most notable hirsutism, hypertension and oedema, through increased levels of androgen and mineralocorticoid precursors. Metyrapone strongly inhibits the enzyme 11-beta hydroxylase (CYP11B1) which converts deoxycorticosterone and deoxycortisol to 18-hydroxycorticosterone and cortisol respectively. This subsequently increases levels of ACTH which in turn increases androgen and mineralocorticoid precursors.

In one recent study only 20% of patients with Cushing's syndrome received pre-operative medical treatment and treatment (including metyrapone and ketoconazole) was reserved for patients with more complex disease and those deemed to have high a risk of complications and/or recurrence(6).

For Peer Review

In addition to reducing serum cortisol levels a recent study of patients with adrenal Cushing's syndrome found that pre-operative metyrapone use also improved urinary free cortisol levels, blood pressure levels and quality of life (7). This study concluded by recommending metyrapone use even for those with mild-moderate symptoms of cortisol excess and those with adrenal CS. This is somewhat different to the 2015 Endocrine Society guidelines from 2015 which recommend medical treatment in the following situations(4):

- as second-line treatment after transsphenoidal surgery (TSS) in patients with Cushing's Disease (CD), either; as primary treatment of ectopic ACTH secretion in patients with occult or metastatic ectopic ACTH secretion; and as adjunctive treatment to reduce cortisol levels in adrenocortical carcinoma
- patients with CD who are not surgical candidates or who have persistent disease after TSS
- patients with diabetes or glucose intolerance who are not surgical candidates or who have persistent disease after TSS

One of the most interesting aspect of our case is the presence of adrenal Cushing's syndrome with hypercalcaemia; particularly given both the young age of the patient and atypical parathyroid gland histological findings.

It is estimated that 10% of patients with hypercalcaemia aged <45 years have a genetic variant causing hypercalcaemia. One such genetic cause is MEN1 syndrome which is characterised by at least 2 endocrine neoplasia in the same patient and is caused by pathogenic variants in the tumour suppresser gene on chromosome 11. It can occur as either a familial autosomal dominant (roughly 90% of cases) or sporadic (10%) condition and is characterised by parathyroid (95%), pancreatic (41%) and pituitary nodules (30%)(8). Non-secreting adrenal adenomas occur in 24% of patients with MEN1 and a total of 73% of patients will have some degree of adrenal involvement (9). While many patients with MEN1 will experience both ACTH-dependent Cushing's disease and hypercalcaemia, ACTH-independent Cushing's syndrome is rare in MEN1 syndrome (10).

Patients with MEN4 (a recently described syndrome with similarities to MEN1) show high rates of hypercalcaemia, however to date there have been no reported cases of adrenal

For Peer Review

Cushing's syndrome in such patients. MEN2 has been linked to ACTH-dependent Cushing's syndrome (from both pituitary and ectopic ACTH) but not with adrenal Cushing's syndrome (11, 12). We have not identified any reported cases of adrenal Cushing's syndrome and hypercalcaemia in the setting of *CDC73, CASR, CDKN2B* or *CDKN2C* mutations in the literature.

Atypical parathyroid adenomas are rare lesions which demonstrate some features of but are not diagnostic of carcinoma. They account for roughly 1.2% of all parathyroid adenomas(13). Histologically they may contain features such as dense fibrous bands and prominent nuclear atypia however they do not display invasion into the lymphovascular, perineural or surrounding space (14).

Patients presenting with atypical parathyroid adenomas have a higher calcium, PTH and urinary calcium than patients with typical adenomas(15). Clinically they present at the same age as patients with typical adenomas however the sex distribution is different and goes from a 1:1 ratio in typical adenomas to a female:male 4:1 ratio(16).

From a histological perspective one case series found a number of differences between typical and atypical adenomas including increased rates of (15, 16)

- Pseudocapsular invasion
- Bands of fibrosis
- Higher mitotic rates
- Thick capsule
- Ki-67 >4%
- Heavier gland (grossly)

Atypical adenomas may occur sporadically or as part of an inherited syndrome - they account for <1% of adenomas in MEN1 (17) and have also been observed in HPT-JT syndrome (18). They are seen more commonly in Asian countries (19).

