

McCune-Albright syndrome diagnosed from the ovarian tissue of a 5-year-old girl: a case report

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Background: The McCune-Albright syndrome (MAS) (OMIM#174800) is a rare congenital disease, involving a triad of fibrous dysplasia (FD), café au lait skin spots, and peripheral precocious puberty; however, other endocrinological problems are also noted. The rarity of this disease and its variable clinical manifestations have led to delayed diagnoses and misdiagnoses. We report a case that was diagnosed by laparoscopy for early intervention to decrease skeletal lesions.

Case Description: We reported the case of a 5-year-old East Asian Chinese girl with breast enlargement, vaginal bleeding, and an ovarian cyst. Examination revealed normal anthropometric parameters. Pelvic ultrasound identified right ovarian cyst and multiple follicles. Biochemical investigations before and after cystectomy revealed no changes in the follicle-stimulating hormone and luteinizing hormone levels. We performed a cystectomy and collected a small tissue sample from the right ovary for genetic sequencing. She was diagnosed with MAS based on a genetic analysis of the ovarian tissue after laparoscopic cystectomy. Genetic testing of the right ovarian tissue revealed a mutation in guanine nucleotide-binding protein of the alpha-stimulating activity polypeptide (GNAS) (p.Arg201 + p.Gln227), and cyst was pathologically diagnosed as a follicular cyst. The patient recovered immediately after the surgery. She was treated with oral vitamin D subsequently and both of her breasts decreased in size and no vaginal bleeding occurred until the last follow-up. The patient had no café au lait skin spots or FD during follow-up.

Conclusions: Our observations indicate that early diagnosis and intervention are crucial for improving the prognosis of patients with MAS. Ovarian cystectomy, when indicated, should be considered for establishing the diagnosis of MAS on a histological and genetic basis.

Keywords: McCune-Albright syndrome (MAS); precocious puberty; ovarian cyst; case report; GNAS mutation

Received: 20 August 2022; Accepted: 28 April 2023; Published online: 11 May 2023. doi: 10.21037/gpm-22-27 View this article at: https://dx.doi.org/10.21037/gpm-22-27

Introduction

The McCune-Albright syndrome (MAS) affects both men and women, and its prevalence ranges from 1/100,000 to 1/1,000,000 (1). MAS is difficult to diagnose. It originates from somatic postzygotic activating mutations in the guanine nucleotide-binding protein of the alpha-stimulating activity polypeptide (GNAS) gene (1). The mutations do not affect all cells; therefore, genetic analysis of the affected tissue is the most reliable method of obtaining a definite diagnosis (2). Because genetic analysis often requires

invasive procedures for specimen collection, it is not often recommended to patients. We present the case of a 5-year-old East Asian Chinese girl with peripheral precocious puberty that was characterized by breast enlargement, vaginal bleeding, and the presence of ovarian cysts. The girl did not present with the characteristic features of MAS, such as fibrous dysplasia (FD), or café au lait skin spots; thus, diagnosis was difficult, even with genetic blood testing. The final diagnosis was established using a genetic analysis of the cystic ovarian tissue, which was performed after multidisciplinary consultations. We report a case that was diagnosed by laparoscopy for early intervention to decrease skeletal lesions. We present this case in accordance with the CARE reporting checklist (available at https://gpm. amegroups.com/article/view/10.21037/gpm-22-27/rc).

Case presentation

A 5-year-old East Asian Chinese girl (5 years and 9 months) was admitted to our hospital because of breast enlargement and recurrent vaginal bleeding on October 8th, 2021; she was initially diagnosed with peripheral precocious puberty. Her delivery was via the vagina with a birth weight of 3,900 g. Her family history was unremarkable, and she was not a descendant of consanguineous parents. Breast development and ovarian cysts were initially observed at the age of 3 years. She was previously diagnosed with precocious puberty at another hospital and had been taking medications for approximately one year; however, her parents could not provide additional details on a relevant medication history. After the medications were withdrawn, she experienced breast enlargement and development of an ovarian cyst.

Highlight box

Key findings

• Early diagnosis is crucial for patients with McCune-Albright syndrome.

What is known and what is new?

- The rarity of this disease and its variable clinical manifestations have led to delayed diagnoses and misdiagnoses.
- We performed the laparoscopy for early diagnosis and intervention to decrease skeletal lesions in our patient with McCune-Albright syndrome.

What is the implication, and what should change now?

