Ectopic adrenocortical carcinoma located in the ovary

Farida Chentli¹, Nadia Terki² and Said Azzoug¹

¹Department and Endocrine and Metabolic Diseases, Bab El Oued Teaching Hospital Algiers, Algiers, Algeria and ²Department of Pathology, Pierre and Marie Curie Centre, Algiers, Algeria

Correspondence should be addressed to F Chentli
Email
chentli.f@gmail.com

Abstract

Aim: Ovarian corticosteroid-producing tumors are exquisitely rare. Our aim was to describe the first case observed in our practice.

Case history: A 34-year-old female was referred for Cushing's syndrome (CS) occurring in the postpartum period. Clinical examination showed severe CS with diabetes mellitus, hypertension, and a large mass in the right lower abdomen. Biochemistry demonstrated corticotropin (ACTH)-independent CS (cortisol = 1900 ng/mL ($n = 50$ –250), ACTH < 10 pg/mL ($n = 20$ –46)) with estradiol and testosterone overproduction.

Investigations: Abdomen CT scan revealed a 14 cm right ovarian mass and small adrenal glands. Surgical exploration found the ovarian tumor with hemoperitoneum and enlarged lymph nodes. Histological study confirmed adrenocortical tumor located in the ovary with a Weiss score >5, associated with peritoneal and lymph node metastases. Immunohistochemical staining was positive for inhibin- α , melan-A, and SF1, demonstrating tissue of adrenal origin. After surgery, plasma glucose level spontaneously returned to normal. However, the patient died on the second post-surgical day due to catastrophic pulmonary embolism.

Conclusion: In this reported case, clinical, hormonal, histological, and immunohistochemical findings confirmed a cortisol and sex hormone-producing ovarian tumor with peritoneal and lymph node metastases, a very rare but important condition to recognize.

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Introduction

It is well known that corticotropin (ACTH)-independent Cushing's syndrome (CS) is rarer than the ACTH-dependent CS (1, 2).

ACTH-independent CS is usually due to benign or malignant tumors located in the adrenal glands (3, 4, 5). However, in exceptional situations, a tumor located far from the adrenal area may synthesize adrenocortical hormones, mimicking perfectly adrenal secretion.

Ectopic tumors secreting cortisol are so rare that they are not discussed in current reviews on adrenocortical tumors in general and even in adrenocortical carcinomas. Among ectopic neoplasms, ovarian tumors secreting cortisol causing overt CS with metastases are exceptional. To the best of our knowledge, there are six reported cases in English literature: five in human beings (6, 7, 8, 9) and

one in a dog (10). Given its rarity, our aim was to describe the first case observed in our practice.

Case report

A 34-year-old female was referred to our unit for CS with psychiatric signs, diabetes mellitus, and lower limb edema occurring 2 months postpartum. Her medical history was unremarkable. During pregnancy, apart from tiredness, the patient denied having any abnormal symptoms. Her baby was delivered at term by Cesarean section weighing 4.3 kg.

Clinical examination showed severe CS with metabolic and androgenic features including facial plethora, bruises, lower limb edema, severe muscular

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Table 1 Hormonal mean values at diagnosis.

Cortisol (ng/mL)	ACTH (pg/mL)	DHEA-S (pg/mL)	17-OHP (nmol/L)	TT (ng/mL)	E₂ (pg/mL)	FSH (U/mL)	LH (U/mL)	PRL (ng/mL)	TSH (μU/mL)	FT₄ (pmol/L)
Before DXM 1990	<10	548	28.8	4.5	124	0.16	0.7	13	0.58	13.8
After 2 mg DXM= 1840										
After 8 mg= 848										
Reference values 50–250	20–46	50–580	0.3–3	0.1–1.2	<50	2.8–11	1.1–11	3–20	0.2–4	9–20

17-OHP, 17-hydroxyprogesterone; ACTH, adrenocorticotropin; DHEA-S, dehydroepiandrosterone sulfate; DXM, dexamethasone; E₂, estradiol; FSH, follicle-stimulating hormone; FT₄, free thyroxine; LH, luteinizing hormone; PRL, prolactin; TSH, thyroid-stimulating hormone; TT, total testosterone.

