CASE REPORT

Precocious puberty secondary to massive ovarian oedema in a 6-month-old girl

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Abstract
A 6-month-old girl was referred with breast and pubic hair development. Investigations excluded an adrenal or central cause for her precocity. Ovarian ultrasound scans showed bilaterally enlarged ovaries with both solid and cystic changes. A follow-up examination suggested progression of the precocity and in view of the young age of the child, and concerns regarding underlying malignancy, she underwent laparotomy. Histology showed no evidence of neoplasia but there was stromal oedema consistent with a diagnosis of massive ovarian oedema. This entity is poorly recognised in the paediatric literature as a cause of sexual precocity, and has never previously been described in such a young patient. This is an unusual cause of precocity in a young child and its recognition and management are reviewed.

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Introduction
A 6-month-old girl was referred with a 3-month history of pubic hair and breast development. She was a non-identical twin, born at 36 weeks’ gestation to non-consanguineous Caucasian parents following an uncomplicated pregnancy. There was no history of consumption of any hormonal preparations during pregnancy. Her father, paternal grandfather and paternal great uncle suffered from multiple lipomas. Her twin brother was healthy. As far as we can ascertain his testicular size and consistency was normal. Her birth weight, length and head circumference plotted at the 98th, 75th and 98th centile respectively compared with current UK standards (1).

Clinically she had Tanner stage 2 breasts and pubic hair development. There was no clitoromegaly but her labia were slightly rugose with a normal looking introitus with thin red mucosa. No gonads were palpable. Chromosomes were normal (46XX). Gonadotrophins were in the normal pre-pubertal range (serum luteinising hormone, 0.5 IU/l, serum follicle-stimulating hormone 2.2 IU/l). Oestradiol was below the lower limit of our assay (<73 pmol/l). It is possible that oestrogen levels were higher than normal; certainly there was clinical evidence of oestrogenisation, but not detected because of the limitations of our assay. There was no evidence of congenital adrenal hyperplasia or Cushing’s syndrome (17-hydroxyprogesterone < 1.6 nmol/l, 0900 h cortisol 233 nmol/l, 0900 h adrenocorticotrophin 25 ng/l). Androgens were elevated, with testosterone 0.5 nmol/l and dehydroepiandrosterone sulphate (DHEAS) 0.8 µmol/l (normal ranges for a pre-pubertal child are testosterone < 0.5 nmol/l and DHEAS < 0.5 µmol/l). Bone age estimation by the Tanner–Whitehouse 2 method (2) was advanced by 6 months. Ultrasound scans of her ovaries showed bilaterally enlarged ovaries with cystic and solid components and some follicles seen bilaterally (right ovary 3.2 ml, left ovary 9 ml (Fig. 1A and B); normal ovarian volumes up to 5 years of age vary between 0.75 and 0.85 ml (3–5)). The left ovary was described as having a more solid central component than the right ovary. The uterine volume was 1.7 ml (normal pre-pubertal volume < 2 ml). Tumour markers were normal (alpha-fetoprotein 30 kU/l and beta-human chorionic gonadotrophin < 2 U/l).

Follow-up examination 2 weeks later suggested further progression of puberty with an increased breast volume and pubic hair but no change in clinical staging. Her extremely young age, progression of physical signs and concerns regarding underlying malignancy prompted surgical referral and she underwent laparoscopy, which identified a degree of bilateral torsion, worse on the left side. She then underwent open left oophorectomy. At operation both ovarian pedicles showed torsion, with preservation of the blood supply. The right ovarian pedicle was un-twisted but it was decided to defer right oophorectomy until histology was available. Microscopic examination of the enlarged ovary (3.5 × 2.2 × 1.2 cm, weight 5.1 g (normal values at birth are about 1.3 × 0.5 × 0.3 cm, weight < 0.3 g and in adults about 4 × 2 × 1 cm, weight 5–8 g) showed pronounced stromal oedema with sections...
showing normal numbers of oocytes and occasional cystic follicles (Fig. 2A and B). There was no evidence of stromal luteinisation or neoplasia. The findings were consistent with massive stromal oedema of the ovary. In an attempt to prevent further progression of her sexual maturation our patient subsequently underwent elective laparoscopic right oophoropexy and right inguinal herniotomy. A year later she remains well with no further progression of her physical signs and a reduction in her right ovarian swelling (ovarian volume 1.3 ml, Fig. 1C). Her hormone levels have returned to normal (testosterone <0.3 nmol/l, androstenedione <0.3 nmol/l and DHEAS <0.8 μmol/l).

Discussion

We describe the youngest patient reported in the literature with massive ovarian oedema (MOO) as a cause of precocious puberty. MOO is a rare but now well-recognised condition that occurs predominantly in adolescents and young women (5–33 years, with a mean age of 21 years) (6). It has been reported to occur in pregnancy (7, 8). It was initially described by Gustafson et al. (9) in 1954, and characterised by Kalstone et al. (10) in 1969. It is a rare ‘tumour-like’ condition of the ovary and defined in the World Health Organisation’s Histological Classification (11) as ‘An accumulation of oedema fluid within the ovarian stroma separating normal follicular structures. In some cases the stroma contains lutein cells and the patient is virilised’.

