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Case Report

Diagnostic value of ovarian tissue biopsy in McCune–Albright syndrome presenting with recurrent hemorrhagic ovarian cysts and precocious puberty

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ABSTRACT

We report the case of a 12-year-old girl with recurrent hemorrhagic ovarian cysts and peripheral precocious puberty (PPP), managed sequentially with gonadotropin-releasing hormone analogs, aromatase inhibitors, and combined oral contraceptives. Pelvic imaging revealed a complex hemorrhagic cyst in the left ovary. Owing to the atypical presentation and inconclusive peripheral blood genetic testing, an ovarian tissue biopsy was undertaken. Molecular analysis of the ovarian tissue identified a pathogenic heterozygous variant, c.602G>A (p.Arg201His), in exon 8 of the GNAS gene, confirming the diagnosis of McCune–Albright syndrome (MAS). This case highlights the diagnostic utility of ovarian tissue biopsy and targeted molecular testing in suspected MAS, particularly in the absence of classical phenotypic features and when peripheral testing fails to detect mosaic GNAS mutations.

Keywords: Mccune–Albright syndrome, Peripheral precocious puberty, Ovarian cyst, Ovarian biopsy, GNAS mutation

INTRODUCTION

McCune–Albright syndrome (MAS) is a rare genetic disorder with an estimated incidence of 1 in 100,000 to 1,000,000 live births[3].The condition results from post-zygotic activating mutations in the GNAS gene, which encodes the α-subunit of the stimulatory G protein (Gsα). These mutations lead to constitutive activation of adenylate cyclase, resulting in increased intracellular cyclic adenosine monophosphate (cAMP) and downstream endocrine hyperfunction.[1,2]

As a mosaic disorder, MAS exhibits wide phenotypic variability. The classical triad includes polyostotic fibrous dysplasia, café-au-lait macules, and endocrine hyperfunction.[2,3] In girls, the most frequent endocrine manifestation is peripheral precocious puberty (PPP), typically associated with recurrent, estrogen-producing hemorrhagic ovarian cysts.[2]

Diagnosis can be challenging because the mosaic distribution of GNAS mutations often results in negative findings on peripheral blood testing, even in clinically evident cases.[2,4] Tissue-specific molecular testing-particularly from affected tissues such as bone or ovary-significantly enhances diagnostic yield and may confirm MAS in cases lacking the classical phenotype.[2]

We report a case of a 12-year-old girl with recurrent hemorrhagic ovarian cysts and PPP, in whom MAS was diagnosed via ovarian tissue biopsy and molecular genetic analysis. This case emphasizes the diagnostic value of direct tissue sampling when GNAS mosaicism is suspected and peripheral blood testing is inconclusive.

CASE REPORT

A 12-year-old girl, previously diagnosed with peripheral precocious puberty (PPP) progressing to central precocious puberty (CPP) since the age of 5.5 years, presented with recurrent lower abdominal pain and intermittent vaginal spotting. Her prior treatments included intermittent courses of leuprolide and letrozole, followed by combined oral contraceptive therapy containing drospirenone and ethinyl estradiol at the time of symptom recurrence.

Table 1: Lab reports at initiation of treatment.

Test	Report
LH	<0.3 mIU/ml
FSH	<0.3 mIU/ml
Estradiol	54 pg/ml

Pelvic ultrasonography and magnetic resonance imaging (MRI) revealed a complex hemorrhagic cyst measuring 3.2×4.7×5.5 cm in the left ovary. Serum CA 19-9 levels were mildly elevated (57.4 U/ml), while CA-125 and β-hCG were within normal limits. Despite adequate hormonal suppression, the ovarian cysts recurred periodically.

