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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 traditionally described as an energy reservoir, but recently it has become clear that adipose tissue is 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.

1. Introduction

Androgen-secreting ovarian tumours are rare, accounting for less than 0.5% of all ovarian neoplasms (Le Donne et al., 2018). They are more frequent in postmenopausal women, and should be suspected in the case of rapid onset of androgenic symptoms (Subbaiah et al., 2017). 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.

2. Present case

A 77-year-old woman was seen in clinic with signs of virilisation (baldness, body hair growth, change of voice tone) and a testosterone secreting tumour was suspected. The history included previous hysterectomy for pelvic pain, with ovaries left in situ. 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 minimally complex 5 cm right ovarian cyst (Fig. 1). Both adrenals had normal morphology. Simple hepatic cysts and a small left renal calculus were also noted. The patient's serum markers were HCG=<1.2 IU/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). The patient underwent laparoscopic bilateral salpingo-oophorectomy for a suspected androgen secreting ovarian tumour. A right ovarian cyst 5 cm in diameter with a smooth surface was excised. The patient was discharged on the same day as surgery and had an uneventful postoperative course. 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, focally hypercellular, fibrous septa containing bland spindle cells and numerous scattered mast cells (Fig. 2*a, 2b*). Occasional enlarged cells were identified (Fig. 2*c*). Foci of fat necrosis were also a feature. No ropey collagen or floret tumour cells were identified. No evidence of haemorrhage or necrosis was seen. Mitoses were inconspicuous. The most prominent feature was the presence of widespread nests of hyperplastic Leydig/hilar cells (Fig. 2*d*). No significant hyperchromasia, and only occasional

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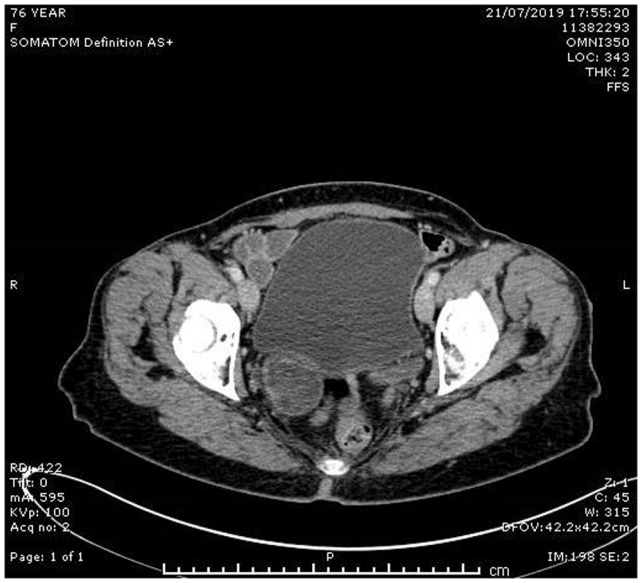

Fig. 1. CT scan showing minimally complex right ovarian cyst.

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 showed negativity for Desmin, S100, SMA, GFAP, p16 and CD34 (the latter should be positive in SCL). The proliferation index, as evaluated by Ki67, was low (<1%). Nuclear staining for CDK4 was observed in Leydig cells and background ovarian cortical stromal cells, as well as in adipocytes and spindle cells within the fibrous cords (Fig. 3a). Further immunohistochemistry, performed in a tertiary centre showed absence of immunoreactivity in the spindle cells for MUC4, ERG and ALK-1. 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) expression was not identified. In view of the unusual morphology and CDK4 positivity in the adipose tissue (Fig. 3), fluorescence in situ hybridization (FISH) analysis for MDM2 gene amplification was performed using the Vysis MDM2/CEP 12 FISH Probe, Abbot Diagnostic. Although MDM2 gene amplification is not entirely specific for ALT, it has been used successfully as an adjunctive tool for ALT diagnosis (Thway et al., 2015). The results showed no evidence of amplification, and the features were regarded as benign adipocytic differentiation within an androgen secreting teratoma.

3. Discussion

The causes of hyperandrogenism in postmenopausal women are diverse, and can be generally categorized as non-tumorous (functional) or tumorous. The differential diagnosis of non-neoplastic hyperandrogenism in a postmenopausal woman includes endocrinopathies such as Cushing's syndrome, acromegaly, states of insulin resistance, partial congenital adrenal hyperplasia, ovarian hyperthecosis and iatrogenic causes such as medication. 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 (Markopoulos et al., 2015; Nardo et al., 2005). 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 (Hofland et al., 2013).

