An adolescent girl with coexisting ovarian mature cystic teratoma and HAIR-AN syndrome, an extreme subtype of polycystic ovarian syndrome

Jin Hui Ho1, Ana Vetiana Abd Wahab2, Yin Khet Fung1 and Serena Sert Kim Khoo1

1Endocrinology Unit, Department of Internal Medicine, Queen Elizabeth Hospital, Kota Kinabalu, Sabah, Malaysia and
2Department of Obstetrics and Gynaecology, Sabah Women and Children Hospital, Kota Kinabalu, Sabah, Malaysia

Summary
Polycystic ovarian syndrome (PCOS) is associated with menstrual irregularities, ovulatory dysfunction, hirsutism, insulin resistance, obesity and metabolic syndrome but is rarely associated with severe hyperandrogenaemia and virilisation resulting in male pattern baldness and clitoromegaly. Total serum testosterone greater than twice the upper limit of the reference range or free androgen index of over five-fold elevated suggests a diagnosis other than PCOS. We reported a case of a 15 years old obese girl presented with secondary amenorrhoea, virilising signs: frontal baldness, clitoromegaly and prominent signs of insulin resistance and marked acanthosis nigricans. Her total testosterone level was markedly elevated at 9.4 nmol/L (0.5–1.7 nmol/L) and MRI pelvis revealed a right ovarian mass with fat and cystic component and a left polycystic ovary. The patient underwent laparoscopic right ovarian cystectomy and histologically confirmed mature cystic teratoma. Post-operatively, her testosterone level declined but did not normalise, menses resumed but remained irregular. Her fasting insulin was elevated 85.2 mIU/L (3–25 mIU/L) and HOMA-IR was high at 13.1 (>2) with persistent acanthosis nigricans suggesting co-existing HAIR-AN syndrome, an extreme phenotype of polycystic ovarian syndrome.

Learning points:
- Rapid onset of hyperandrogenic symptoms, especially if associated with signs of virilisation must raise the suspicion of an androgen-secreting tumour.
- Total serum testosterone greater than twofold the upper limit of the reference range or free androgen indices over fivefold suggest a diagnosis other than polycystic ovarian syndrome (PCOS).
- High levels of testosterone with normal levels of the DHEA-S suggest an ovarian source.
- Ovarian androgen-secreting tumour and HAIR-AN syndrome, an extreme spectrum of PCOS can co-exist.

Background
Polycystic Ovarian Syndrome (PCOS) is common among women in the reproductive age group with a prevalence of 6–13% and affecting 6–18% of adolescent girls depending on the diagnostic criteria used and the population studied (1). Rotterdam criteria have been used as diagnostic criteria for PCOS in adults which include (i) oligo- or anovulation, (ii) clinical and/or biochemical signs of hyperandrogenism, (iii) polycystic ovaries and exclusion of other aetiologies such as congenital adrenal hyperplasia, androgen-secreting tumours, Cushing’s syndrome and hyperthecosis. HAIR-AN syndrome is an extreme phenotype of PCOS characterised by hyperandrogenism...
(HA), insulin resistance (IR) and acanthosis nigricans (AN) commonly presenting in the adolescent age group.

Rapid progression of virilising signs and symptoms along with markedly elevated serum testosterone level make the diagnosis of PCOS less likely. Ovarian tumours causing virilisation are exceedingly rare, accounting for <5% of all ovarian neoplasm and frequently reported in postmenopausal women and should be suspected in the case of a rapid onset of androgenic symptoms (2). Androgen-secreting ovarian tumours are exceptionally rare among adolescents. We describe a case of a 15 years old girl with signs of virilisation, menstrual abnormality, marked insulin resistance and acanthosis nigricans secondary to coexisting ovarian mature cystic teratoma and HAIR-AN syndrome.

