A retroperitoneal ectopic adrenocortical carcinoma in a patient with Cushing's syndrome

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Introduction

Ectopic adrenocortical carcinoma is an extremely rare tumour of unknown incidence and prognosis, arising from ectopic adrenal rest tissue (nests of adrenal cells distant from the standard anatomical location of the adrenal glands) (Tsai et al, 2021). Ectopic adrenal rest tissue is derived from detached cortical tissue when medullary cells penetrate into the cortical primordium or from multiple primordia, often along the route of gonadal descent or migration path of the adrenal cortex (Falco et al, 2021). Ectopic adrenocortical carcinoma has been reported in the ovary (Tsai et al, 2021), testis, pelvis, retroperitoneum, kidney, liver, spinal cord (Cornejo et al, 2017) and colonic mesentery (See et al, 2022). This article presents a case of a retroperitoneal ectopic adrenocortical carcinoma, initially identified incidentally on an ultrasound of the abdomen and successfully treated with surgery and medical therapy.

Case report

A 55-year-old woman with polycystic ovary syndrome presented with insomnia and facial hirsutism approximately 6.5 years ago. These were initially considered to be consistent with stress and polycystic ovary syndrome. However, following this initial presentation, she rapidly developed more concerning symptoms, including 5–6 kg weight gain, easy bruising, difficulty in climbing the stairs with recurrent falls, alopecia, acne and new-onset hypertension. On examination, she had a dorsocervical fat pad, moon facies, facial plethora and hirsutism, proximal myopathy, bruising, centripetal obesity and lower limb oedema. Her blood pressure was 145/92 mmHg. This prompted investigations to exclude hypercortisolaemia.

The patient's random 9 am cortisol level was 867 nmol/litre (normal range 145–619 nmol/litre). Two 24-hour urinary cortisol levels were elevated: >4138 and 3076 nmol/24 hours (normal range 57.7–806.8 nmol/24 hours). Serum cortisol level following a low-dose dexamethasone suppression test was unsuppressed: 1482 nmol/litre (normal range <50 nmol/litre). Adrenocorticotropic hormone was <5 pg/ml (normal range 10–485 pg/ml). Serum metanephrine levels were normal. Total testosterone level was high (6.73 nmol/litre).

An ultrasound of the abdomen, performed to investigate the mildly deranged liver function tests, revealed two closely attached 6 cm hypoechoic masses in the right hypogastrium, which were thought to indicate either a lymphoma or a carcinoid tumour. A computed tomography scan of the trunk was performed, which showed a lobulated 5.04x6.96x5.55 cm soft tissue mass in the right retroperitoneal space (Figure 1). Multiple collateral vessels fed into the mass, which had three tiny flecks of calcifications. Visible intra-abdominal organs and lymph nodes were normal. The mass was thought to be a sarcoma or lymphoma, so a biopsy was performed. Despite being consistent with an ectopic adrenocortical rest, a superimposed adrenocortical neoplasm (benign or malignant) could not be excluded.

She was started on metyrapone 250 mg twice daily in view of adrenocorticotropic hormone-independent Cushing's syndrome, and bumetanide 1 mg daily for lower limb oedema and hypertension. She was also taking metformin 500 mg twice daily for polycystic ovary syndrome. The tumour was excised laparoscopically. Histology (Figure 2) revealed an adrenocortical carcinoma. Mitotic activity was >20 per 50 high-power fields. Ki67 index was about 25%. It was difficult to assess completeness of excision as the tumour had a disrupted connective tissue capsule.

Postoperatively, her serum cortisol level was low (20 nmol/litre) and she was treated with hydrocortisone. Since mitotane was unavailable locally, she received six cycles of etoposide and cisplatin, with regular computed tomography scanning of her trunk (3-monthly for the first 2 years, 6-monthly for the next 3 years and annually for 5–10 years, unless recurrence was detected). The patient has remained disease-free to date.

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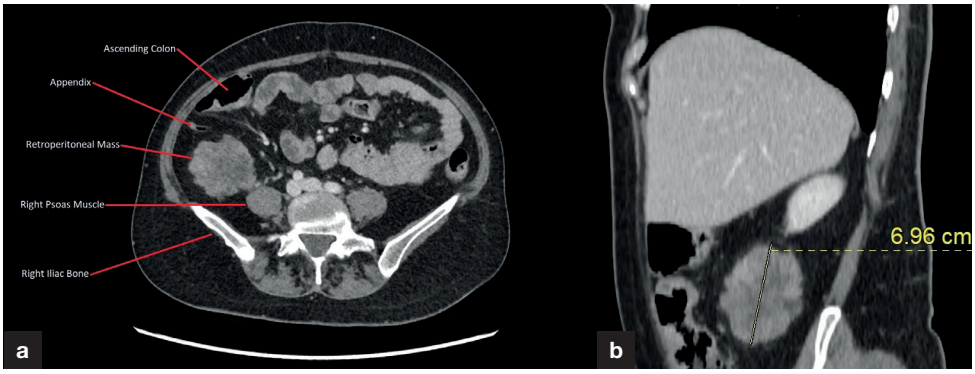

Figure 1. Computed tomography scan demonstrating (a) coronal view of the soft tissue mass in relation to surrounding structures, situated behind the ascending colon, below the right kidney and lateral to the psoas muscle. The mass demonstrated mostly homogeneous peripheral enhancement, while its centre was relatively void of contrast, which is non-specific for delayed contrast uptake or central necrosis. b. Sagittal view illustrating the craniocaudal length of the mass.