Patients with an inherited syndrome causing atpical parathyroid disease

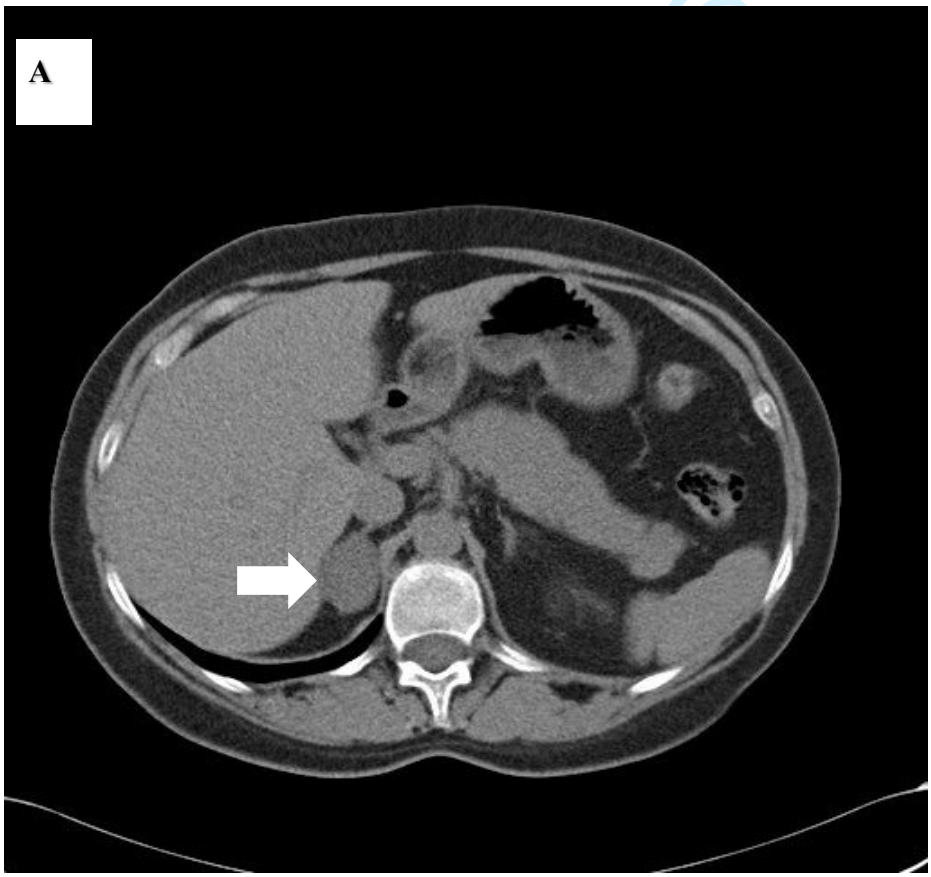
Present much younger (often in the third decade) and are more likely to have a palpable neck mass. Up to 40% of these patients will experience a recurrence compared to just 2% of patients with sporadic disease (15).

For Peer Review

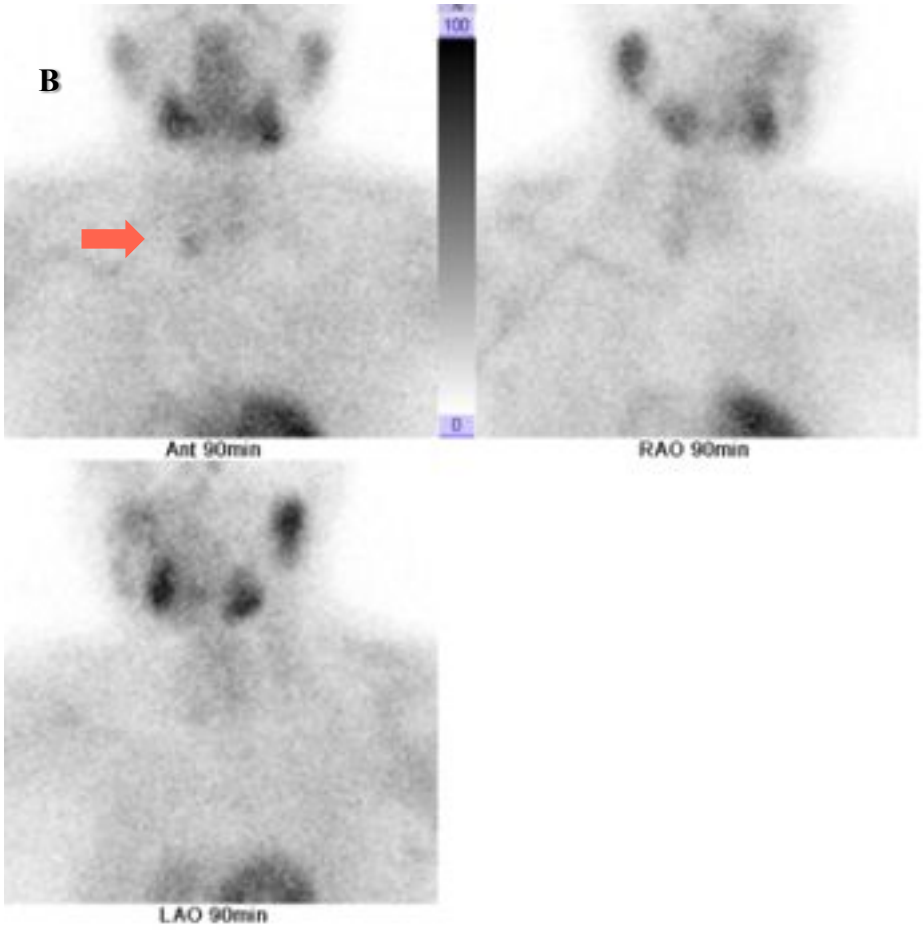
Although recurrence in sporadic atypical disease is rare, long term follow up is advised . While there is no agreed follow-up protocol, in this case we have decided to perform biochemical testing for hypercalcaemia and hyperparathyroidism every 6 months for at 5 years and annually thereafter and assess for evidence of hypercortisolaemia annually.

