CASE REPORT

Delayed presentation of a virilising, pure testosterone-secreting adrenocortical carcinoma with coexistent composite myelolipoma and a venous thrombus extending to the heart

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Accepted 20 December 2017

SUMMARY

A 40-year-old normotensive woman presented with abnormal facial hair for 4 years and amenorrhoea for 13 years. Hormonal, biochemical and haematological evaluation showed isolated elevation of serum testosterone and free testosterone. Her follicle-stimulating hormone and luteinising hormone were in the premenopausal range. Until recently she had reconciled to early 'menopause' and visited beauty clinics but never sought medical evaluation. Imaging revealed an enhancing left adrenal mass with fat densities and venous thrombus extending through the inferior vena cava to a 7 cm mass in the right atrium. She underwent left kidney-preserving surgery utilising hypothermic cardiopulmonary bypass with early clamping of the pulmonary artery without circulatory arrest. Histology showed adrenocortical carcinoma with composite incidental myelolipoma and neoplastic thrombus. At 2 months, testosterone has normalised and she is doing well. Isolated testosterone-secreting adrenocortical carcinoma with massive venous thrombus is rare as is coincidental composite macroscopic myelolipoma.

BACKGROUND

Hirsutism is a common problem affecting about 10% of women.¹ Polycystic ovarian disease is the the most common cause responsible for close to three-fourths with tumours accounting for only 0.3% of 2601 pooled patients in a recently published guideline.¹

However, many women consult a beautician rather than a physician.

Our 40-year-old patient had obvious facial hair growth for 4 years for which she was advised laser therapy by a cosmetic clinic. She also had what she regarded as 'early menopause' at 27 years that was never evaluated but in retrospect had biochemical features consistent with secondary amenorrhoea due to a testosterone-secreting tumour.

Other unusual aspects of this patient were the extent of the venous thrombus despite a functioning adrenal tumour, the pure testosterone-secreting nature of the adrenocortical carcinoma and the coincidental composite macroscopic myelolipoma. Each of these three have been unusual enough to constitute individual case reports on their own merit.

Notwithstanding the late presentation she was managed surgically successfully and given the documented indolent course may carry an unusually good prognosis.

CASE PRESENTATION

A 40-year-old woman noticed abnormal facial hair growth for the last 4 years. She had sought treatment to remove the hair from a cosmetic clinic and was advised laser treatment for facial hair but was not advised a medical consultation. She consulted a physician 3 weeks ago when a functioning left adrenal mass was identified and she was referred for management. On presentation, she had no complaint other than the obvious facial hair. She had no recent weight gain, muscle weakness, cramps, headache, sweating, tremors, visual disturbances, irritability or anxiety. She had height 160 cm, weight 56 kg, blood pressure 110/74 mm Hg and pulse 80/min. Physical examination was unremarkable except for the facial hair growth involving primarily the upper lip, chin and lower part of both cheeks (figure 1). She had a modified Ferriman Gallwey (mFG) score of 9 (upper lip 3, chin 3, lower abdomen 2, lower back 1). There was no acne, skin stria, baldness, oedema or abnormality of bodily habitus. Abdominal and genital examination was normal. There was no clitoromegaly.

She has two children but had amenorrhoea for the last 13 years that was never evaluated.

INVESTIGATIONS

On biochemical evaluation she was noted to have elevation of serum testosterone 5.6 ng/mL (<0.8 ng/mL) and free testosterone 18 pg/mL (<4 pg/mL) but normal dehydroepiandrosterone (DHEA) 1.0 µg/mL (<3.6 µg/mL). Serum and urinary cortisol, adrenocorticotrophic hormone, urinary metanephrines, 17-ketosteroids, thyroid-stimulating hormone, prolactin, glucose, creatinine, bilirubin, liver enzymes and serum electrolytes were all within normal range. The follicle-stimulating hormone (FSH) (7.4 mIU/mL), luteinising hormone (LH) (2.3 mIU/mL) and estradiol (82 pg/mL) were consistent with secondary amenorrhoea due to a testosterone-secreting tumour.