**Case presentation**

The patient is a 15 years old girl, referred for secondary amenorrhoea over a period of 4 years. She attained menarche at the age of 11, however, her menses ceased after the first cycle. She also noticed the development of thick velvety skin over a period of 2 years, frequent hair loss and prominent frontotemporal baldness. At the age of 12, she developed hirsutism above the upper lip, breasts and thighs but did not require shaving. She had no deepening of voice, galactorrhoea, or symptoms suggestive of thyroid disorder. She was born full term after an uneventful pregnancy with no significant medical illnesses during childhood. Her paternal grandparents had diabetes mellitus but there was no family history of malignancy.

Physical examination revealed she was 149 cm tall and weighed 72.5 kg, BMI of 32.7 kg/m² and normotensive. She had hirsutism above the upper lip, breasts and back with Ferriman–Gallwey score of 4. She had mild acne over the face, frontotemporal baldness, and severe acanthosis nigricans associated with skin tags over the neck, both axillae, antecubital fossa, inframammary line, chest, back, popliteal fossa and ankles (Fig. 1). Both her breast and pubic hair development were Tanner 4 and there was no palpable abdominal mass. She had phenotypical female external genitalia though clitoromegaly (17 mm × 15 mm) was noted. She had neither acral nor Cushingoid features.

**Investigation**

Laboratory measurements were normal except the total testosterone level (Table 1): Total testosterone 9.4 nmol/L (0.5–1.7 nmol/L), dihydroepiandrosterone sulphate (DHEA-S) 1.3 µmol/L (0.9–11.7 µmol/L), luteinising hormone 4.8 IU/L (1.8–11.8 IU/L), follicle-stimulating hormone 3.4 IU/L (3.0–8.1 IU/L), progesterone 0.8 nmol/L (0.3–0.9 nmol/L), oestradiol 225 pmol/L (77–921 pmol/L), 24 h urine cortisol 62.7 nmol/24 h (11.8–485.6 nmol/24 h), serum cortisol 19.5 nmol/L (overnight 1mg dexamethasone suppression test), thyroid-stimulating hormone 1.3 mIU/L (0.4–4.9 mIU/L), free thyroxine 13.9 pmol/L (10.2–17.3 pmol/L), 17-hydroxyprogesterone 3.1 nmol/L (follicular phase: 0.9–2.7 nmol/L, luteal phase: 0.9–7.6 nmol/L), prolactin 17.7 ng/mL (5.2–26.5 ng/mL). Her tumour markers were normal: alpha feto-protein 2.6 U/mL (0.74–7.3 U/mL), carcinoembryonic antigen 1.0 ng/mL (<5 ng/mL), Ca 125 14.4 U/mL (<35 U/mL), β HCG < 1.2 mIU/mL (< 5 mIU/mL).

Pelvic ultrasonography showed an anteverted uterus with a right adnexal mass with solid component measuring 6 × 5 cm. Contrasted CT scan of the abdomen and pelvis revealed a well-circumscribed cystic lesion at the right adnexa measuring 4.9 × 4.4 × 4.5 cm. Within the cystic lesion, there was a solid nodule seen protruding into the cystic lumen, representing the Rokitansky nodule. There was also mural calcification and fat fluid level suggestive of mature cystic teratoma (Fig. 2). Left ovary and both adrenals appeared normal. However, MRI pelvis revealed a right ovarian lesion with fat and cystic component suggestive of mature cystic teratoma and left polycystic ovary.

**Treatment**

The patient was subjected to a laparoscopic resection of the right ovarian cyst, which intraoperatively measured 4 cm × 4 cm. The cyst which ruptured during specimen
retrieval showed sebum material. Left ovary appeared normal. Histological examination revealed right fibro-ovarian stroma cyst wall lined by true epidermis producing keratin material and columnar epithelium in areas. The cyst wall also contained pilosebaceous unit, hair follicles, adipocytes, cartilage, glial tissue and nerve bundles with areas of calcification with no malignant transformation consistent with mature cystic teratoma (Fig. 3).