atrophy, and hirsutism. She weighed 58 kg, height 159 cm (BMI=27.5 kg/m²), and had an increased abdominal girth of 102 cm. Blood pressures varied between 150/90 and 170/100 mmHg. There was a large palpable mass in the right pelvic area. Galactorrhea and skin hyperpigmentation were absent. Hormonal parameters, done through chemiluminescence, confirmed an ACTH-independent CS (Table 1) with high sex hormones (estradiol and testosterone) and 17-OH progesterone. The very high serum cortisol failed to be suppressed by both 2 and 8 mg dexamethasone. Other evaluated hormonal parameters were within the normal range, except for low FSH and LH levels.

Routine analyses showed normal liver and renal function; however, hyperglycemia, mild dyslipidemia, hypokalemia, and a normocytic hypochromic anemia were present (Table 2).

Abdomen ultrasound did not show any adrenal masses. CT scan showed small adrenal glands and a 14 cm heterogeneous tumor in the right pelvic area (Fig. 1) with ascites.

Chest x-ray was unremarkable and echocardiography showed an increase in septal size related to systemic hypertension. Work up for distant metastases was negative.

Table 2 Routine analyses.

Plasma parameters	Patient's values	Normal values
Glucose	267	70–100 mg/dL
Triglycerides	1.61	≤1.5 g/L
HDL cholesterol	0.36	≥0.50
Total cholesterol	1.95	≤2 g/L
Sodium	144	135–145 meq/L
Potassium	2.4	3.5–5 meq/L
Hemoglobin	6.8	11–14 g/dL
Hematocrit	21	35–45%
MCV	94	80–99 fL
MCHC	31	33–37 g/dL

MCHC, mean cell hemoglobin concentration; MCV, mean corpuscular volume or mean cell volume.

In this patient with rapid evolution, lack of skin hyperpigmentation and low plasma ACTH levels suggested ACTH-independent CS. As both adrenals were small in size with no masses, ectopic glucocorticoids production by the large pelvic tumor was suspected.

Tumor markers were normal (CEA: 1.09 ng/mL ($n \leq 10$), AFP: 3.8 IU/mL ($n \leq 10$), and beta HCG: negative), except for Ca 125, which was slightly increased= 52.5 IU/mL ($n=0.1–35$).

At surgery, a malignant process was encountered by a large friable ovarian mass with abnormal lymph nodes and 400 mL hemoperitoneum. The patient underwent total resection with immediate normalization of plasma glucose without any treatment, apart from hydrocortisone given for adrenocortical substitution. On the second postoperative day, the patient died of acute pulmonary embolism.

Macroscopic examination showed a brown lobulated mass measuring 14.5×13.7 cm located in the ovary. Cut sections were heterogeneous with numerous hemorrhage and large necrotic areas.

Histological examination showed an encapsulated tumor within the ovary, but with some areas that had breached the capsule (Fig. 2).

The pathological tissue composed of cells arranged in an endocrine and trabecular aspect with vascular embolism and large necrotic areas, with nests of cells similar in appearance to different layers of adrenocortical gland (Fig. 2). A large part of tumor cells was pleomorphic: some were polygonal, others had a round shape. Their cytoplasm was finely granular. The nuclei were vesicular and hyperchromatic with abnormal mitotic figures. Spongicytic aspects, composed of lipid-laden cells (similar to those of the glomerular zone), with prominent and monstrous nuclei were also observed. The Weiss score was >5.

Immunohistochemical staining was positive for inhibin-α, melan-A, and steroidogenic factor 1 (SF1) (Fig. 3). The positivity was discrete for synaptophysin and

Figure 1

(A) Abdomen CT scan showing two small adrenals (orange arrows). (B) Pelvic CT scan showing a large heterogeneous tumor reaching the parietal wall (red arrows). A full colour version of this figure is available at <http://dx.doi.org/10.1530/EJE-16-0224>.

negative for ACTH, CD 99 (cluster of differentiation 99), cytokeratin AE1/AE3, and calretinin.