To cite: Sharma RM, Sinha S, Kishan HB, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-223117

Figure 1 Clinical photograph showing pigmented hair growth over the chin (score 3) and upper lip (score 3). The maximum score of 4 implies hair growth equivalent to that in a hairy male.

A triphasic 500-slice CT scan of the abdomen showed a left adrenal mass 3.9 cm size with two distinct hypodense areas with density of -50 , consistent with fat (figure 2 CT plain). Arterial phase showed patchy enhancement with washout in venous phase leaving a heterogeneous isointense to a hypointense lesion replacing the entire left adrenal gland (figure 3 intravenous contrast CT). There was a long thrombus extending through the left renal vein into the inferior vena cava and right atrium. The left kidney was functioning normally with collateral circulation via the engorged left gonadal vein (figure 4).

2D Echocardiography showed a 7 cm right atrial mass with a normal ejection fraction.

DIFFERENTIAL DIAGNOSIS

The clinical practice guideline on hirsutism and androgen excess notes five important causes of hirsutism.¹ These are polycystic ovarian disease, idiopathic hyperandrogenism, idiopathic hirsutism, non-classic congenital adrenal hyperplasia and androgen-secreting tumours. Concomitant secondary amenorrhoea for 13 years is only consistent with the latter two and the hormonal profile excluded all but the last cause.

Figure 2 Plain CT of the abdomen, axial section showing a left adrenal mass (arrow) with two distinct hypodense areas of with a 50 HU density consistent with fat.

Figure 3 CT scan of the abdomen with intravenous contrast showing contrast enhancement in the arterial phase with uneven washout in the venous phase leaving heterogeneous isodense and hypodense areas. The entire adrenal gland is replaced by a tumour.

Myelolipoma was a possibility going exclusively by imaging in view of the fat densities seen within the mass. However, other clinical, biochemical and imaging features were not consistent with myelolipoma. Myelolipomas are almost always metabolically inactive and do not produce a venous thrombus.²

TREATMENT

Surgery was performed in the supine position with transoesophageal echocardiography monitoring (video 1). After placing a cannula into the inferior vena cava through the right femoral vein the abdomen was explored by a midline laparotomy. There was no evidence of metastasis. The entire bowel was mobilised to expose the inferior vena cava, aorta and their branches in the retroperitoneum (figure 5). Renal vessels were dissected and

Figure 4 Coronal reconstruction image showing a left adrenal mass 3.9 cm $\times$ 3.5 cm $\times$ 3.2 cm with tiny calcifications and macroscopic fat. A large venous thrombus can be seen extending through the left adrenal vein, left renal vein and inferior vena cava into the right atrium. The left kidney can be seen to enhance normally similar to the right one with a grossly engorged left gonadal vein representing collateral circulation.

Video 1 Intraoperative transoesophageal echocardiographic monitoring was carried out throughout the surgery. The large atrial tumour thrombus can be seen playing 'tag' with the tricuspid valve in a macabre dance. Early clamping of the pulmonary artery is a critical step in avoiding embolism.

taped on both sides as was the infrarenal inferior vena cava. On the left side, a tape was placed between the renal vein–gonadal vein segment (the collateral maintaining kidney viability) and the distal renal vein–adrenal vein segment. The left adrenal was dissected completely, left adrenal vein ligated and specimen removed. Limited mobilisation of the liver was performed in preparation for opening the inferior vena cava. At this stage, the heart was approached by midline sternotomy.

The standard cardiopulmonary bypass procedure was performed with hypothermia 24°C and reduced flow of 1.7L/min but no circulatory arrest. Additional pulmonary artery clamping was performed to avoid embolisation of the thrombus.

The renal vessels and infrarenal vena cava were clamped, the inferior vena cava was opened by a midline incision and the thrombus was extracted. There was no vascular wall invasion and the entire long thrombus up to the tricuspid valve could be extracted intact from the abdominal end (figure 6). A separate incision was given on the renal vein with removal of the previously placed ligature over the adrenal stump. All remaining thrombus was removed. The inferior vena cava and right atrium

Figure 5 Intraoperative clinical photograph showing venous anatomy and thrombus (the bluish discolouration of the left renal vein and suprarenal inferior vena cava).