Outcome and follow-up

One week after the surgery, the patient’s menses resumed for 3 days. Her total testosterone level had significantly reduced 2 months post-operation from 9.4 to 4.7 nmol/L (0.5–1.7 nmol/L) (Fig. 4). Her sex hormone binding globulin (SHBG) was low at 9 nmol/L (30–90 nmol/L), with a high free androgen index of 52.8. Her OGTT showed impaired glucose tolerance with fasting blood sugar and 2 h post 75 g glucose of 3.5 and 9.6 mmol/L respectively. Her fasting insulin level was high at 85.2 mIU/L (3–25 mIU/L). Calculated Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was 13.1 (>2). IGF-1 level was 307 µg/L (270–660 µg/L). Total cholesterol 3.9 mmol/L (<5.2 mmol/L), triglycerides 1.1 mmol/L (<1.7 mmol/L), LDL cholesterol 2.4 mmol/L (2.6–4.1 mmol/L), HDL cholesterol 1.0 mmol/L (1.0–1.5 mmol/L). Her acanthosis nigricans and skin tags had reduced and frontal baldness had become less obvious. However, her menses remained irregular. Three months post-operation, she was started on oral Metformin and advised for weight loss.

Discussion

PCOS can present with a myriad of symptoms namely menstrual irregularities, ovulatory dysfunction, hirsutism, insulin resistance, obesity and metabolic syndrome but rarely present with virilising signs and severe hyperandrogenaemia causing male pattern baldness and

| Table 1 | Laboratory results of pre- and at 2, 8, 10 months post-operation. |
|---------|--------------------------------------------------------------------------------------------------|
|         | Pre-operation                  | Post-operation 2 months | Post-operation 8 months | Post-operation 10 months | Reference range |
| Testosterone, nmol/L | 9.4                              | 4.8                      | 5.0                      | 4.4                      | 0.5–1.7         |
| LH, IU/L                | 4.8                              | 3.5                      | 2.8                      | 4.2                      | 1.8–11.8        |
| FSH, IU/L               | 3.4                              | 3.5                      | 1.8                      | 3.4                      | 3.0–8.1         |
| Progesterone, nmol/L    | 0.8                              | 0.4                      | 1.0                      | 0.4                      | 0.3–0.9         |
| Estradiol, pmol/L       | 225                              | 163                      | 208                      | 186                      | 77–921          |
| DHEA-S, µmol/L          | 1.3                              | ND                       | ND                       | ND                       | 0.9–11.7        |
| Fasting Insulin, mIU/L  | ND                               | 85.2                     | 47.2                     | ND                       | 3–25            |
| HOMA-IR                 | ND                               | 13.1                     | 8.5                      | ND                       | >2              |
| OGTT, mmol/L            | 3.3*/6.5a                        | 3.5*/9.6a                | ND                       | ND                       | <6*<7.8a        |
| 17-Hydroxyprogesterone, nmol/L | 3.1                            | 5.2                      | ND                       | ND                       |                  |

*Baseline fasting blood glucose level; *2 hours post 75 g glucose load blood glucose level.
DHEA-S, dihydroepiandrosterone sulphate; FSH, follicle-stimulating hormone; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LH, luteinising hormone; ND, not done; OGTT, oral glucose tolerance test.

Figure 2
CT pelvis in axial (A) and coronal (B) view showed well-circumscribed cystic lesion seen at the right adnexa with solid nodule protruding into the cystic lumen, represent Rokitansky nodule (red arrow).
clitoromegaly. Total serum testosterone greater than twofold the upper limit of the reference range or indices of free testosterone over fivefold elevated suggest a diagnosis other than PCOS (3). The diagnostic threshold of total testosterone measured by liquid chromatography tandem mass spectrometry to identify androgen producing tumour was >5.1 nmol/L (4). The very high total testosterone levels in this patient led to the suspicion and investigation of an androgen producing tumour.

