# Case report

# Differential diagnosis of adipocytic differentiation in androgen-secreting mature ovarian teratoma with Leydig cell hyperplasia

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## Abstract

Mature cystic teratomas (dermoid cysts) of the ovary are very rarely associated with androgen production. The source of androgens in these cysts may be tumours such as Sertoli–Leydig cell tumour or Leydig cell hyperplasia. In this study, we present a case of virilisation in a postmenopausal female patient, where Leydig cell hyperplasia in a mature cystic teratoma was found to be responsible for the production of testosterone. In addition, extensive areas of lipomatous differentiation were identified. These areas showed significant alterations in adipocytic morphology, and differential diagnoses such as spindle cell lipoma (SCL) and atypical lipomatous tumour (ALT) were excluded after additional workup. Adipose tissue is not only an energy reservoir, but (is recently identified as) a complex endocrine organ with additional metabolic roles in whole body homeostasis. Exuberant proliferation of lipomatous tissue in this teratoma raises the possibility of a synergistic role of Leydig cells and adipocytes in the development of hyperandrogenism.

## Introduction

Androgen-secreting ovarian tumours are rare, accounting for less than 0.5% of all ovarian neoplasms . They are more frequent in postmenopausal women, and should be suspected in the case of rapid onset of androgenic symptoms . We present a case of virilisation in a postmenopausal female patient with a mature cystic teratoma, where Leydig cell hyperplasia was found to be the source of testosterone. In addition, extensive lipomatous areas with altered morphology were identified. These features were reported as fiboblastic and adipocytic differentiation within a teratoma after additional analysis permitted exclusion of differential diagnoses such as SCL and ALT. The possibility that there is a synergistic role between Leydig cells and adipocytes to promote androgenic effects is hypothesised.




**Figure 1.** CT scan showing minimally complex right ovarian cyst.

## Present Case

- A 77-year-old woman with signs of virilisation
- A testosterone-secreting tumour was suspected.
- Total blood count showed mild erythrocytosis and slightly increased Haematocrit (Htc) and Haemoglobin (HB) (Rbc= 5.25 ($10^{12}$/L), Hct= 48.2%, HB= 159 g/l (120-150)), with all other values within normal limits.
- CT of abdomen and pelvis with contrast reported a 5 cm, minimally-complex, right ovarian cyst (Figure 1). Both adrenals had normal morphology.
- Patient's serum markers were HCG=<1.2IU/L (<5), Testosterone=37.0 nmol/L (0.1-1.4), Alpha-fetoprotein 6.7kU/L (0.0-10.0) and CA125= 5.8ku/L (0.0-35.0).
- Laparoscopic bilateral salpingo-oophorectomy for a suspected androgen secreting ovarian tumour was performed. A right ovarian cyst 5 cm in diameter with smooth surface was excised.
- Histology showed an ovarian tumour with scattered cysts lined by bland columnar epithelium in fibrous tissue. In addition, there were infiltrative foci of differentiated adipocytic proliferation traversed by variably wide fibrous septa containing bland spindle cells and numerous scattered mast cells (Figure 2*a, 2b*). Occasional enlarged cells were identified (Figure 2*c*). No ropey collagen, no floret tumour cells and no haemorrhage or other necrosis was seen. Mitoses were inconspicuous. The most prominent feature was widespread nests of hyperplastic Leydig/hilar cells (Figure 2*d*). No significant hyperchromasia, and only occasional pleomorphic cells were identified in the lipomatous component, however, the possibility of an ALT could not be entirely excluded. The Leydig cells were thought to be responsible for the androgen secretion.
- Immunohistochemistry: Desmin, S100, SMA, GFAP, p16 and CD34 were negative. Ki67 proliferation index was low (<1%). Nuclear staining for CDK4 was observed in Leydig cells as well as in adipocytes and spindle cells within the fibrous cords (Figure 3a). Androgen receptors (AR) were expressed in Leydig cells, surrounding adipose tissue and residual ovarian stroma. There was also patchy immunoreactivity for progesterone receptors (PR), but oestrogen receptor (ER) was negative
- In view of the unusual morphology and CDK4 positivity in the adipose tissue (Figure 3), fluorescence in situ hybridization (FISH) analysis for MDM2 gene amplification was performed (Vysis MDM2/CEP 12 FISH Probe, Abbot Diagnostic). The results showed no evidence of amplification and the features were regarded as benign adipocytic differentiation within an androgen secreting teratoma.