Lymph node examination demonstrated that one out of three nodes contained abnormal cells similar to those observed in the ovarian tumor. The peritoneal fluid contained pathological cells.

All these features classified the ovarian tumor as ectopic and poorly differentiated (high grade of malignancy) adrenocortical tumor responsible for ACTH-independent CS. The tumor was considered malignant because of lymph node and peritoneal metastases.

Discussion

Primary or eutopic adrenocortical carcinomas are very rare tumors with an incidence of 0.5–2 per million per year (11). Due to their poor prognosis, they are considered the second most aggressive endocrine malignancy behind anaplastic thyroid cancers.

Adrenocortical neoplasms arising in ectopic locations are extremely rare, and those secreting cortisol are even rarer. Their frequency, incidence and follow-up are totally unknown.

Ovarian localization seems to be exceptional, as to the best of our knowledge; fewer than ten cases have been reported so far in the world literature. Their main characteristics and follow-up are summarized in Table 3.

The first well-documented ovarian carcinoma producing cortisol was reported by Marieb in 1987 (6). On the pathological point, this type of tumor was classified as a lipid cell tumor of the ovary, as ovarian lipid tumors are commonly associated with androgenic and estrogenic effects and less frequently with other endocrinological abnormalities (8).

In our case, there is no doubt about the overproduction of cortisol by the tumor located in the ovary, as ACTH was very low, the adrenal glands were small and tumor free, and with ectopic adrenal tissue within the ovary. The ectopic adrenal tissue was

Figure 2

(A) Tumor tissue surrounded by a layer of normal ovarian tissue. Notice the numerous vascular embolisms. (B) High cellular density with granular, hyperchromatic and giant nuclei. (C) Abnormal mitoses. A full colour version of this figure is available at <http://dx.doi.org/10.1530/EJE-16-0224>.

Figure 3

Immunohistochemical staining showing positivity to melan-A (A) and SF1 (B), and negativity to ACTH (C). A full colour version of this figure is available at <http://dx.doi.org/10.1530/EJE-16-0224>.

confirmed by immunostaining positivity to inhibin- α , melan-A, SF1, and synaptophysin. Although distant metastases were absent, the large size, histopathological characteristics, and presence of lymph node and peritoneal metastases defined a malignant process. The negativity of tumor markers does not argue at all against malignancy, especially in tumors secreting cortisol, as glucocorticoid excess inhibits tumor markers (12).

Overt or subclinical CS (13) due to ovarian tumor is an exceptional phenomenon. Only two types of ovarian tumors may be responsible for CS: the first group secretes ACTH or an ACTH-like substance generating paraneoplastic CS, where both adrenals are large as stimulated by an ectopic ACTH, and the second group, which is uncommon, synthesizes some or most adrenocortical steroids that inhibit pituitary corticotropin hormone. In this situation, the adrenal glands are usually atrophic and non-functioning as demonstrated by postmortem studies (Table 3).

Most ovarian tumors secreting adrenal hormones reported in the literature are considered benign (14) probably because histological examination is generally unable to give the certainty of malignancy, or because they are published after a short follow-up period.

Searching Pub Med and Google scholar, we found only six malignant intra-ovarian tumors secreting cortisol with proven metastases. Five were described in humans (6, 7, 8, 9), and one in a dog (10). Our case is the sixth human case.

The mechanism of adrenal tumors arising from the ovary is still debated. One theory is that these tumors originate from transformation of the adrenocortical embryonic remnants that broke off during adrenal migration or descent with gonadal cells (15). For the second theory, ectopic adrenal adenomas/carcinomas may result from mutation of ovarian tissue and its steroid enzymes and/or acquisition of aberrant receptors (16) that are stimulated not by ACTH but by LH and/or HCG, especially during pregnancy (which may be the case in our patient). This pathological situation allows the ovary to synthesize adrenal hormones.

For the first theory, adrenal embryonic remnants are well known, as they were demonstrated for the

first time in 1740 by Schelter and then confirmed by Marchand in 1843 (17). Necropsy studies revealed that ectopic adrenal tissue is frequently found in newborns and children, but it is less common in adults. Adrenal aberrant tissue can be situated anywhere, especially in the pathway of the genital tract migration: celiac trunk, ovaries, testes, spermatic cord, and kidneys (18). Although very rare, normal, hyperplastic, or tumorous adrenal tissue has been observed in unusual sites such as pulmonary area, liver, stomach, brain, and spinal cord (19).