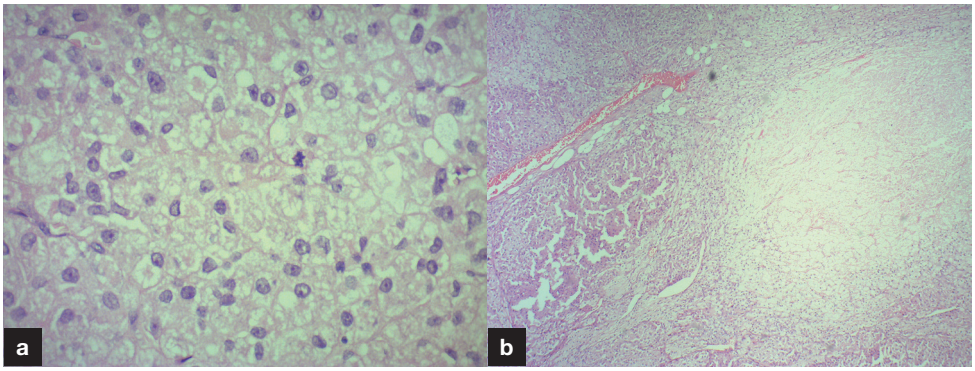

Figure 2. Histology of the resected mass demonstrating (a) haematoxylin and eosin staining on high power illustrating pleomorphic nuclei and mitotic figures and (b) marked tumour necrosis with a nest of viable cells adjacent to an area of necrosis.

Discussion

Table 1 outlines the differential diagnosis of a retroperitoneal mass. Since the tumour was devoid of fat, without nodal involvement and located away from smooth muscle, it was unlikely to be a fat-containing tumour, leiomyosarcoma or lymphoma (Mota et al, 2018). A neurogenic tumour such as a paraganglioma was possible, especially because of homogenous contrast uptake with foci of low attenuation/necrosis and the presence of calcifications (Banks, 2005). However, paragangliomas are commonly associated with raised serum levels of metanephrines. Sarcoma, particularly undifferentiated pleiomorphic sarcoma, could also have been possible given the potential presence of necrotic tissue (Mota et al, 2018). Although ectopic adrenocortical tumours are not mentioned as part of the differential diagnosis of retroperitoneal tumours, these should be considered, especially in patients with hormonal excess. Functionality has been reported in 62% of ectopic adrenocortical carcinomas, and cortisol production in 54% (Cornejo et al, 2017).

Since the radiological appearance was uncertain and lymphoma is primarily treated with chemotherapy and/or radiotherapy, a biopsy was recommended. However, on biopsy it is difficult to differentiate malignant from benign adrenocortical tumours (Fassnacht et al, 2018). Furthermore, biopsy can result in seeding of malignant cells, albeit the risk of dissemination is low (Williams et al, 2014).

European guidelines suggest use of adjuvant mitotane to treat tumours at high risk of recurrence (Fassnacht et al, 2018). This tumour was considered to be high risk in view of a high Ki-67 index and a disrupted connective tissue capsule, making complete excision uncertain. Moreover, autonomous cortisol secretion is associated with increased mortality (Vanbrabant et al, 2018). Etoposide and cisplatin have mostly been studied in phase II trials in combination with mitotane, in patients with advanced adrenocortical

Table 1. Differential diagnosis of a retroperitoneal mass in adults	
Fat containing	Teratoma
	Liposarcoma
	Lymphangioma
	Extra-adrenal myelolipoma
	Extramedullary haematopoesis
	Cystic lymphangioma
Necrotic lesion	Pleiomorphic liposarcoma
	Leiomyosarcoma
	Undifferentiated pleiomorphic sarcoma
Mantle zone growth pattern	Lymphoma
	Retroperitoneal fibrosis
Neurogenic tumour	Paraganglioma
	Neurofibroma
	Schwannoma
Fibroblastic tumour	Solitary fibrous tumour
	Myxofibrosarcoma

Learning points

- Symptoms like facial hirsutism and weight gain can be easily mistaken for polycystic ovary syndrome. However, symptoms like easy bruising, facial plethora, proximal myopathy, osteoporosis and new-onset hypertension are more specific for Cushing's syndrome and should prompt further investigations.
- Rapid onset of symptoms of Cushing's syndrome and androgen excess should point towards a more sinister cause, ie malignancy.
- Knowledge of the radiological features of retroperitoneal tumours in conjunction with clinical and biochemical data can help to narrow the differential diagnosis. However, a biopsy may be required for histological diagnosis to guide management and decision making.
- Biopsy will disrupt the tumour capsule and can lead to tumour tracking and recurrence along the tract, requiring regular radiological surveillance.
- Ectopic adrenocortical tumours should be included in the differential diagnosis of primary retroperitoneal tumours, especially in patients with adrenocorticotropic hormone-independent Cushing's syndrome or androgen excess.

carcinoma. Adjuvant platinum-based chemotherapy reduced recurrence and mortality risk by approximately 65% and 70% respectively (Kimpel et al, 2021). Because mitotane was locally unavailable, adjuvant cisplatin and etoposide were used, and the patient remained disease-free approximately 6.5 years later. These drugs may offer an alternative to treat high-risk adrenocortical carcinomas if mitotane is unavailable.

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