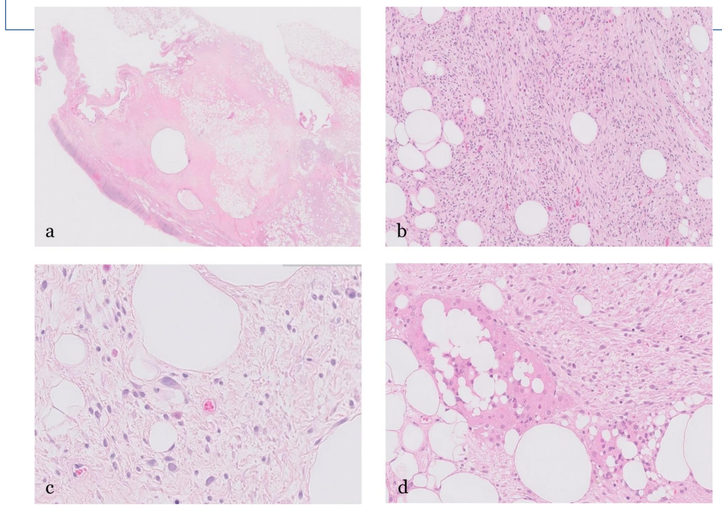


**Figure 2.** Multiloculated cyst with abundant adipose and fibrous tissue component (2a); Spindle cell component (2b); Occasional pleomophic stromal cells (2c); Nests of Leydig cells (2d)(H&E stain).

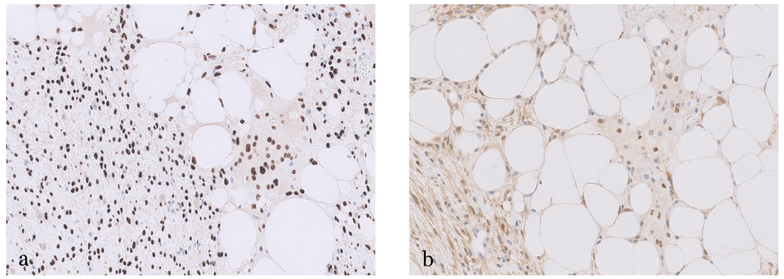


**Figure 3.** Expression of AR (3a) and CDK4 (3b) in Leydig cells, spindle stromal cells and adipocytes

## Discussion

- The causes of hyperandrogenism in postmenopausal women can be generally categorized as non-tumorous (functional) or tumorous. Neoplastic hyperandrogenism includes androgen secreting adrenal and ovarian tumours, the latter group including Sertoli–Leydig cell tumors, Leydig cell tumors (hilar and non-hilar type), steroid cell tumors and gynandroblastomas .
- Leydig cell hyperplasia is a rare cause of hyperandrogenism after menopause and can be the source of androgen even if the ovaries look normal on imaging. The distinction between Leydig cell hyperplasia and Leydig cell tumour is based on the size and the pattern of growth of the cell nests; hyperplasia usually being nodular, but widely separated. A nodule of more than 1 cm is generally considered a Leydig cell tumour .
- Hormonal and radiological investigation is essential to establish the diagnosis and differentiate between ovarian and adrenal sources. Oophorectomy is recommended as a diagnostic test, and definitive treatment.
- In line with the referred symptoms in literature, hyperandrogenism-related symptoms and manifestations were the main clinical features in our patient. The patient's rapid onset of progressive virilisation raised the suspicion of an androgen-secreting tumour. High levels of testosterone and an ovarian cyst on imaging suggested an ovarian source. In this case, the pre-operative diagnosis of mature cystic teratoma was proposed, but the source of androgens could not be identified. Histopathological examination revealed the source to be Leydig cell hyperplasia in the dermoid cyst.
- An unusual additional finding was exuberant proliferation of adipose tissue with altered morphology ,which prompted a detailed immunohistochemical and molecular evaluation. After exclusion of SCL and ALT, we considered other (than mere co-incidence) alternatives for this exuberant proliferation of adipose tissue around the Leydig cell nests .
- Adipose tissue is a complex and highly active metabolic and endocrine organ . Hyperandrogenism is the most consistent feature observed in PCOS patients, and recently aberrant neuroendocrine signaling and adipose tissue function have been proposed as playing a role in the development of PCOS. Women with PCOS, and preclinical PCOS animal models, exhibit altered adipocyte morphology, aberrant secretion of circulating adipokines, impaired adipocyte lipolysis, altered steroidogenic mechanisms, dysregulated adipokine secretion, dysfunctional glucose metabolism, and altered gene expression profiles, highlighting the differences between PCOS and normal adipose tissue . There have been reported cases of androgen-secreting teratomas where only adipocytes and metaplastic bone were found . The possibility that adipose tissue may be at least partially responsible for androgen effects needs further studies.

## Conclusions

The presence of abundant lipomatous proliferation within an androgen secreting teratoma of the type described in this report is rare and may be partly responsible for the hyperandrogenism. It is important, however, to exclude the differential diagnoses of spindle cell lipoma and/or atypical lipomatous tumours by appropriate analysis in lesions with these features.

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