Tumors arising from adrenal remnants are usually scarce. They are often benign (20) and non-functioning. They are discovered incidentally, or after surgery for inguinal hernia (21), pathology of the testis or spermatic cord (22), or at autopsy studies. However on occasion, these tumors may be functional (13, 14, 20) and produce glucocorticoids, androgens (19), or mineralocorticoids (23).

Functioning, benign or malignant, ectopic adrenocortical tumors may also arise from the kidneys (24) or near it (17, 18), near the adrenal gland, in the retro-hepatic space (25), in the testis (26), placenta (27), large intestine (28), or in the ovary (7, 8, 9, 10, 13).

The prognosis of ectopic ovarian tumors secreting cortisol seems to be worse in comparison with eutopic tumors, with mean survival of 8 months (0–18) for the six ovarian tumors secreting cortisol (Table 3) vs 31.5 months for eutopic adrenal carcinomas reported by Bilimoria *et al.* (29). When the tumor appears and/or overgrows during pregnancy, as in the reported case, the prognosis is the worst. Rapid progression during pregnancy or in the early postpartum period can be explained by an increased sensitivity of ovarian receptors to LH, HCG, or to aberrant, illicit, or inappropriate membrane hormone receptors as postulated for eutopic adrenocortical tumors (16).

The treatment of ectopic adrenocortical carcinoma does not differ from that of eutopic tumors. Surgery is the cornerstone, but mitotane and ketoconazole alone or with metyrapone (30) can be useful as in eutopic disease. Classical or targeted chemotherapy may also be used. However, the results are generally poor because of the

Table 3 Malignant ovarian tumors secreting cortisol published from 1987 in Pub Med and Google Scholar including current case.