Figure 6 The specimen showing left adrenal and the long venous thrombus extracted intact. The cardiac end of the thrombus had a 'snail-head' shape and was smooth. There was no invasion of the venous wall.

were flushed to ensure that there was no residual thrombus and the vena cava and left renal vein was closed using 5–0 prolene sutures and the clamps over the vessels released (figure 7).

Standard closure was performed. Cell-saver suction was used to minimise blood loss. One unit of packed red blood cells was used during the surgery. There was satisfactory urine output through the procedure and the patient was extubated 3 hours after surgery.

OUTCOME AND FOLLOW-UP

Her subsequent recovery was uneventful and she was discharged on the sixth postoperative day. Follow-up 2D echocardiography and chest X-ray were satisfactory at discharge. She is doing well at 1 month. Her serum testosterone level is now normal (0.4 ng/mL).

Histopathology showed a 4.3×4.0×2.8 cm well-encapsulated adrenocortical carcinoma with sheets of neoplastic round cells having mildly pleomorphic nuclei and abundant eosinophilic cytoplasm (figure 8). There were no mitotic figures nor capsular invasion or cellular pleomorphism. Tumour cells displayed a compact cytoplasm and some areas of necrosis consistent with a

Figure 7 Intraoperative photograph showing venous structures after removal of thrombus and closure of all venotomies. Note the dramatic reduction in the left renal vein diameter. IVC, inferior vena cava.

Figure 8 Histopathology of the adrenal tumour showing adrenocortical carcinoma and intimately associated composite myelolipoma. The adipose tissue (A) and marrow elements (B) are juxtaposed with carcinoma composed of sheets of cells with uniform nuclei and compact cytoplasm (C). Seen in 20× using H&E stain. Inset (D) in the right lower corner showing a high-power view of tumour exhibiting uniform nuclei with compact cytoplasm (40× using H&E stain).

Weiss score of 3. On immunohistochemistry, tumour cells were positive for inhibin and melan-A (figure 9). Focal mild positivity for AE1/AE3 was seen. Chromogranin and calretenin were negative. The vena cava thrombus measured 18.5 cm, intact, and was composed of similar neoplastic tissue mandating a diagnosis of carcinoma, although low grade (figure 10). The mass also showed foci of adipose tissue with lipomatous and myeloid cells consistent with incidental composite myelolipoma.

DISCUSSION

There are several unusual features about this patient that merit discussion.

This woman noticed prominent pigmented facial hair growth for 4 years but sought help from a beauty clinic rather than a physician. She was advised laser hair removal but no evaluation for a cause for her hirsutism. A reassuringly rapid diagnosis was made once she visited a physician despite residing in a small town. Clinical practice guidelines on hirsutism recommend

Figure 9 Immunohistochemistry showing positivity for inhibin (A) and melan-A (B).

Figure 10 Venous thrombus composed of tumour cells identical to that seen in the adrenal. Consistent with a low-grade adrenocortical carcinoma (10× using H&E stain).

hormonal evaluation for women who present with hirsutism and discuss a scoring system for abnormal hair growth (mFG score ≥ 8 abnormal).¹ However, the guideline emphasises strong ethnic variations, recognises that normal body hair does not exclude an androgen excess syndrome and that the severity of hirsutism does not predict the severity of androgen excess.¹ Insufficient suppression of serum DHEA and cortisol by oral dexamethasone has been shown to have a very high accuracy in identifying women with hirsutism due to an adrenal tumour.³ However, these hormones were not elevated in our patient who had exclusive elevation of serum testosterone.

The patient had reconciled herself to what she thought was early ‘menopause’ at the age of 27 years. Given that her serum FSH, LH, prolactin and estradiol were in the normal premenopausal range, her ‘menopause’ 13 years ago was in fact secondary amenorrhoea due to the testosterone-secreting tumour. Unfortunately she never sought medical attention for this. The algorithm for diagnosis of secondary amenorrhoea in the clinical practice guidelines would presumably have led to diagnosis.⁴ Clinical guidelines specifically mention the critical importance of excluding an androgen-secreting tumour in a setting of virilisation despite its rarity in view of the profound implications of the diagnosis.¹

Clinical practice guidelines are targeted at clinicians but their core message needs to be communicated to beauty clinic professionals since they are often the first point of contact for women with virilisation. This patient faced no delay in diagnosis once she presented to her physician.