 Clinicians should pay more attention to atypical manifestations of McCune-Albright syndrome. Irregular vaginal bleeding (in the form of spotting) occurred subsequently; each time, lasting for 7 days.

Examination revealed normal development with the following indices: height, 113 cm (median, 114.86 cm; Z-score, -0.07); weight, 19.6 kg (median, 19.77 kg; Z-score, -0.41); and body mass index, 15.35 kg/m² (median, 14.96 kg/m²; Z-score, 0.27). However, her bone age was 7.3 years. According to the Tanner staging, her breast enlargement stage was B3. No café au lait spots were observed on the skin. Moreover, abdominal and other systemic examinations were unremarkable.

Biochemical investigations before and after cystectomy revealed no changes in the follicle-stimulating hormone and luteinizing hormone levels (0.1/<0.1 IU/L). Serum estradiol level was 604.5 pg/mL before the surgery and <11.8 pg/mL after the surgery. Serum phosphate and thyroid hormone levels were normal before and after the surgery.

Pelvic ultrasound examination revealed a right ovarian cyst (3.6 cm \times 4.0 cm \times 3.6 cm), uterine width of 1.9 cm, and an endometrial thickness of 0.15 cm. The left ovary measured 1.7 cm \times 0.9 cm \times 1.9 cm in the sagittal plane and had 4–5 follicles. Breast ultrasound revealed mammogenesis with hypoechoic masses in the left and right breasts (measuring 4.8 cm \times 1.0 cm \times 4.3 cm and 3.3 cm \times 1.1 cm \times 3.3 cm in the transverse plane, respectively). No bone lesions were observed.

The patient did not present with the characteristic features of MAS. There were no precise evidence to support her diagnosis of MAS. According to the literature, a genetic analysis of the cystic ovarian tissue was significant to make the final diagnosis. Therefore, we performed a laparascopic surgery on October 9th, 2021. We identified right ovarian enlargement with a cyst and multiple follicles, intraoperatively. The cyst measured 3.5 cm × 2.0 cm × 2.0 cm, while the left ovary measured 1.7 cm × 0.9 cm × 2.0 cm. We performed a cystectomy for pathological examination and collected a small tissue sample from the right ovary for genetic sequencing (whole exome sequencing, WES).

The patient recovered immediately after the surgery. The right ovarian cyst was pathologically diagnosed as a follicular cyst. Genetic testing of the right ovarian tissue revealed a mutation in *GNAS* (p.Arg201 + p.Gln227). We decided to treat the patient with oral vitamin D (took vitamin D3 700 IU daily until her level of vitamin D in serum was normal) after a multidisciplinary consultation, only because all symptoms regressed spontaneously after the surgery. We made a final diagnosis of MAS postoperatively.

The parents were informed about the need for regular medical follow-up. Both of the breasts decreased in size and no vaginal bleeding occurred until the last follow up on February 4th, 2022. There was no sides effects or unexpected events occurring during the entire course of treatment.

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's parent for publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

The co-occurrence of FD, café au lait spots, and peripheral precocious puberty is very common in patients with MAS. In most cases, MAS can be diagnosed based on typical clinical manifestations. Our patient did not present with FD, abnormal renal phosphate transport, Cushing's syndrome, hyperthyroidism, or other endocrinological features; however, genetic testing of the affected ovarian tissues yielded positive results for a *GNAS* mutation (chr20:57484421, p.Arg201 + p.Gln227), which indicated MAS. Ovarian surgery for cysts should be avoided unless there is severe abdominal pain or a risk of torsion (2).

The rarity of this disease and its variable clinical manifestations have led to delayed diagnoses and misdiagnoses. FD is the most frequent characteristic feature of MAS; only a very small percentage of atypical cases present with a lack of FD. Mutations in GNAS impair the differentiation of skeletal stem cells, which leads to FD of the bone. Patients with FD lesions generally experience pain, fractures, and functional loss, especially in the craniofacial region; this results in facial asymmetry. Most FD lesions begin to present during early childhood, because the final skeletal burden is established by the age of 15 years. A study by Hart et al. reported that the majority of skeletal lesions are identified between 3-10 years of age (3). Medical intervention for endocrinopathies can reduce skeletal morbidities (4). Successful management of MAS depends on early diagnosis and intervention. Many patients with delayed or inappropriate treatments have complications and poor prognoses. Genetic testing of the affected tissues is recommended in atypical cases. A biopsy is usually the only way to confirm a diagnosis in questionable cases; however, the biopsy results may be false-negative if the specimen only contains normal tissue. Our patient did not present

with the typical clinical features of MAS, and the blood tests were negative; therefore, we performed a cystectomy for the genetic testing of the affected tissues. Ovarian surgery for cysts should be considered when the diagnosis is unclear.