Cases	Age (years)	Clinical features	Hormones	ACTH	Radiological aspect	Surgery	Pathological examination	Follow-up	Autopsy
Marieb <i>et al.</i> (1983) (6)	35	- Cushing's syndrome - Severe hirsutism - Peripheral edema - Amenorrhea - Mass in lower abdomen - Blood pressure=150/80 mmHg	Increased: - Urinary and plasma cortisol - Urinary 17-hydroxysteroids and 17-ketosteroids - Cortisol levels from the venous effluents higher than that in peripheral plasma Low -FSH and LH Increased cortisol	NI low = 28 pg/mL (20–100)	Bilateral ovarian tumors No adrenal masses Adrenals normal in size	Bilateral ovarian tumors Implants in the omentum cul-de-sac, and mesentery Normal adrenals	Right ovarian carcinoma=15cm Left one=8cm Extensive metastases Classification: Ovarian tumor of the malignant lipid cell group	Steroids' normalization then relapsing Chemotherapy failure Death after 17 months	Extensive tumor of the pelvis Extensive abdomen metastases Atrophic adrenal
Young <i>et al.</i> (1987) (7)	48	- Cushing's syndrome - Mild virilization - Blood pressure: 180/110 mmHg - Diabetes mellitus	-FSH and LH Increased cortisol	Undetectable	Right adrenal mass	Ovary replaced by a yellow brown tumor Brown yellow nodules on visceral and parietal peritoneum greater omentum and diaphragm	steroid cell (lipid cell) type abdomen metastases	Normalization of cortisol and blood pressure Relapsing at 3 months Chemotherapy failure Death at 10th month Death at 6 months	
52		- Cushing's syndrome - Hirsutism - High blood pressure for 17 years (170/100) - Diabetes mellitus	Increased - Plasma and urinary cortisol - Urinary 17-ketosteroids and 17-hydroxysteroids	Normal	Normal venographic studies of the adrenal glands	Large right ovary Extensive metastases to the omentum	Large ovary of 135g (9 x 7 x 5cm) with intact external surface Malignant tumor The omental lesions with the same aspect		
Donovan <i>et al.</i> (1993) (8)	66	- Abdominal-pelvic mass - Legs edema - Diabetes mellitus - Cushing's syndrome + hypertension appeared after surgery	Hypokalemia Increased - CA125 - Plasma and urinary cortisol - DHEA-S - Testosterone - Androstenedione High: - Plasma and free urinary cortisol - Testosterone - Estradiol - 17-OHP Low: FSH and LH High: - Cortisol - Estradiol - Testosterone - 17-OHP	Normal	No adrenal masses No ovarian tumor, but venous catheter showed a left ovarian source	8 cm multi-lobulated right ovarian tumor with multiple adherent loops of the small bowel	Ovarian steroid cell tumor Metastases: the small and large bowels, the omentum, and liver	Ketoconazole and classical chemotherapy failure Death at 4 months	Extensive tumor arriving to the right lower lung Bilateral adrenal atrophy
Elhadd <i>et al.</i> (1996) (9)	73	- Rapid Cushing's syndrome - Virilism (clitoromegaly + severe hirsutism) - Hypertension - 220/120 mmHg	High: - Plasma and free urinary cortisol - Testosterone - Estradiol - 17-OHP Low: FSH and LH High: - Cortisol - Estradiol - Testosterone - 17-OHP	Low <10 pg/mL	No adrenal masses No ovarian tumor, but venous catheter showed a left ovarian source	Left ovarian tumor Atrophy of right ovary	2 x 2 x 1 cm lipid cell tumor, but no definite evidence of malignancy	No adjuvant treatment - After 12 months: recurrence and peritoneal metastases	
Our case (2016)	34	- Cushing's syndrome - Psychiatric problems - Hirsutism - Hypertension - Diabetes mellitus - Legs' edemas - Pelvic mass	High: - Cortisol - Estradiol - Testosterone - 17-OHP	Low <10 pg/mL	No adrenal masses small adrenals Large ovarian tumor Ascites	- Ovarian tumor: - Hemoperitoneum - Lymph nodes	- Ovarian tumor 14 x 13 cm - Peritoneum and lymph node metastases	No adjuvant treatment Death day 2 postoperatively due to pulmonary embolism	

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aggressive and poorly differentiated character of ectopic adrenocortical tumors.

The prognosis is poor as death may be caused by metabolic disorders such as severe hypokalemia and ketoacidosis. However, the most threatening causes are metastatic disease and thromboembolism. The later occurs frequently in CS in general (31), and especially in adrenocortical tumors because of the hypercoagulable state due to an increase in pro-coagulant factors (32).

Conclusion

In our observation, ACTH-independent Cushing's syndrome with small adrenals was suggestive of an ectopic tumor producing glucocorticoids and sex hormones. Abdomen CT scan and surgical exploration revealed an ovarian primary mass with metastatic spread. Histological, immunohistochemical staining, and normalization of glucose metabolism just after ovarian tumor resection support glucocorticoids and other hormone secretion from the ovary.

Although this phenomenon is exceptional, gynecologists, endocrinologists, and pathologists should be aware that ectopic adrenocortical tumors might arise in ovaries. Morphological features combined with immunophenotype (melan-A, inhibin- α , and synaptophysin) and ultrastructural findings are essential in ruling out other forms of ovarian tumors. High mortality is associated with this disease.

Declaration of interest

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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References