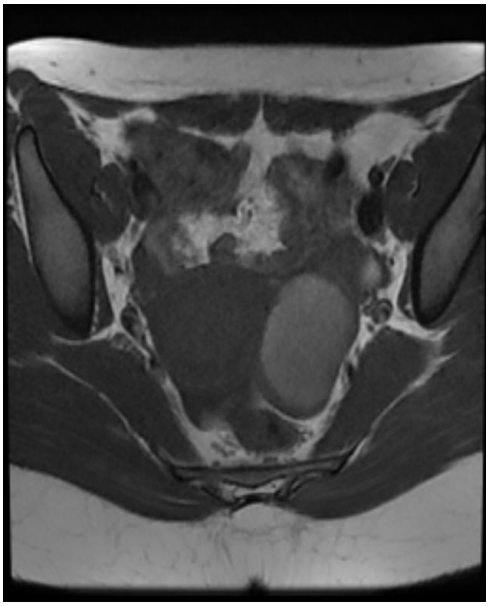

Figure 1: Large well defined multiobulated multiseptated complex cyst is noted in left adnexa, measuring approximately 3.2 x 4.7 x 5.5cm (CC x AP x ML), stretching the ovary to the periphery. Areas of haemorrhage in various stages and blood fluid levels (T2 staging) are noted within the cyst. The walls and septae (maximum thickness = 1.5mm) of the cyst show post contrast enhancement. No enhancing solid mural nodule is seen within the cyst.

In view of the absence of skeletal lesions or café-au-lait macules, but with ongoing estrogenic ovarian activity and an inconclusive peripheral blood genetic panel, a diagnostic laparoscopic ovarian biopsy was performed to evaluate for an underlying mosaic GNAS mutation.

Methodology

The ovarian tissue biopsy was submitted for molecular genetic analysis. Genomic DNA was extracted from the biopsy specimen, and whole-exome sequencing (WES) was performed to identify pathogenic variants, including single nucleotide variants (SNVs), insertions/deletions (indels), and copy number variations (CNVs).

Bioinformatic analysis revealed a heterozygous pathogenic variant, c.602G>A (p.Arg201His), located in exon 8 of the GNAS gene. This mutation is a well-established activating variant known to cause constitutive Gsα protein signaling and is pathognomonic for McCune–Albright syndrome (MAS).[1-3] The molecular finding was consistent with the patient's clinical phenotype of recurrent estrogen-producing ovarian cysts and precocious puberty.

DISCUSSION

This case illustrates an atypical presentation of McCune–Albright syndrome (MAS), characterized by recurrent estrogen-producing hemorrhagic ovarian cysts and peripheral precocious puberty (PPP), without the classical features of café-au-lait macules or fibrous dysplasia.

The pathogenic GNAS variant identified, c.602G>A (p.Arg201His), results in constitutive activation of the Gsα protein, leading to unregulated intracellular cAMP signaling and autonomous estrogen production.[1,2] This mechanism explains the recurrent cystic ovarian activity and the incomplete response to standard hormonal suppression, including GnRH analogs and aromatase inhibitors.

In typical MAS, diagnosis can often be suggested clinically and confirmed by peripheral blood testing. However, due to somatic mosaicism, the mutation may be absent in peripheral leukocytes, resulting in false-negative genetic results despite characteristic clinical features.[2-4] In such cases, targeted molecular testing of affected tissue—such as bone lesions, ovarian cysts, or skin—becomes essential for definitive diagnosis.[2-4]

This case represents one of the few reported instances where MAS was confirmed through ovarian tissue biopsy, reinforcing the diagnostic value of tissue-specific sampling when clinical suspicion remains high but peripheral results are inconclusive. Identifying the GNAS mutation directly within the ovarian tissue established a definitive molecular diagnosis, avoiding unnecessary surgical interventions and guiding long-term medical management with agents such as dienogest and continued hormonal suppression.

Moreover, this case underscores the heterogeneous spectrum of MAS, in which disease expression depends on the timing and tissue distribution of post-zygotic GNAS mutations. Clinicians should maintain a high index of suspicion for MAS in girls presenting with recurrent ovarian cysts and PPP, even in the absence of skeletal or cutaneous findings.

CONCLUSION

This case reinforces the importance of considering McCune–Albright syndrome (MAS) in girls presenting with recurrent or persistent ovarian cysts and peripheral precocious puberty, even in the absence of the classical triad of fibrous dysplasia, café-au-lait macules, and endocrine hyperfunction.

When peripheral blood genetic testing is inconclusive, tissue-specific molecular analysis, such as from ovarian biopsy, can provide a decisive diagnosis by detecting mosaic GNAS mutations that may not be present in blood samples. Early and accurate identification of MAS enables individualized management, avoids unnecessary surgical interventions, and preserves both reproductive and endocrine function in affected patients.

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