It typically presents with abdominal pain and a pelvic/adnexal mass. Menstrual irregularities are present in many of the post-pubertal women and resolve after treatment. Virilisation occurs in about 25% of the cases (6). There have been few reported cases of precocious puberty or early puberty (12, 13). It has been associated with Meig’s syndrome and, in a single case, with retroperitoneal and omental nodules of fibroma-like proliferations (14).

The aetiology of this condition is thought to relate to intermittent or partial torsion of the ovarian pedicle (8, 10, 15). One half of the cases show evidence of torsion at surgery. Torsion results in venous and lymphatic
obstruction, but not arterial occlusion so there is no evidence of haemorrhage or infarction seen in the ovaries of these patients (16). The resulting lymphoedema leads to proliferation of the stromal cells and in some to conversion to lutein cells. This luteinisation and stromal hyperplasia result in an increase in ovarian androgen and oestrogen production, which is responsible for the virilisation and pubertal signs seen in some of the patients (17). For this reason de-torsion and pexy was performed in our patient, with subsequent

Figure 2 (A) Microscopic section of the left ovary showing normal oocytes (thin arrows) alongside an area of pronounced stromal oedema (large arrow). (B) Section of the ovary showing massive stromal oedema. (× 40).
remission of her clinical and biochemical abnormalities. Alternatively it has been suggested that stromal proliferation or stromal hyperthecosis can occur with resultant ovarian enlargement (6). The enlarged ovary is subsequently more prone to undergo torsion and oedema. This hypothesis is supported by the fact that MOO has also been described in a previously fixed ovary (18), but would not account for the improvement seen in this case.

Fifteen per cent of cases are bilateral, 85% unilateral and 75% affect the right ovary (8). The predisposition of the right ovary may be due to elevated right ovarian vein pressure relative to the left reducing the tolerance of the right ovary to partial torsion (8). Alternatively it may be because the sigmoid colon decreases mobility of the left adnexae (19).

The definitive diagnosis of MOO cannot reliably be made pre-operatively. Ultrasound (US) scanning and magnetic resonance imaging (MRI) have both been reported to help in establishing the diagnosis. The sono- graphic findings are variable, but multiple ovarian follicles located in the peripheral cortex of an enlarged ovary have been suggested as an important diagnostic indicator of MOO (20). There are only four reports in the literature discussing the MRI findings in MOO. Two report a heterogeneous low-intensity lesion on T1-weighted images (8, 21). The third reports multiple non-enlarged follicular lesions located in the peripheral ovarian regions detected using phase-array pelvic coil MRI (22). The fourth case reports diffuse ovarian enlargement with low intensity in T1-weighted images, with multiple follicles located peripherally in the enlarged ovary (23). The diameter of the enlarged ovaries has been reported to vary from 5 to 35 cm and averages 11 cm. Hence use of the term ‘massive’ may be somewhat misleading.

As no single test is diagnostic of MOO, we recommend that besides investigation of the pituitary–ovarian axis, US scanning of the ovaries with or without an MRI (depending on the local facility), ovarian tumour markers (alpha-feto protein, beta-human chorionic gonadotrophin, oestrogen, progesterone, androgens, thyroxine) (24, 25) and laparoscopic assessment of the ovaries followed by frozen-section histology, be performed. Macroscopically the ovaries in MOO are typically opaque and white, resembling those of an oedematous fibroma or Krukenberg tumour (6), but identification of cystic follicles and sometimes corpora lutea within the oedematous tissue strongly suggests the diagnosis of MOO. Microscopic examination reveals oedematous, hypocellular stroma in the central portion of the ovary surrounding rather than displacing follicles and their derivatives. The peripheral cortex is typically composed of dense collagenous tissue and does not participate in the oedema (6).

Neoplasia is usually the principal concern when an ovarian mass is diagnosed. MOO should be considered in the differential diagnosis particularly in pre-pubertal girls and women of childbearing age. Ovarian tumours account for approximately 1% of childhood malignancies (24). They are rare in early childhood with the median age for most ovarian tumours being greater than 8 years (25, 26). Consideration should be given to pre-operative ovarian tumour markers and to frozen-section biopsy to help with intraoperative management and pathological diagnosis. Traditionally oophorectomy has been the commonest treatment for MOO (27, 28). Conservative management should be considered in younger patients. Wedge resection to debulk the ovary followed by ovarian suspension may be more appropriate in young patients if the histology on frozen section is suggestive of MOO rather than of malignancy. Because of our lack of awareness of this condition and its possible reversibility our patient underwent oophorectomy. With hindsight we would have adopted a more conservative approach with preservation of the left ovary.

Conclusion
MOO is a rare but well-recognised ‘benign tumour-like’ condition that is a potentially reversible cause of sexual precocity. It has not previously been described in such a young girl. Increased awareness of this condition is important to prevent unnecessary oophorectomy and concomitant ovarian loss especially in young patients. Laparoscopic assessment of the ovaries followed by frozen-section histology to rule out malignancy may be helpful before proceeding to any form of definitive surgery.

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