Oni *et. al.* Babcock Univ. Med. J.2024 7(2):108-113
https://doi.org/10.38029/babcockuniv.med.j..v7i2.560
eISSN: 2756-4657

CASE REPORT OPEN ACCESS

Pseudo-precocious puberty secondary to Juvenile Granulosa cell tumour in a 30-month-old female toddler: A case report

Juvenile granulosa cell tumour in a female toddler

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Submitted: 24th July 2024
Accepted: 2nd October 2024
Published: 31st December 2024
ID: Orcid ID

Abstract

Background: Precocious puberty is rare globally and its incidence in Nigeria is unknown, as few reported cases exist.

Case presentation: We report a 30-month-old female toddler with abnormal vaginal bleeding and breast enlargement of three months duration, with associated pubic and axillary hair. Height increase and unusual temper tantrums were also noticed. She had a 2-year history of steroid-containing cream use. The unrelated parents had normal puberty. There was no similar history in the siblings.

Her height was 94 cm (97th centile) and weighed 12 kg (50th centile). There were no café-au-lait spots. Breast development and pubic hair both corresponded to Tanner Stage 2. A firm mass was palpated in the lower abdominal region. A pelvic magnetic resonance imaging scan revealed a round heterogenous mass with multiple focal cystic areas in the left pelvic cavity. Bone age was normal.

Serial oestradiol levels were elevated. Tumor markers were within normal ranges. The cytological analysis of excised tissues during exploratory laparotomy with left oophorectomy revealed Call-Exner bodies which are pathognomonic for granulosa cell tumours. She has remained stable after the surgery.

Discussion and conclusion: This case report highlights the importance of considering and investigating rare causes of pseudo-precocious puberty in pre-pubertal girls.

Keywords: Female, Juvenile granulosa cell tumour, Pseudoprecocious puberty, Toddler

Background

Puberty is the transition between childhood and adulthood, involving physical and psychosocial development and maturation (1). It is normally triggered by activation of the hypothalamic-pituitary-gonadal (HPG) axis leading to a cascade of events. The hypothalamus secretes gonadotropin-releasing hormone (GnRH), which, in turn, stimulates the anterior pituitary to release luteinising hormone (LH) and follicle-stimulating

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hormone (FSH). These hormones act on the gonads to produce testosterone in males and oestradiol in females (2, 3). The first clinical sign of puberty is breast bud development in girls, and an increase in testicular volume in boys (4).

In precocious puberty, there is an age-inappropriate activation of the HPG axis, leading to the development of secondary sexual characteristics before the expected age. Traditionally, it is defined as the onset of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys (2, 4, 5). Worldwide, the prevalence of precocious puberty is estimated to range from 1/5,000 to 1/10,000 children, with a male-to-female ratio of 1:10 (6). Precocious puberty can be central (true) or peripheral (pseudo). Central precocious puberty is gonadotropin-dependent and results from premature but normal activation of the HPG axis. Pseudo- or peripheral precocious puberty is independent of the maturation of the HPG axis, resulting from the production of sex hormones from the gonads, adrenal glands or exogenous sources (7). The incidence of precocious puberty in Nigeria is unknown, as few reported cases exist (8). Precocious puberty may induce anxiety, embarrassment, mental stress, or stigmatisation for both parents and affected individuals, potentially exposing patients to the risk of sexual assault (9). It can also trigger the premature fusion of bones, leading to short stature (1). Consequently, prompt evaluation and treatment are imperative upon the presentation of symptoms.

There are several causes of precocious puberty. Ovarian granulosa cell tumours (GCT) are a rare sex cord-stromal tumour, comprising 2-5% of ovarian tumours (10). Ovarian GCTs are hormonally active and secrete high levels of estrogen. In pre-pubertal girls, elevated estrogen levels can lead to the early development of secondary sexual characteristics, which is the hallmark of precocious puberty (10). Common symptoms include abnormal uterine bleeding, acne, breast enlargement, the appearance of facial, axillary, or pubic hair, abdominal swelling, or abdominal pain (11).

Surgical intervention is the primary treatment for ovarian granulosa cell tumours (12). Early detection is crucial, as it is associated with a good prognosis. Recurrences are uncommon, with relapses most commonly occurring within the first year following treatment (7).

Case report

A 30-month-old girl presented with vaginal bleeding and breast enlargement persisting for three months. The bleeding gradually increased in volume, necessitating changing underwear up to six times a day. In the first 2 months, the vaginal bleeding occurred for two to three days monthly with a 28-day interval but in the third month, it happened at 14-day intervals. There was no bleeding from other parts of the body. The development of sparse public and axillary hair accompanied the symptoms. Height increase and unusual temper tantrums were noticed, but there was no history of vomiting, rashes, or seizures. She was not on any routine medications and had no exposure to ionising radiation or chemotherapy. However, there was a 2-year history of the use of a steroid-containing cream (Skineal®) on her skin by her mother to preserve her skin colour and tone. The cream was discontinued three months before the onset of symptoms. The birth, neonatal period, and developmental milestones were normal. She is the only girl and the last of 3 children in a monogamous, non-consanguinous marriage. The parents had normal puberty. There was no similar history in the siblings.