Our case details the rare co-presentation of ACTH-independent Cushing's syndrome with atypical Primary Hyperparathyroidism in a young female with no known genetic variant. We have shown our centre's successful use of pre-operative metyrapone, which is not currently universal practice and outlined our evidence-based approach to the management of this patient's hypercalcaemia.

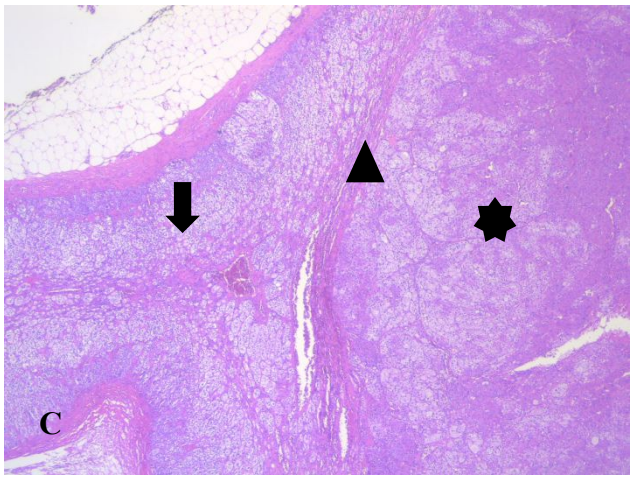
For Peer Review



Dedicated adrenal CT showing an adenoma (white arrow)

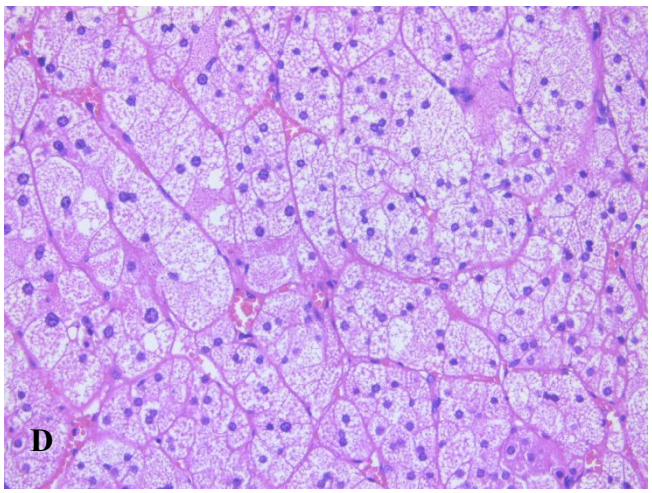


Sestamibi scan showing tracer uptake in the lower right parathyroid gland (red arrow)

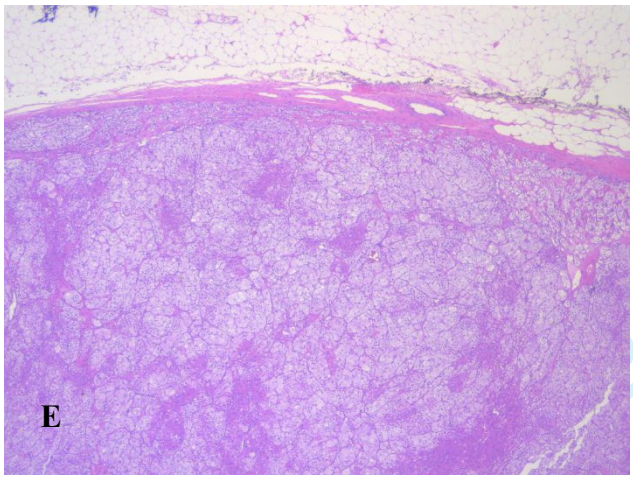


Adrenal adenoma on right hand side of slide (*), normal adrenal tissue on left hand side (downwards arrow), capsule intact (triangle)