- Lahera Vargas M & da Costa CV. Prevalence, etiology and clinical findings of Cushing's syndrome. *Endocrinología y Nutrición* 2009 **56** 32–39. (doi:10.1016/S1575-0922(09)70191-3)
- Bhansali A, Walia R, Rana SS, Dutta P, Radotra BD, Khandelwal N & Bhadada SK. Ectopic Cushing's syndrome: experience from a tertiary care centre. *Indian Journal of Medical Research* 2009 **129** 33–41.
- Terzolo M, Bovio S, Pia A, Reimondo G & Angeli A. Management of adrenal incidentaloma. *Best Practice & Research: Clinical Endocrinology & Metabolism* 2009 **23** 233–243. (doi:10.1016/j.beem.2009.04.001)
- Pollack RP & Brett E. ACTH-independent Cushing's syndrome presenting during pregnancy. *Endocrine Practice* 2009 **6** 1–11.
- Louiset E, Gobet F, Libé R, Horvath A, Renouf S, Cariou J, Rothenbuhler A, Bertherat J, Clauser E, Grise P *et al.* ACTH-independent Cushing's syndrome with bilateral micronodular adrenal hyperplasia and ectopic adrenocortical adenoma. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 18–24. (doi:10.1210/jc.2009-0881)
- Marieb NJ, Spangler S, Kashgarian M, Heimann A, Schwartz ML & Schwartz PE. Cushing's syndrome secondary to ectopic cortisol production by an ovarian carcinoma. *Journal of Clinical Endocrinology and Metabolism* 1983 **57** 737–740. (doi:10.1210/jcem-57-4-737)
- Young RH & Scully RE. Ovarian steroid cell tumors associated with Cushing's syndrome: a report of three cases. *International Journal of Gynecological Pathology* 1987 **6** 40–48. (doi:10.1097/00004347-198703000-00005)
- Donovan JT, Otis CN, Powell JL & Cathcart HK. Cushing's syndrome secondary to malignant lipid cell tumor of the ovary. *Gynecologic Oncology* 1993 **50** 249–253. (doi:10.1006/gyno.1993.1202)
- Elhadd TA, Connolly V, Cruickshank D & Kelly WF. An ovarian lipid cell tumor causing virilization and Cushing's syndrome. *Clinical Endocrinology* 1996 **44** 723–725. (doi:10.1046/j.1365-2265.1996.693515.x)
- Yamini B, Vandenbrink PL & Refsal KR. Ovarian steroid cell tumor resembling luteoma associated with hyperadrenocorticism (Cushing's disease) in a dog. *Veterinary Pathology* 1997 **34** 57–60. (doi:10.1177/030098589703400112)
- Yokoyama H, Adachi T, Tsubouchi K, Tanaka M & Sasano H. Non-functioning adrenocortical carcinoma arising in an adrenal rest: immunohistochemical study of an adult patient. *Tohoku Journal of Experimental Medicine* 2013 **229** 267–270. (doi:10.1620/tjem.229.267)
- Karlan BY, Amin W, Casper SE & Littlefield BA. Hormonal regulation of CA125 tumor marker expression in human ovarian carcinoma cells: inhibition by glucocorticoids. *Cancer Research* 1988 **48** 3502–3506.
- Diab DL, Faiman C, Siperstein AE, Grossman WF, Rabinowitz LO & Hamrahian AH. Virilizing ovarian Leydig cell tumor in a woman with subclinical Cushing syndrome. *Endocrine Practice* 2008 **14** 358–361. (doi:10.4158/EP.14.3.358)
- Adeyemi SD, Grange AO, Giwa-Osagie OF & Elesha SO. Adrenal rest tumour of the ovary associated with isosexual precocious pseudo-puberty and Cushingoid features. *European Journal of Pediatrics* 1986 **145** 236–238. (doi:10.1007/BF00446077)
- Vassiliadi D & Tsagarakis S. Unusual causes of Cushing's syndrome. *Arquivos Brasileiros de Endocrinologia & Metabologia* 2007 **51** 1245–1252. (doi:10.1007/BF00446077)
- Lacroix A, Ndiaye N, Tremblay J & Hamet P. Ectopic and abnormal hormone receptors in adrenal Cushing's syndrome. *Endocrine Reviews* 2001 **22** 75–110. (doi:10.1210/er.22.1.75)
- Leibowitz J, Pertsemlides & Gabrilove JL. Recurrent Cushing's syndrome due to recurrent adrenocortical tumor fragmentation or tumor ectopic adrenal tissue? *Journal of Clinical Endocrinology and Metabolism* 1998 **83** 3786–3789. (doi:10.1210/jcem.83.11.5260)
- Ayala AR, Basaria S, Udelsman R, Westra WH & Wand GS. Corticotrophin independent Cushing's syndrome caused by an ectopic adrenal adenoma. *Journal of Clinical*