Her height was 94cm (97th centile) and she weighed 12kg (50th centile) using the WHO growth chart. There were no café-au-lait spots. Breast development and pubic hair both corresponded to Tanner Stage 2. A firm, 4cm by 6cm smooth and non-tender mass was palpated in the lower abdomen. Neurological examination was normal.

Bone age using the Atlas of Greulich and Pyle (13) was compatible with the chronological age. Serial hormonal assays are shown in Table 1. Tumor markers (alpha-fetoprotein, CA125, and beta-human chorionic gonadotropin) were within normal ranges.

Table 1: Summary of the hormonal profile

Date	At presentation	6 months later	1 month after surgery	Reference
Oestradiol (pg/ml)	< 9.0	64.6	26.9	<15
Progesterone (ng/ml)	<1.5	0.2	2.7	0.1 - 0.3
FSH (mIU/L)	<1.07	1.0	1.5	<0.1 - 7.1
LH (mIU/ml)	<1.0	1.9	1.0	<0.1 - 3.3

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An abdominopelvic ultrasound scan showed a heterogeneous mass in the left lower abdomen, measuring 62.1 x 33.6 x 53.8mm with an estimated volume of 60mls. A Doppler interrogation of the mass revealed moderate peripheral and mild central vascular flow. The right ovary and other findings were normal. A pelvic magnetic resonance imaging (MRI) scan revealed a heterogeneous mass with multiple focal cystic areas in the left pelvic cavity (Figures 1 and 2). The mass measured 47.8 x 38.6 x 50.4mm. The left ovary was not discernibly separate from the mass. The right ovary was normal.

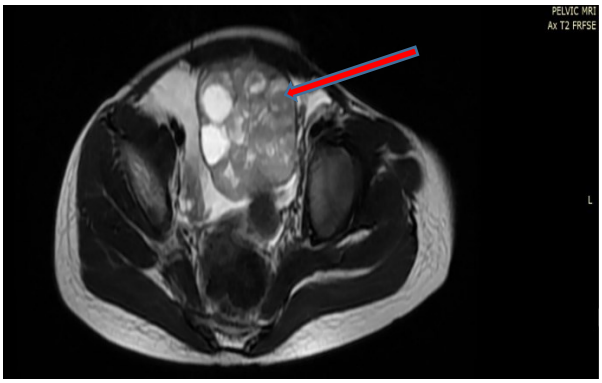

Figure 1: Axial view of Pelvic MRI (T2) showing a round heterogenous mass with multiple focal cystic areas in the left pelvic cavity

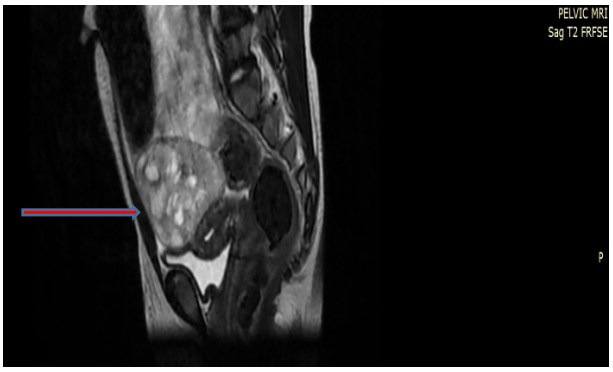

Figure 2: Sagittal view of Pelvic MRI (T2) showing a round heterogeneous mass (arrow) with multiple focal cystic areas in the left pelvic cavity

Exploratory laparotomy done 7 months after presentation revealed an enlarged encapsulated left ovary with regular boundaries, measuring 6cm x 4cm, with the left fallopian tube adhered to it and approximately 60mls of ascites. Pelvic and para-aortic nodes were normal, with no evidence of metastasis. The patient was discharged 5 days post-surgery but has had financial challenges undergoing follow-ups.

The cytological analysis of the straw-coloured peritoneal fluid demonstrated cohesive clusters of stromal cells with oval to polygonal bland nuclei, regular nuclear membrane, and scant to moderate cytoplasm set against a background of mild mixed inflammatory infiltrates with no malignant cells seen (Figure 3). Histological sections of the excised tissue (Figures 4 and 5) showed a cellular lesion composed of tumour cells disposed in solid sheets, interspersed with small immature follicles of varying sizes and shapes containing secretions. The component cells had round, hyperchromatic ungrooved nuclei with abundant eosinophilic to clear cytoplasm. Occasionally, Call-Exner bodies were identified. Overall features were consistent with a juvenile granulosa cell tumour.