Generally, MAS treatment is mainly focused on controlling symptoms and delaying the disease progression. Letrozole and tamoxifen are administered as the first-line therapy, while fulvestrant is administered as the secondline or adjuvant therapy. Letrozole effectively decreases the frequency of vaginal bleeding. Children may require gonadotropin-releasing hormone agonist therapy for secondary central precocious puberty. Conversely, adult women should be monitored for abnormal uterine bleeding associated with intrauterine devices and use of progestin or oral contraceptives. Meanwhile, the risk of estrogen receptor-positive breast cancer should also be considered in women with MAS (5). Patients with peripheral precocious puberty always have a higher estrogen level, which may increase the risk of breast cancer in them.

A good control of precocious puberty is essential for stabilizing bone maturity and improving adult height (6). Uncontrolled precocious puberty can not only elevate the risk of cancer, but can also cause psychological problems in children. Therefore, precocious puberty should be managed carefully. Treatments range from simple observation to combinations of several medications. The treatment goal is to decrease the number of medical problems caused by excess estrogen in a long-term.

Using PubMed, we reviewed some literatures on MAS (in association with precocious puberty) that were published (Table 1). One patient presented with precocious puberty as the only feature, while 32 patients presented with a triad of FD, café au lait spots, and peripheral precocious puberty. Therefore, it is very important to screen for bony lesions in patients who present with an isolated manifestation. Assessment of the bone system requires detailed medicalhistory taking, laboratory tests, physical examination, and radiological and nuclear imaging; furthermore, bone-age and growth-rate evaluations should also be performed. The resultant data from these assessments help determine the treatment options. It is crucial for physicians to monitor patients who present with isolated manifestations. Of the patients presented in Table 1, 38 had FD and 34 had craniofacial FD (CFFD). Additionally, 20 patients with CFFD were diagnosed with MAS before the age of 15 years. The incidence of CFFD may not be low in patients with MAS and precocious puberty; however, reliable data on this are lacking. Functional loss, such as hearing and loss of

Table 1 Clinical	l characteristics of ou	r patient and of the	patients identified	from the literature review
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Serial No.	Age at dx of MAS	Age at dx of PP	Café au lait spots	FD	CFFD	Height Z-score ^ª	Other endocrinopathies	Ovarian ultrasound findings
1	5.8 years	3 years	-	-	-	-0.4	-	Unilateral ovarian cyst
2 (7)	6.3 years	5 years	+	+	+	3.3	-	Unilateral ovarian cyst
3 (7)	4.7 years	1 year	+	+	+	4.0	-	Bilateral ovarian cysts
4 (7)	7 years	7 years	-	+	+	-0.7	-	-
5 (7)	4.3 years	4 years	-	+	+	-0.7	-	Unilateral ovarian cyst
6 (7)	2.1 years	1 year	+	+	+	1.9	Hyperthyroidism	Unilateral ovarian cyst
7 (8)	24 years	NA, menarche at 7 years	+	+	+	NA	Hyperthyroidism	NA
8 (9)	26 years	9 years	+	+	+	NA	-	NA
9 (10)	36 years	NA	+	+	+	NA	Hyperthyroidism	NA
10 (11)	13 years	NA	+	+	+	NA	Hyperthyroidism	NA
11 (12)	29 years	NA	+	+	+	NA	Hyperthyroidism	NA
12 (12)	19 years	NA	+	+	+	NA	Hyperthyroidism	NA
13 (13)	3 years	NA	-	NA	+	NA	-	NA
14 (14)	8.2 years	5 years	-	+	+	NA	-	NA
15 (15)	29 years	NA	+	+	+	NA	-	NA
16 (16)	5 years	4 years	+	-	+	NA	Hyperthyroidism	NA
17 (17)	27 years	NA	+	+	+	NA	Hyperthyroidism	NA
18 (18)	34 years	NA	+	+	+	NA	-	NA
19 (18)	5 years	NA	+	+	+	NA	Hyperthyroidism	NA
20 (18)	26 years	NA	+	+	+	NA	-	NA
21 (18)	11 years	NA	+	+	+	NA	Hyperthyroidism	NA
22 (18)	4 years	NA	+	+	+	NA	-	NA
23 (18)	13 years	NA	+	+	+	NA	Hyperthyroidism	NA
24 (19)	6 months	6 months	+	+	+	NA	Hyperthyroidism	NA
25 (20)	26 years	3 years	+	+	+	NA	Adrenal insufficiency	NA
26 (21)	36 years	8 years	-	+	+	NA	Hyperthyroidism	NA
27 (22)	9 years	9 years	+	+	+	NA	-	NA
28 (23)	8 months	8 months	+	+	+	NA	Hyperthyroidism	NA
29 (24)	4 years	4 years	+	+	+	NA	-	NA
30 (25)	19 years	NA	+	+	+	NA	-	NA
31 (26)	22 years	5 years	+	+	+	NA	-	NA
32 (27)	30 years	19 months	+	+	+	NA	-	NA
33 (28)	2.5 years	2.5 years	+	-	-	NA	Hyperglycemia	Ovarian enlargement withou any cysts