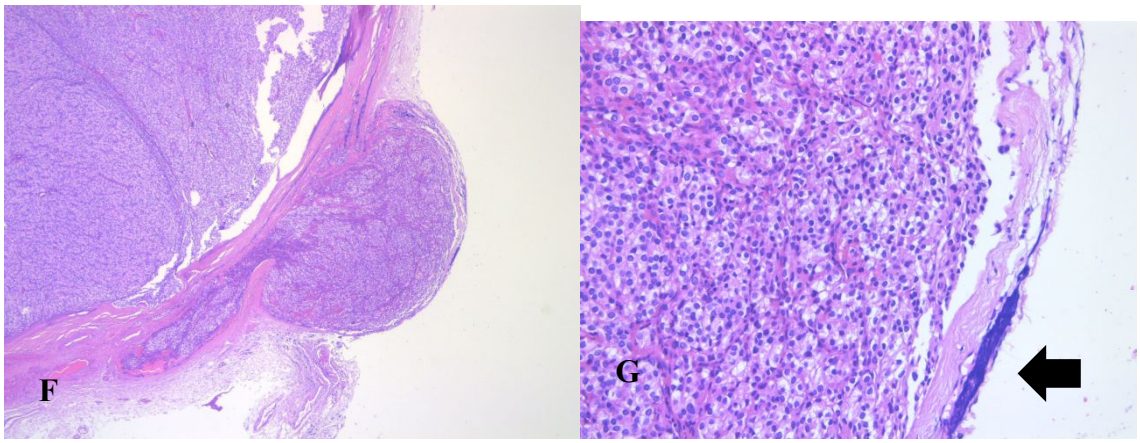
Review



High power view of adrenal adenoma

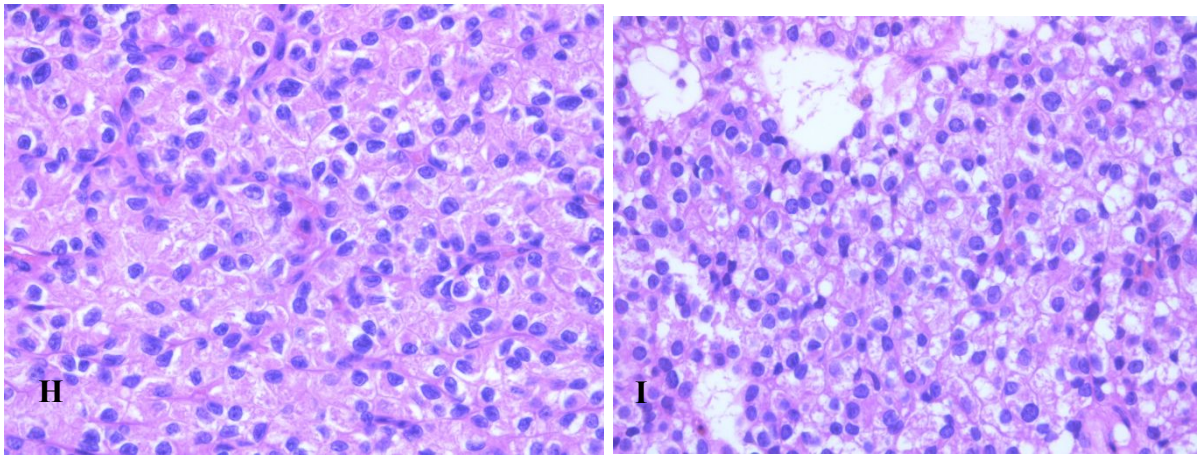


Intact capsule of the adrenal adenoma



Extension of the parathyroid adenoma through the capsule (F) however a thin rim of capsule in left intact (G) (arrow)

