Precocious pseudo-puberty presenting with bilateral ovarian involvement and progressing to juvenile granulosa cell tumor in a 2-year-old girl

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01 Background

Feminising precocious pseudo-puberty in McCune-Albright syndrome (MAS) and juvenile granulosa cell tumour (JGCT) arises from bilateral and unilateral estradiol hypersecretion respectively. GNAS mutations cause MAS but have been also been described in some cases of JGCT.

02 Aim

To describe an unusual case of precocious pseudopuberty and discuss the overlap between two entities: the Mc Cune Albright syndrome and juvenile granulosa cell tumor

03 Case

A girl aged 2.17 years presented with isolated bilateral breast development

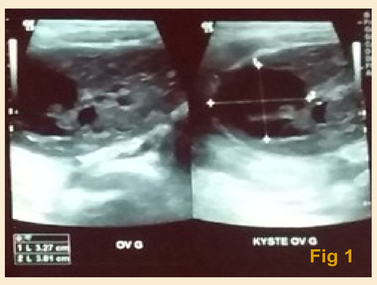
Past history:
-Birth weight: 3650 g, birth length: 50 cm
-Parents unrelated, no relevant family history

Examination:
- **Weight:** 13.2 kg (+1SD), **Height:** 94 cm (+2.6 SD)
- Tanner stage: B3P2A1
- Parental heights: Mother:160cm, Father 174 cm. -
-Midparental height: 160.5 cm (-0.4 SD)
-Single « café au lait » patch on the antero-lateral border of the left thigh, 3cm in its largest axis, with irregular outline.
- No bony deformity
- Liver edge 7 cm below costal margin, no splenomegaly,
- No other significant findings

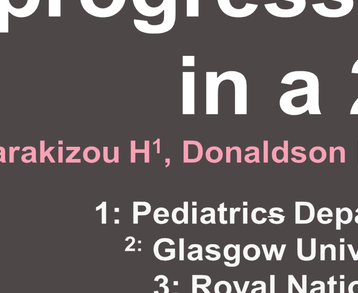
Investigations:
Bone age: 5 years
Estradiol: 190 pg/ml (normal < 20 pg/ml)
LHRH stimulation test:

t(min)	t 0	t 15	t 30	t 60	t 90
FSH(mUI/ml)	<0,1	<0,1	<0,1	<0,1	<0,1
LH (mUI/ml)	0,43	0,39	0,3	0,25	0,18

Pelvic ultrasound (Fig1, Fig 2):



-Left ovary: Enlarged, **63mm** in longitudinal axis, multiple cysts (largest **38 mm)** with thin septa



-Right ovary: Enlarged, **66mm** in longitudinal axis, multiple cysts (maximum **33mm)** with thin septa

Provisional diagnosis:
McCune Albright syndrome
([screening of anomalies associated witth MAS (serum phosphate ,calcium, IGF1 , TSH, free T4, urinary free cortisol, bony scintigraphy) : negative]

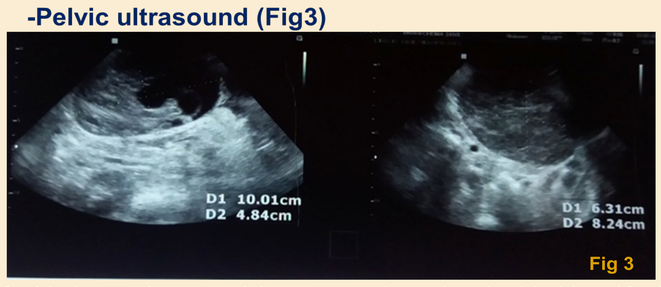
Treatment: Tamoxifen 20 mg daily.

Progress:
After **only** 1 ½ months:
- 4 cm increase in height, Tanner stage: B3-4
- Menorrhagia, Bone age: 6.5 years

Further investigations:
-LH RH stimulation test

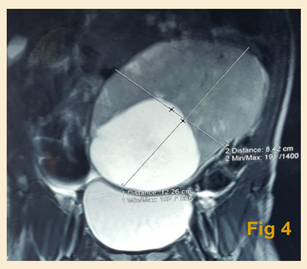
t(min)	t 0	t 1	t 30	t 60	t 90
FSH (mUI/ml)	<0.1	<0.1	<0.1	<0.1	<0.1
LH (mUI/ml)	0.13	0.25	0.23	0.22	0.15

-Pelvic ultrasound (Fig3)



Left-sided vascular mass lying postero-lateral to the bladder, 10x 8x6 cm, mixed solid/cystic with multiloculated cysts of ovarian origin
Right ovary: normal appearance and dimensions!