- Endocrinology and Metabolism* 2000 **85** 2903–2906. (doi:10.1210/jc.85.8.2903)
- 19 Skórka A, Moszczyńska E, Kot K, Roszkowski M, Jurkiewicz E, Grajkowska W, Pronicki M, Pilecki O & Szalecki M. Ectopic virilising adrenocortical tumour in the spinal region in an 8 year-old boy: a case report and review of the literature. *Italian Journal of Pediatrics* 2015 **41** 62. (doi:10.1186/s13052-015-0169-8)
 - 20 Cariou J, Grise P, Caremel R, De Fourmestreaux A & Albouy B. Treatment by iterative endoscopic retroperitoneal adrenalectomy of an ectopic adrenal adenoma revealed by Cushing's syndrome. *Progrès en Urologie* 2008 **18** 68–70. (doi:10.1016/j.purol.2007.12.004)
 - 21 Vuong P, Bazza F, Houssa-Vuong S, Baviera E & Janzen J. The ectopic adrenal tissue in an inguinal hernia. *Schweizerisches Medizin-Forum* 2006 **6** 327–328.
 - 22 Chacar H, Gebran S, Hajje MJ, Bedoyan Z & Jalbout N. Aberrant adrenocortical tissue along the spermatic cord in a 2 months old boy. *Revue Medicale Libanaise* 2003 **15** 121–122.
 - 23 Todesco S, Terribile V, Borsatti A & Mantero F. Primary aldosteronism due to a malignant ovarian tumor. *Journal of Clinical Endocrinology and Metabolism* 1975 **41** 809–189. (doi:10.1210/jcem-41-5-809)
 - 24 Baydar D & Aydin O. Confusing cases: clear cell but not renal cell lesions in kidney. *Pathology International* 2008 **58** 713–717. (doi:10.1111/pin.2008.58.issue-11)
 - 25 Ney RL, Hammon W, Wright L, Davis WW, Acker J & Barter FC. Studies in a patient with an ectopic adrenal tumor. *Journal of Clinical Endocrinology and Metabolism* 1966 **26** 299–304. (doi:10.1210/jcem-26-3-299)
 - 26 Jain SH, Sadow PM, Nosé V & Dluhy RG. A patient with ectopic cortisol production derived from malignant testicular masses. *Nature Clinical Practice Endocrinology & Metabolism* 2008 **4** 695–700. (doi:10.1038/ncpendmet0985)
 - 27 Labarrere CA, Caccalo D, Telenta M, Althabe O & Gutman R. A nodule of adrenocortical tissue within a human placenta: light microscopic and immunocytochemical findings. *Placenta* 1984 **5** 139–143. (doi:10.1016/S0143-4004(84)80057-0)
 - 28 Bal A, Adhya AK & Manhadjar JK. Ectopic adrenal rest in the wall of the large intestine. *Indian Journal of Pathology and Microbiology* 2009 **52** 130–131. (doi:10.4103/0377-4929.44980)
 - 29 Bilimoria KY, Shen WT, Elaraj D, Bentrem DJ, Winchester DJ, Kebebew E & Sturgeon C. Adrenocortical carcinoma in the United States: treatment utilization and prognostic factors. *Cancer* 2008 **113** 3130–3136. (doi:10.1002/cncr.23886)
 - 30 Corcuff JB, Young J, Masquefa-Giraud P, Chanson P, Baudin E & Tabarin A. Rapid control of severe neoplastic hypercortisolism with metyrapone and ketoconazole. *European Journal of Endocrinology* 2015 **172** 473–781. (doi:10.1530/EJE-14-0913)
 - 31 Van der Pas R, Leebeek FW, Hofland LJ, de Herder WW & Feelders RA. Hypercoagulability in Cushing's syndrome: prevalence, pathogenesis and treatment. *Clinical Endocrinology* 2013 **78** 481–488. (doi:10.1111/cen.2013.78.issue-4)
 - 32 Aung SY, Parentea P & McKendricka J. Pulmonary embolism as an initial presentation of adrenocortical carcinoma. *World Journal of Oncology* 2014 **5** 149–152. (doi:10.5306/wjco.v5.i2.149)

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