For Review



Cellular atypia

For Peer Review

References

1. Nieman LK, Biller BMK, Findling JW, Newell-Price J, Savage MO, Stewart PM, et al. The Diagnosis of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism. 2008;93(5):1526-40.
2. Dekkers OM, Horváth-Puhó E, Jørgensen JO, Cannegieter SC, Ehrenstein V, Vandenbroucke JP, et al. Multisystem morbidity and mortality in Cushing's syndrome: a cohort study. J Clin Endocrinol Metab. 2013;98(6):2277-84.
3. Graversen D, Vestergaard P, Stochholm K, Gravholt CH, Jørgensen JO. Mortality in Cushing's syndrome: a systematic review and meta-analysis. Eur J Intern Med. 2012;23(3):278-82.
4. Nieman LK, Biller BMK, Findling JW, Murad MH, Newell-Price J, Savage MO, et al. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism. 2015;100(8):2807-31.
5. Broersen LHA, Jha M, Biermasz NR, Pereira AM, Dekkers OM. Effectiveness of medical treatment for Cushing's syndrome: a systematic review and meta-analysis. Pituitary. 2018;21(6):631-41.
6. Valassi E, Franz H, Brue T, Feelders RA, Netea-Maier R, Tsagarakis S, et al. Preoperative medical treatment in Cushing's syndrome: frequency of use and its impact on postoperative assessment: data from ERCUSYN. European Journal of Endocrinology. 2018;178(4):399-409.
7. Puglisi S, Perotti P, Barbot M, Cosio P, Scaroni C, Stigliano A, et al. PREOPERATIVE TREATMENT WITH METYRAPONE IN PATIENTS WITH CUSHING'S SYNDROME DUE TO ADRENAL ADENOMA. Endocr Connect. 2018;7(11):1227-35.
8. Kamilaris CDC, Stratakis CA. Multiple Endocrine Neoplasia Type 1 (MEN1): An Update and the Significance of Early Genetic and Clinical Diagnosis. Frontiers in Endocrinology. 2019;10(339).
9. Schaefer S, Shipotko M, Meyer S, Ivan D, Klose KJ, Waldmann J, et al. Natural course of small adrenal lesions in multiple endocrine neoplasia type 1: an endoscopic ultrasound imaging study. Eur J Endocrinol. 2008;158(5):699-704.
10. Alzahrani AS, Al-Khaldi N, Shi Y, Al-Rijjal RA, Zou M, Baitei EY, et al. Diagnosis by serendipity: Cushing syndrome attributable to cortisol-producing adrenal adenoma as the initial manifestation of multiple endocrine neoplasia type 1 due to a rare splicing site MEN1 gene mutation. Endocr Pract. 2008;14(5):595-602.

For Peer Review

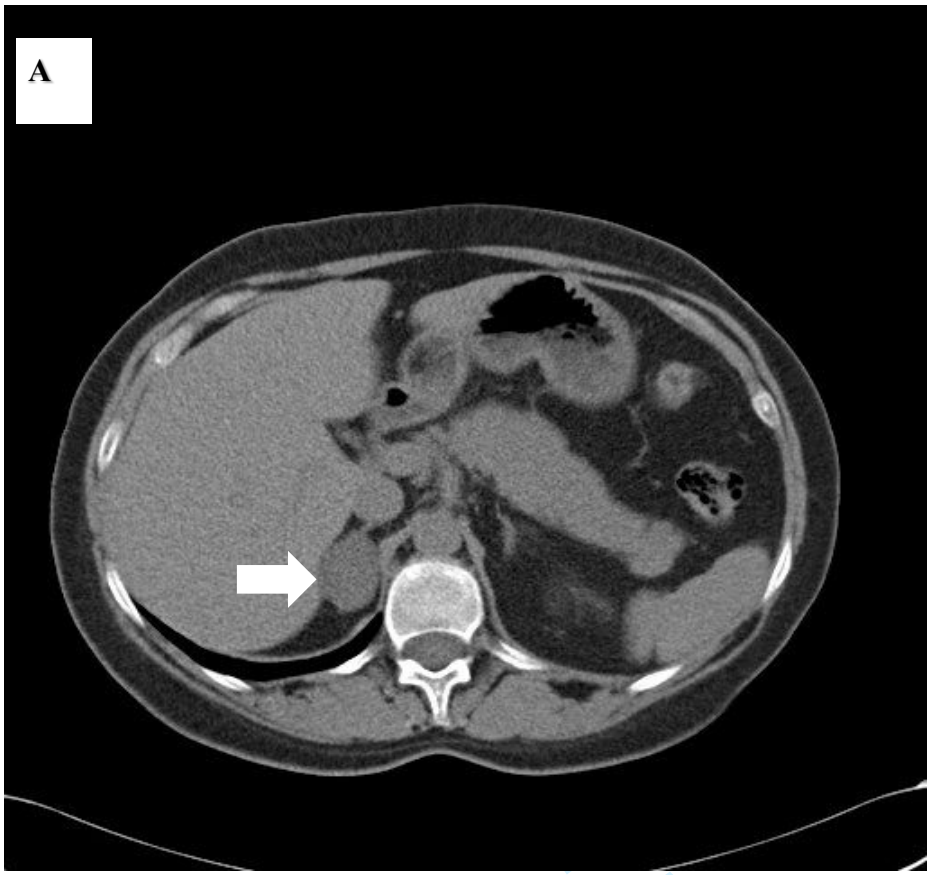
11. Kasturi K, Fernandes L, Quezado M, Eid M, Marcus L, Chittiboina P, et al. Cushing disease in a patient with multiple endocrine neoplasia type 2B. Journal of Clinical and Translational Endocrinology: Case Reports. 2017;4:1-4.
12. Singer K, Heiniger N, Thomas I, Worden FP, Menon RK, Chen M. Ectopic Cushing syndrome secondary to metastatic medullary thyroid cancer in a child with multiple endocrine neoplasia syndrome type 2B: clues to early diagnosis of the paraneoplastic syndromes. J Pediatr Endocrinol Metab. 2014;27(9-10):993-6.
13. McCoy KL, Seethala RR, Armstrong MJ, Nikiforova MN, Stang MT, Carty SE, et al. The clinical importance of parathyroid atypia: is long-term surveillance necessary? Surgery. 2015;158(4):929-35; discussion 35-6.
14. Guilmette J, Sadow PM. Parathyroid Pathology. Surg Pathol Clin. 2019;12(4):1007-19.
15. Cetani F, Marcocci C, Torregrossa L, Pardi E. Atypical parathyroid adenomas: challenging lesions in the differential diagnosis of endocrine tumors. Endocrine-Related Cancer. 2019;26(7):R441-R64.
16. Galani A, Morandi R, Dimko M, Molfino S, Baronchelli C, Lai S, et al. Atypical parathyroid adenoma: clinical and anatomical pathologic features. World Journal of Surgical Oncology. 2021;19(1):19.
17. Christakis I, Busaidy NL, Cote GJ, Williams MD, Hyde SM, Silva Figueroa AM, et al. Parathyroid carcinoma and atypical parathyroid neoplasms in MEN1 patients; A clinico-pathologic challenge. The MD Anderson case series and review of the literature. Int J Surg. 2016;31:10-6.
18. Marx SJ, Goltzman D. Evolution of Our Understanding of the Hyperparathyroid Syndromes: A Historical Perspective. J Bone Miner Res. 2019;34(1):22-37.
19. Ya Hu MC, Yu Xia, Zhe Su, Xiang Zhang, Quan Liao, Yuxin Jiang, Yupei Zhao. The Clinical Features of Cystic Parathyroid Adenoma in Chinese Population: A Single-Center Experience. International Journal of Endocrinology. 2018;2018.