Mature cystic teratomas account for more than 95% of all ovarian teratomas and are almost invariably benign. Besides the usual components of skin, bone, glial tissue, fat, smooth muscle and respiratory epithelium, the tumour also contained Leydig cells which were thought to be the source of large amounts of testosterone, the driver for virilising signs (5). Several cases have been reported on the association of virilisation due to mature cystic ovarian teratoma among adults and postmenopausal women (2, 3) frequently presenting with acne, hirsutism, baldness, obesity, elevated levels of testosterone, hyperinsulinism, and ultrasonography evidence of unilateral ovarian mass. However, virilisation secondary to ovarian teratoma is extremely rare among adolescents and to date only 3 cases have been reported in this age group (6, 7, 8). We hereby report the 4th case, an adolescent presenting with secondary amenorrhea lasting more than 4 years, clinical signs of virilisation and insulin resistance, markedly high levels of testosterone and presence of unilateral ovarian mass that was histologically identified as mature cystic teratoma. The lack of a significant increase in DHEA-S distinguishes ovarian from adrenal androgen-producing tumours. In this case, while DHEA-S levels were within the normal range, testosterone and FAI measurements were markedly increased, hence suggesting an ovarian origin. Following the surgery, the marked reduction of her testosterone level and the return of her menses after 4 years indicate that the mature cystic teratoma was the predominant source of the excess androgen.

The observation that the serum testosterone concentrations did not return completely to the normal reference range raises the possibility of co-existing PCOS in the remaining ovary. HAIR-AN syndrome is a specific and rare sub-phenotype of the PCOS characterised by the presence of severe insulin resistance and elevated insulin levels secondary to the defects in the insulin receptor genes. High levels of insulin can directly stimulate the overproduction of androgens in the ovaries. High insulin levels may also cross-react with receptors for insulin-like growth factors (IGF) leading to increased ovarian androgen production. Furthermore, in severe insulin resistance, hyperinsulinemia is responsible for a decrease in the liver production of SHBG and IGF binding protein-1 (IGFBP-1),

Figure 3
(A and B) Fibro-ovarian stroma cyst wall contained pilosebaceous unit (red arrow), cartilage (blue arrow), glial tissue (yellow arrow), respiratory type epithelium (orange arrow), and smooth muscle (green arrow) consistent with mature cystic teratoma (H&E stain, 100×).

Figure 4
Total testosterone level pre-, 2 months, 8 months and 10 months post-operation.
further enhancing the increase in free testosterone and IGF levels (9). HAIR-AN syndrome can cause menstrual irregularities, hyperandrogenic symptoms and insulin resistance among adolescents. This syndrome is seen in almost 5% of women with hyperandrogenism. Obesity, acne, hirsutism and acanthosis nigricans often manifested in adolescent around puberty. Our patient had markedly elevated fasting insulin of 85.2 mIU/L (normal fasting insulin levels are below 20–25 mIU/L) however we did not perform stimulated insulin level after OGTT. In patients with severe forms of the HAIR-AN syndrome, maximal insulin concentrations during a glucose tolerance test are in the range of 500–1500 mIU/L, with simultaneous glucose values of 5.6–22 mmol/L (10).

Over the years, ovarian and adrenal venous catheterisation has been used as investigation for hyperandrogenism. However, this procedure is invasive and technically challenging. This should not be routinely performed in women presenting with symptoms and signs of hyperandrogenism, but reserved for women in whom transvaginal ultrasonography, pelvic CT or MRI failed to demonstrate any pathology.

In conclusion, this case highlights the possibility of co-existing HAIR-AN syndrome a spectrum of PCOS and androgen producing ovarian mature cystic teratoma warranting further evaluation in adolescents with clinical features of rapid virilisation and biochemically severe hyperandrogenism.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Patient consent
A full written consent has been obtained from the patient and her mother.

Author contribution statement
Dr J H Ho wrote the case report and perform literature search for writing discussion. Dr A V Abd Wahab is the primary Gynaecologist and authorised the final version of the case report. Dr Y K Fung reviewed the case report and provide suggestions for further improvement. Dr S K Khoo is the primary Endocrinologist of this patient, reviewed the case report, provide suggestions for further improvement, and authorised the final version of the case report.