Pelvic MRI (Fig 4)



- Well defined solid-cystic abdomino-pelvic mass (5 x 10 x 12 cm) with **left ovarian origin** and extending to aorta and kidney
- No local invasion
- **Normal right ovary**
- Uterus: 4 x 2 cm / Endometrium: 10 mm

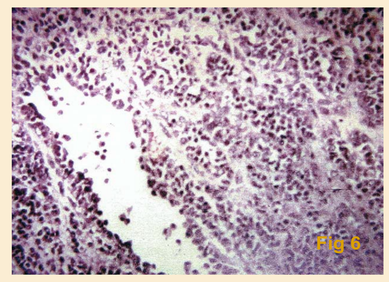
- αFP: 4.2 IU / l (reference range <10ng / ml)
- HCG <0 (reference range <2ng / ml)
- ACE: 2,3ng / ml (reference range <5ng / ml)
- CA 125: 43IU / ml (reference range <35nUI / ml)
- Inhibin B: N/A

Ovarian tumor suspected and girl transferred to the surgical team that recommended a **Simple clinical and radiological surveillance**

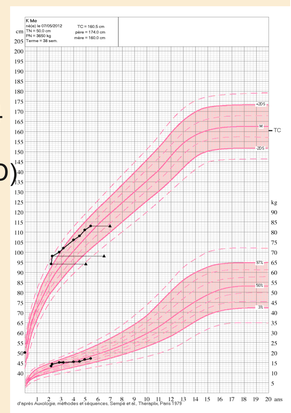
After a week : torsion of the ovarian annex

Urgent laparotomy with removal of left ovary and annexectomy (Fig 5).
- Tumour weight = 850g, capsule intact
- No malignant cells found on peritoneal lavage
- Macroscopic appearance: **Juvenile granulosa cell tumour**
-no infiltration of capsule; no spread to Fallopian tube

Histopathology of tumour specimen (Fig 6):
- Large cells with abundant eosinophilic cytoplasm and large hyperchromatic nuclei with many abnormal mitosis
- Very polymorphic architecture, most often solid, richly vascularized with some hyaline and haemorrhagic foci.
- Several Call -Exner bodies
- No capsular infiltration
- **Immunochemistry**: **inhibin B +++** α-fetoprotein and anti-CD30 below the detection limit



Post-operative progress
-Immediate regression of metrorrhagia
-Estradiol: 18 pg / ml
-Review aged 3 years and 4 months
Height: 113 cm (+ 0.9 SD)
Weight: 17.2 kg (0 SD)
Pubertal stage: B1 P1
Hormonal profile:
Estradiol: 13 µg / ml,
FSH: 2.52 mIU / ml,
LH: 2.49 mIU / ml
Pelvic ultrasound: no abnormalities



Genetic studies in tumour
- ***GNAS1* mutation** negative for the common hot-spots (R201C, R201H and Q227L)
- Sequencing of exon 3 in ***AKT1* gene** is pending (laboratory of Prof Veitia, Paris)

03 DISCUSSION

-McCune Albright syndrome (MAS): somatic mutation of GNAS gene1 which encodes the G-protein α subunit, affecting tissues (e.g. skin, ovary, bone) in a mosaic pattern:

*Café au lait patches, precocious pseudopuberty, fibrous dysplasia.

*More rarely hyperthyroidism, Cushing's syndrome, gigantism and renal phosphate wasting

Genetic testing is **unnecessary** in classic cases (multisystem involvement) but single organ McCune Albright syndrome may require tissue biopsy and DNA analysis for confirmation [1].

-Juvenile granulosa cell tumor (JGCT): 67% of the sex cord-stromal tumours, 5-12% of all ovarian tumours in children.

Clinical presentation: abdominal mass; isosexual precocious pseudopuberty, disturbance of menstrual cycle +/- signs of hyperandrogenism in adolescents; acute abdomen (torsion of the annexe, or tumour rupture with haemo-peritonitis).

Inhibin B and Anti-Mullerian Hormone levels are raised, and are useful in tumour monitoring .

GNAS mutation: found in 9 of 30 patients with JGCT [2]. Activating oncogene *AKT1* mutation in more than 60% of cases [3]

The case we report is unusual. Feminising precocious pseudopuberty was associated initially with evidence of **bilateral ovarian activity**, which then progressed to a juvenile granulosa cell tumour in one ovary with normal ultrasound and MRI findings in the other ovary.

✓ The diagnosis of McCune Albright syndrome **cannot be** supported in our patient at present since she has only one café au lait patch, no bony lesions, and no ***GNAS* mutation** detected in DNA extracted from paraffin blocks of the ovarian tumour.

✓ While the radiological and histological diagnosis of **juvenile granulosa cell tumour** is secure this **does not explain** the initial features at presentation in our patient.

✓ The current diagnosis therefore is one of pseudopuberty of ovarian origin, with progression to juvenile granulosa cell tumour, in which the **underlying mechanism remains unclear.**

04 CONCLUSION

The aetiology in this case remains unclear, with MAS unproven, and evolution towards JGCT. Studies to determine AKT1 mutation in the tumour are planned. This case highlights current uncertainties in the causes of ovarian precocious pseudopuberty and the relationship between MAS and JGCT.

05 REFERENCES

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