Funding: N/A

Conflict of Interest: N/A

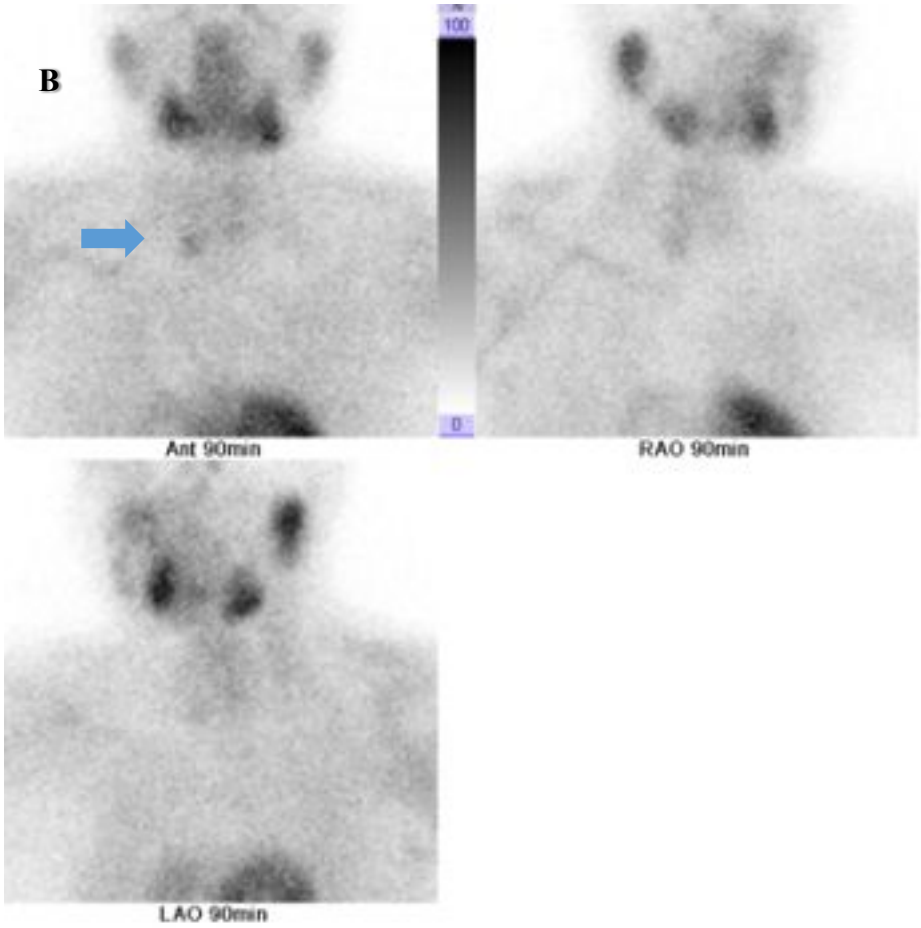
Ethics and Consent: the patient provided written consent for the publication of this case report