References
8 Imperato-McGinley J, Peterson RE, Sturla E, Dawood Y & Bar RS. Primary amenorrhea associated with hirsutism, acanthosis nigricans, dermoid cysts of the ovaries and a new type of insulin resistance. American Journal of Medicine 1978 65 389–395. (https://doi.org/10.1016/0002-9341(78)90838-0)
10 Barbieri RL & Ryan KJ. Hyperandrogenism, insulin resistance, and acanthosis nigricans syndrome: a common endocrinopathy with distinct pathophysiologic features. American Journal of Obstetrics and Gynecology 1983 147 90–101. (https://doi.org/10.1016/0002-9378(83)90091-1)
7 Poduval A, Antal Z, Lee T, Bar A, Dalmau J & Muzumdar R. Immune-mediated encephalitis and virilization in association with a mature cystic ovarian teratoma in an adolescent girl. Hormone Research 2009 72 252–256. (https://doi.org/10.1159/000236087)
5 Hoffman JG, Strickland JL & Yin J. Virilizing ovarian dermoid cyst with Leydig cells. Journal of Pediatric and Adolescent Gynecology 2009 22 e39–e40. (https://doi.org/10.1016/j.jpag.2008.05.012)
2 Palha A, Cortez L, Tavares AP & Agapito A. Leydig cell tumour and mature ovarian teratoma: rare androgen-secreting ovarian tumours in postmenopausal women. BMJ Case Reports 2016 bcr2016215985. (https://doi.org/10.1136/bcr-2016-215985)
3 Denney DC, Smith D, O'Shea D & McKenna JJ. Investigation of patients with atypical or severe hyperandrogenaemia including androgen-secreting ovarian teratoma. European Journal of Endocrinology 2010 162 213–220. (https://doi.org/10.1530/EJE-09-0576)
4 Sharma A, Kapoor E, Singh RJ, Chang AV & Erickson D. Diagnostic thresholds for androgen-producing tumors or pathologic hyperandrogenism in women by use of total testosterone concentrations measured by liquid chromatography-tandem mass spectrometry. Clinical Chemistry 2018 64 1636–1645. (https://doi.org/10.1373/clinchem.2018.290825)
1 Peña AS, Witchel SF, Hoeger KM, Oberfield SE, Vogtizt MG, Misso M, Garad R, Dadagho P & Teede H. Adolescent polycystic ovary syndrome according to the international evidence-based guideline. BMC Medicine 2020 18 72. (https://doi.org/10.1186/s12916-020-01516-x)
2 Palha A, Cortez L, Tavares AP & Agapito A. Leydig cell tumour and mature ovarian teratoma: rare androgen-secreting ovarian tumours in postmenopausal women. BMJ Case Reports 2016 bcr2016215985. (https://doi.org/10.1136/bcr-2016-215985)
3 Denney DC, Smith D, O’Shea D & McKenna JJ. Investigation of patients with atypical or severe hyperandrogenaemia including androgen-secreting ovarian teratoma. European Journal of Endocrinology 2010 162 213–220. (https://doi.org/10.1530/EJE-09-0576)
5 Hoffman JG, Strickland JL & Yin J. Virilizing ovarian dermoid cyst with Leydig cells. Journal of Pediatric and Adolescent Gynecology 2009 22 e39–e40. (https://doi.org/10.1016/j.jpag.2008.05.012)
6 Fidalgo M, Katz O, Fucci A, Navacchia D, Zerba M, Longeiro L & Giambini D. Mature teratoma, a rare cause of virilization in adolescence. Journal of Pediatric Endocrinology and Metabolism 2011 24 227–228. (https://doi.org/10.1515/jpem.2011.096)
7 Poduval A, Antal Z, Lee T, Bar A, Dalmau J & Muzumdar R. Immune-mediated encephalitis and virilization in association with a mature cystic ovarian teratoma in an adolescent girl. Hormone Research 2009 72 252–256. (https://doi.org/10.1159/000236087)
8 Imperato-McGinley J, Peterson RE, Sturla E, Dawood Y & Bar RS. Primary amenorrhea associated with hirsutism, acanthosis nigricans, dermoid cysts of the ovaries and a new type of insulin resistance. American Journal of Medicine 1978 65 389–395. (https://doi.org/10.1016/0002-9341(78)90838-0)
9 Omar HA, Logsdon S & Richards J. Clinical profiles, occurrence, and management of adolescent patients with HAIR-AN syndrome. Scientific World Journal 2004 4 507–511. (https://doi.org/10.1100/tsw.2004.106)