Virilisation in a case of transitional cell carcinoma of the ovary
L J Baldwin, N Singh, A Tiltman

CASE REPORT

A 52 year old woman presented with a five month history of emotional changes, voice changes, and abdominal discomfort. Clinical, biochemical, and radiological examinations showed evidence of virilisation, raised testosterone, and a complex ovarian mass. Microscopy of the resection specimen showed the tumour to be a transitional cell carcinoma of the ovary with luteinisation and hyperplasia of the intervening stromal cells. This is a unique case of virilisation caused by transitional cell carcinoma of the ovary. Theories as to the origin of testosterone production in non-functioning ovarian tumours are discussed.

Endocrine manifestations occur in less than 5% of all ovarian tumours and virilising tumours in postmenopausal women are even more rare. Excess androgen production has been described in numerous ovarian tumours including sex cord stromal tumours and, less commonly, in non-functioning ovarian tumours such as endometrioid tumours, serous cystadenomas, Brenner tumours, leiomyomas, and metastatic tumours.

We present a case of transitional cell carcinoma of the ovary presenting with hyperandrogenism. To our knowledge no such case has been described before.

CASE REPORT

The patient, a 52 year old woman, presented with a five month history of emotional and voice changes and abdominal discomfort. She had been taking hormone replacement therapy (combined estrogen and progesterone) until five months previously and since stopping this had experienced amenorrhoea. Examination revealed a large mass in the lower abdomen and it was noted that she had abnormal abundant facial hair. Initial investigations revealed raised concentrations of testosterone (21.3 nmol/litre) and of CA125 (158 KU/litre). The concentrations of both returned to normal after surgery (postoperative testosterone, 1.0 nmol/litre; postoperative CA125, 6.3 KU/litre). Before surgery, her follicle stimulating hormone (FSH) concentration was normal, at 3.4 IU/litre, and her luteinising hormone (LH) concentration was also normal, at 2.8 IU/litre. Her preoperative dehydroepiandrosterone sulfate, androstenedione, and human chorionic gonadotrophin values were normal. Computer tomography scans revealed a complex mixed cystic and solid mass arising from the pelvis. The adrenal glands were normal on computer tomography scan. She underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy, and during surgery a large smooth walled ovarian mass was identified fixed to the pelvic floor on the right side.

On resection, the mass was shown to be a multiloculated neoplasm measuring 190 × 160 × 80 mm and weighing 1700 g.

Light microscopy revealed a neoplasm that had a partly solid and partly papillary architecture. The solid areas were composed of invasive islands of atypical transitional epithelium set in a dense fibrous stroma. The papillary area showed coarse bulbous papillary projections of malignant transitional epithelium, morphologically similar to a transitional cell carcinoma of the bladder. There were no elements of a benign or proliferating Brenner tumour identified. There was stromal hyperplasia and focal stromal luteinisation. No other virilising lesions were encountered in either ovary or other tissues. Immunocytochemistry showed positivity for CAM5.2 and focal positivity for cytokeratin 7 within the tumour cells. The tumour cells were negative for CA125. The stromal cells showed nuclear and cytoplasmic positivity for α-glutathione S-transferase.

Figure 1 (A) A low power view of the tumour showing the papillary architecture. (B) The stromal cells show positive immunohistochemical staining for α-glutathione S-transferase.
S-transferase and positivity for inhibin. The endometrium was inactive with no evidence of endometrial hyperplasia.

**DISCUSSION**

The investigation of virilisation in a female patient can be challenging because excess androgen production may be caused by adrenal hyperplasia, adrenocortical carcinoma, and ovarian tumours. In this patient, the testosterone values returned to normal directly after surgery, no adrenal lesion was seen on imaging, and no abnormality of the left ovary was seen at surgery.

Non-functioning tumours of the ovary that show evidence of hyperandrogenism are well described. In several of these cases, hyperplasia of the adjacent stroma with or without luteinisation has been found on microscopy, and this is thought to be the source of steroid secretion. In support of this theory, a glutathione S-transferase, a dimeric isoenzyme, which has been shown to be present within steroid producing cells of the ovary, often shows positive cytoplasmic staining in the adjacent ovarian stroma of these tumours, as was seen in our case. The theories as to why the stromal cells react in this way include the mechanical effect theory, which likens the stromal cell reaction to that around an expanding follicle. Other theories include a trophic effect theory, which postulates that the tumour cells produce a substance that stimulates the adjacent stroma. Because of the higher rates of occurrence of virilising ovarian tumours in postmenopausal women and in pregnancy, it has been postulated that high circulating concentrations of human chorionic gonadotrophin or pituitary gonadotrophins are necessary for stromal steroidogenesis. The concentrations of follicle stimulating hormone and luteinising hormone were normal in our case.

"Non-functioning tumours of the ovary that show evidence of hyperandrogenism are well described."

It is important for clinicians and pathologists to be aware of the possibility of androgen secretion by non-functioning epithelial tumours to help in the correct management of the patient.

Transitional cell carcinoma of the ovary causing virilisation has not previously been reported in the literature.

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**Take home messages**

- We report a unique case of a virilisation caused by transitional cell carcinoma of the ovary
- Clinicians and pathologists should be aware of the possibility of androgen secretion by non-functioning epithelial tumours to help in the correct management of the patient

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Accepted for publication 17 November 2003

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J Clin Pathol 2004 57: 1331-1332
doi: 10.1136/jcp.2003.010892

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