For Peer Review



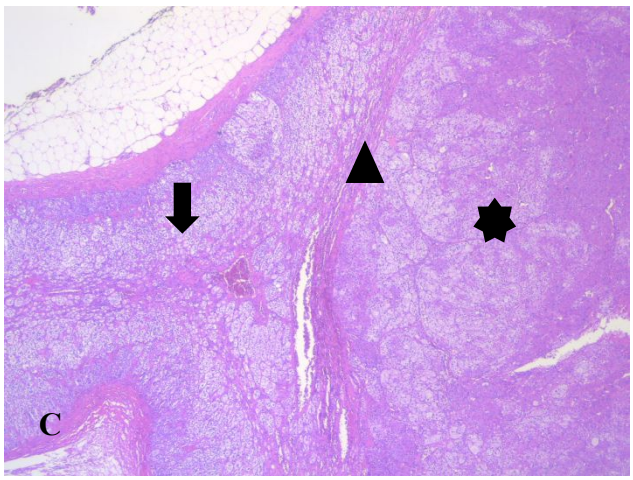
Dedicated adrenal CT showing an adenoma (white arrow)

For Review

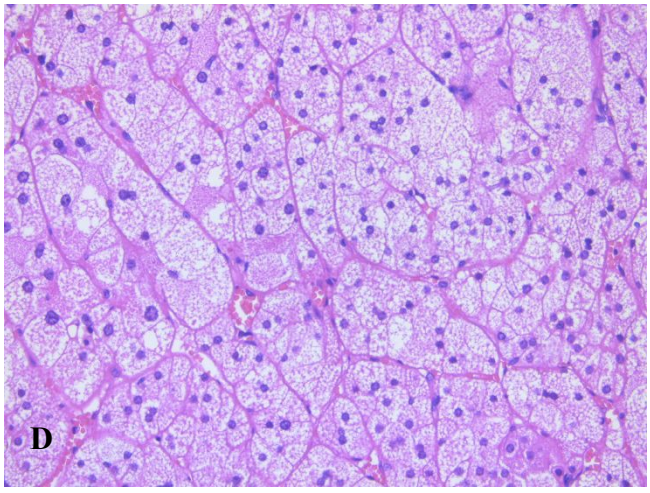


Sestamibi scan showing tracer uptake in the lower right parathyroid gland (red arrow)