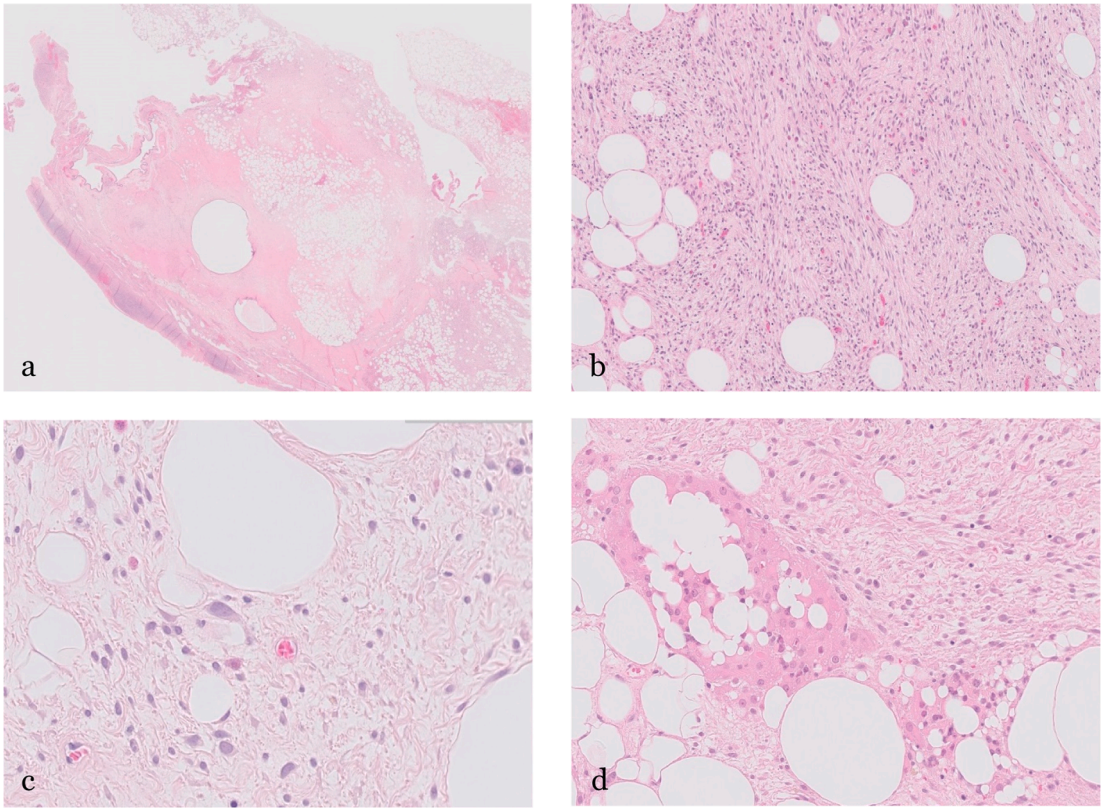

Fig. 2. Multiloculated cyst with abundant adipose and fibrous tissue component (2a); Spindle cell component (2b); Occasional pleomorphic stromal cells (2c); Nests of Leydig cells (H&E stain, 2d).

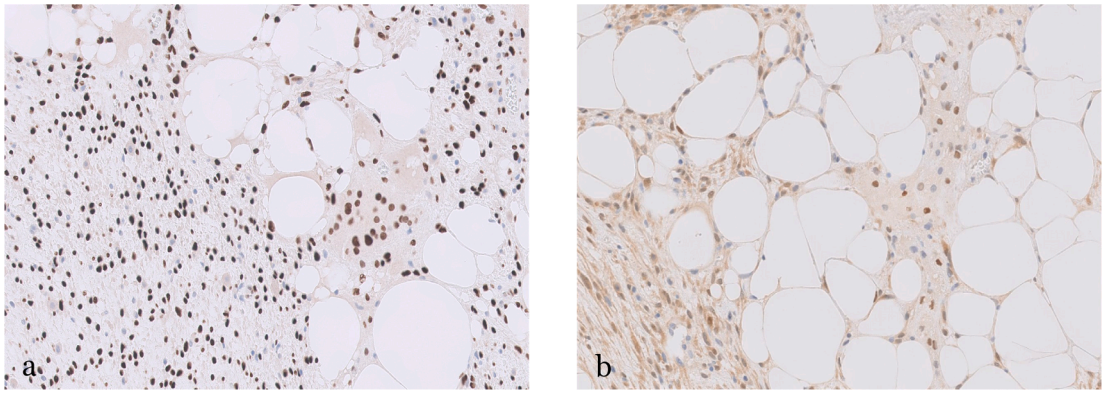

Fig. 3. Expression of AR (3a) and CDK4 (3b) in Leydig cells, spindle stromal cells and adipocytes.

Systemic investigation (hormonal and radiological) is essential to establish the diagnosis and differentiate between ovarian and adrenal sources (Juniarto et al., 2013). In most cases, hormonal abnormalities include increased serum testosterone levels in the presence of normal dehydroepiandrosterone-sulfate (DHEA-S) (Swain et al., 2013). Oophorectomy is recommended as a diagnostic test, and definitive treatment (Palha et al., 2016).

Similarly to what has been reported so far in the literature, hyperandrogenism-related symptoms and manifestations were the main clinical features in our patient. The patient had rapid onset of progressive virilisation which raised the suspicion of an androgen-secreting tumour. High levels of testosterone and an ovarian cyst on imaging suggested an ovarian source. In our patient, 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 possible reasons for this exuberant proliferation of adipose tissue around the Leydig cell nests, other than merely coincidence.

Adipose tissue is a complex and highly active metabolic and endocrine organ (Kershaw & Flier, 2004). 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 (Cox et al., 2020). 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 (Sanchez-Garrido & Tena-Sempere, 2020). There have been reported cases of androgen-secreting teratomas where only adipocytes and metaplastic bone were found (Palha et al., 2016). The possibility that adipose tissue may be at least partially responsible for androgen effects needs further studies.

In conclusion, 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.

Patient anonymity and informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

CRediT authorship contribution statement

Mpatsoulis Diogenis: Investigation, Data curation, Writing - original draft. **Nieto J. Joaquin:** Visualization, Investigation. **Lonsdale Ray:** Writing - review & editing. **Fisher Cyril:** Formal analysis. **Mazibrada Jasenka:** Writing - original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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