This patient had a coincidental myelolipoma that was seen clearly on imaging. Macroscopic fat in an adrenal mass is considered virtually diagnostic of a myelolipoma and such lesions are traditionally left alone.² Coincidental myelolipoma with an adrenocortical carcinoma is very rare⁵ although a small series of coincidental adenoma has been reported.⁶ When myelolipoma is noted with other adrenal tumours, it could be a collision tumour with two distinct tumours or a composite tumour where the myeloid and lipomatous elements are seen admixed with the other tumour (carcinoma as in this case). In our patient, given the unusual venous extension and virilisation there was never any risk of inappropriate observation. However, in the hypothetical situation where these two features are lacking, one can envisage inappropriate observation instead of extirpation

especially since the tumour was below the threshold size that would trigger suspicion of cancer.² Hence, one must exercise caution in patients with adrenal masses and perform a screening hormonal evaluation and serial assessment even if imaging suggests myelolipoma.²

Macroscopic fat within an adrenocortical carcinoma is extraordinarily rare⁷ although it has been suggested that microscopic fat might be seen due to 'myelolipomatous metaplasia'.⁵ As mentioned, our patient had clear histological evidence of myelolipoma.

The patient had extensive venous involvement. Adrenocortical carcinoma has been documented to grow occasionally into the inferior vena cava and rarely into the right atrium. However, most of these are non-functioning tumours that grow unnoticed with only occasional case reports of functioning carcinomas growing extensively through the venous system into the heart.

Testosterone-secreting adrenal tumours usually have coexistent elevated cortisol and DHEA.³ Pure androgen-secreting adrenal tumours are very rare, mostly reported as case reports and are usually adenomas rather than carcinoma.⁸ This presentation of a pure testosterone-secreting adrenocortical carcinoma with venous extension up to the tricuspid cardiac valve is remarkably unusual.

The patient had an adrenal mass with a Weiss score of 3. Many adrenocortical carcinomas especially those with venous thrombosis grow and metastasize fast with a low life expectancy.⁹ The most important determinant of cure is a complete surgical resection.¹⁰ National Comprehensive Cancer Network (NCCN) guidelines recommend considering adjuvant mitotane only in patients at a high risk of recurrence, which they define as those with positive margins, ruptured capsule, high-grade disease or large tumours.¹¹ Other contemporary studies have questioned the benefit of adjuvant mitotane.¹²

Learning points

- Cosmetic measures rather than a medical evaluation can lead to delay in the diagnosis of a virilising adrenocortical tumour.
- Adrenal tumour is a rare but important cause for secondary amenorrhoea.
- A pure testosterone-secreting adrenal tumour can rarely present with venous thrombus up to the right heart.
- Coincidental macroscopic myelolipoma along with an adrenocortical carcinoma although very rare should be kept in mind especially when the imaging features are atypical or the mass is functional.
- One must consider hormonal evaluation in patients with myelolipomas who are otherwise candidates for observation.

Adjuvant therapy for this patient was discussed at a multidisciplinary board meeting. The possibility of recurrence was juxtaposed against the demonstrated indolent course of disease in this patient, the lack of good quality evidence regarding adjuvant mitotane after complete surgical resection and drug toxicity with need for lifelong corticosteroid replacement. The board also took into account the need to import Mitotane at an extraordinarily high cost to the patient (about 1500\$ per month). Other forms of adjuvant therapies such as radiotherapy to the tumour bed and alternative systemic therapies were deemed inappropriate. After a discussion of these issues, a decision was taken to observe the patient.

Contributors RMS and SS: planning, concept, design, case material collection, analysis, reporting, interpretation, revision, final approval, accountable for integrity and overall responsibility. HBK: planning, case material collection, interpretation, revision, final approval, accountable for integrity and overall responsibility. MDP: case material collection, interpretation, revision, final approval, accountable for integrity and overall responsibility.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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