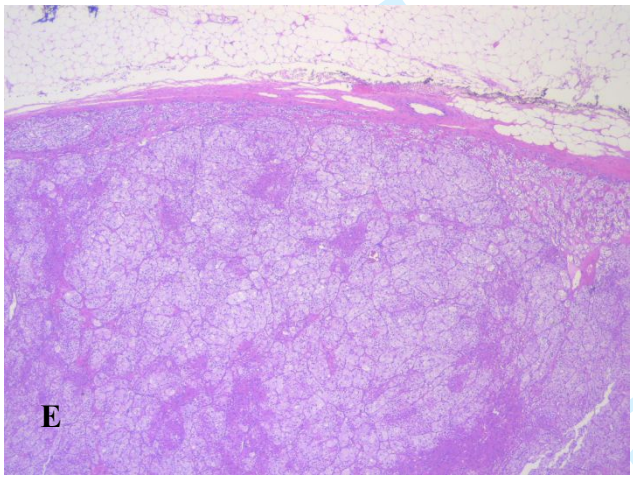
Preview



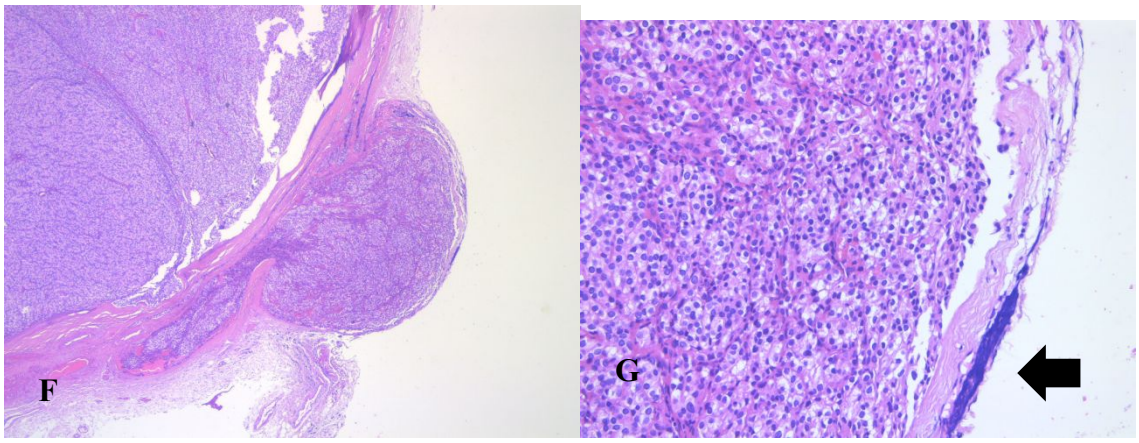
Adrenal adenoma on right hand side of slide (*), normal adrenal tissue on left hand side (downwards arrow), capsule intact (triangle)



High power view of adrenal adenoma

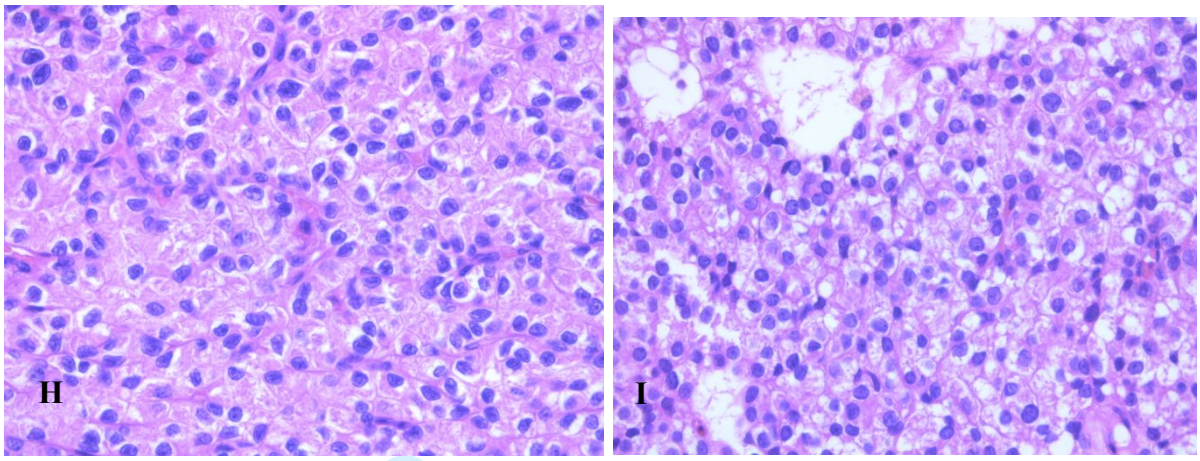


Intact capsule of the adrenal adenoma



Review

Extension of the parathyroid adenoma through the capsule (F) however a thin rim of capsule in left intact (G) (arrow)



Cellular atypia

For Peer Review

Table 1

Result	Level	Reference interval
Testosterone	<0.5	0.3-1.7 nmol/L
Androstenedione	1.3	2-5.4 nmol/l
DHEAS	<0.4	1.6-7.8 umol/L
17-hydroypreogesterone	<1.0	<18 nmol/L (adult female)
Oestrodiol	<100	Varies with cycle phase (pmol/L)
FSH	4.4	Varies with cycle phase (IU/L)
LH	3.0	Varies with cycle phase (IU/L)
Free T4	15.1	10.5-22 pmol/L
TSH	0.71	0.27-4.2 mIU/L
Prolactin	704	102-496 nmol/L
IGF-1	152	73-244 ug/L
Normetanephrine	<300	0-1180 pmol/L
Metanephrine	<100	0-510 pmol/L
3-methoxytyramine	<100	0-180 pmol/L
Aldosterone	130	122-1179 pmol/L
Direct renin	25.8	6.1-62.7 mIU/L

DHEAS: dehydroepiandrosterone

TSH: thyroid stimulating hormone

IGF1: insulin like growth factor 1

FSH: follicle stimulating hormone

LH: luteinising hormone

For Peer Review