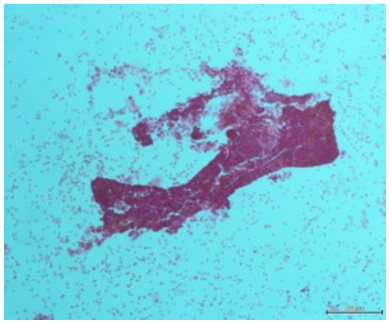

Figure 3: Peritoneal fluid cytology cohesive cluster of fairly uniform stromal cells (Giemsa stained smear @ x100)

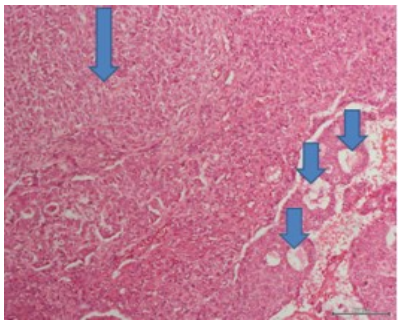

Figure 4: H & E at x100 showing solid sheets of tumour cells (long arrow) admixed with immature follicles containing secretions (short arrows)

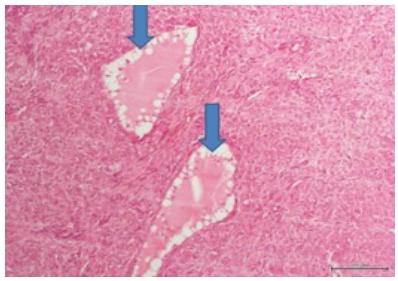

Figure 5: H & E at x100 showing Call-Exner bodies (arrows) consistent with granulosa cell tumour

Discussion and Conclusion

Juvenile granulosa cell tumour is a rare type of ovarian tumour recognised as a cause of pseudo-puberty in pre-pubertal girls (14). They originate from the granulosa cells, responsible for producing sex steroids and proteins essential for ovulation (15). Classified as a low-grade malignant tumour of the granulosa cells of the sex cords, granulosa cell tumours (GCT) represent 1-5% of all ovarian tumours with two distinct types: adult and juvenile (15, 16). The juvenile form, accounting for approximately 5% of GCT cases, predominantly affects pre-pubertal girls, as also seen in the 30-month-old toddler presented in this report (16).

The clinical features of juvenile GCT are usually that of isosexual pseudo-precocity due to excess oestrogen (12). Our patient presented with abnormal vaginal bleeding, breast enlargement, and axillary and pubic hair development which were diagnostic of precocity and in keeping with juvenile GCT. Diagnosing juvenile GCT preoperatively can be challenging due to the absence of consistent hematologic findings or specific indicators (14). However, in most cases, clinical suspicion, hormonal assays and imaging contribute to an accurate diagnosis (17). The prolonged use of steroid-containing cream nearly obscured the consideration of other possible causes of precocious puberty in our patient. This emphasises the need for a thorough review and investigation of precocious puberty, especially in younger female children.

The juvenile GCT staging, according to the Federation International of Obstetrics and Gynecology 2014 criteria includes four stages (IA&B, II, III, IV) (18). Our patient was classified as

stage IA (the tumour is confined to one ovary) with a favourable prognosis and rare recurrences within the first year of treatment. Since operated 17 months ago, there has been no recurrence of the symptoms in our patient. The other stages are associated with poorer prognosis, particularly as the stages advance (18).

Most juvenile GCT cases present with stage I disease, exhibiting a lower likelihood of recurrence after simple resection. However, limited data shows no consensus on chemotherapy for this stage (19). Early detection results in a favourable prognosis, with rare recurrences within the first year following treatment (12).

In conclusion, juvenile granulosa cell tumour is a rare cause of pseudo-precocious puberty and requires prompt evaluation and treatment. Awareness of this condition is essential for early detection and favourable outcomes. This case report highlights the importance of considering rare causes of pseudo-precocious puberty in pre-pubertal girls and the need for multidisciplinary management of such cases.

List of Abbreviations

FSH: Follicle-stimulating Hormone
GCT: Granulosa Cell Tumours
GnRH: Gonadotropin-releasing hormone
HPG: Hypothalamic-pituitary-gonadal
LH: Luteinising Hormone
MRI: Magnetic Resonance Imaging

Declarations

Ethical approval and consent to participate

Written informed consent for publication was obtained from the father of the patient whose management is being reported.

Consent for publication

All authors gave consent for publication of the work under the Creative Commons Attribution-Non-Commercial 4.0 license.

Availability of data and materials

All essential data supporting the findings of this case are available within the article. Additional data are available upon request from the corresponding author.

Competing interests

The authors declare no conflict of interest.

Funding

The authors declare that they had no funding source or financial support.

Authors' contributions

All the authors developed the concept. OTE and AOA designed and drafted the manuscript while GEO, NJI, OVC and AnOA contributed to the design and critically reviewed the manuscript. All the authors read and approved the final draft. All authors agreed to be accountable for all aspects of the work.

Acknowledgements

Not applicable.

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