Table 1 (continued)

Table 1 (continued)

Serial No.	Age at dx of MAS	Age at dx of PP	Café au lait spots	FD	CFFD	Height Z-score ^ª	Other endocrinopathies	Ovarian ultrasound findings
34 (29)	8 days	1.8 years	+	+	_	NA	Hypercortisolism, hyperthyroidism, and the Cushing's syndrome	-
35 (30)	4 years	NA	+	+	-	NA	-	NA
36 (30)	2.5 years	NA	+	+	+	NA	-	NA
37 (30)	7.5 years	NA	-	+	_	NA	-	NA
38 (30)	1.5 years	NA	+	+	+	NA	-	NA
39 (30)	4 years	NA	+	-	-	NA	-	NA
40 (30)	1.5 years	NA	+	-	-	NA	-	NA
41 (30)	5 years	NA	+	-	-	NA	-	NA
42 (30)	6 months	NA	+	+	-	NA	Hyperprolactinemia	NA
43 (30)	5.5 years	NA	+	-	-	NA	Hyperprolactinemia	NA
44 (30)	1.5 years	NA	-	+	-	NA	-	NA
45 (30)	17 years	NA	+	+	_	NA	-	NA
46 (30)	6 years	NA	+	+	+	NA	-	NA
47 (31)	1.4 years	1.4 years	-	+	+	NA	_	Enlargement of uterus, bilateral ovarian cysts

^a, height Z-score was recorded at the first visit. dx, diagnosis; MAS, McCune-Albright syndrome; PP, precocious puberty; FD, fibrous dysplasia; CFFD, craniofacial fibrous dysplasia; NA, not available.

vision, severely affects quality of life. Patients with CFFD usually require multidisciplinary medical options and are at a high risk of complications. There are no effective preventive measures for CFFD; management only focuses on slowing the progression in the early stages.

In this observational study, we only report one sample and it is actually an unrepresentative case. It is difficult to predict development of this disease. We should continue to conduct careful clinical follow up and pay special attentions to children with precocious puberty.

Conclusions

In conclusion, MAS is a rare and challenging condition. Management of MAS focuses on minimizing the risk of complications and optimizing function, particularly in patients with bony lesions. Clinicians should identify FD of the bone, as soon as possible because early diagnosis is crucial for patients with MAS. Appropriate management and medical intervention can decrease the rate of malignancy and improve the quality of life.

Acknowledgments

Funding: This work was supported by the National Key R&D Program of China (No. 2021YFC2009100).

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://gpm.amegroups.com/article/view/10.21037/gpm-22-27/rc

Peer Review File: Available at https://gpm.amegroups.com/ article/view/10.21037/gpm-22-27/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gpm.amegroups.com/article/view/10.21037/gpm-22-27/coif). PW serves as an unpaid editorial board member of *Gynecology and Pelvic*

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Medicine from June 2022 to May 2024. XN serves as an unpaid Executive Editor-in-Chief of *Gynecology and Pelvic* Medicine. TC serves as an unpaid editorial board member of *Gynecology and Pelvic Medicine* from July 2022 to June 2023. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Medical Ethics Committee of West China Second Hospital of Sichuan University. All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's parent for publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

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doi: 10.21037/gpm-22-27

Cite this article as: Yu Y, Chen Y, Wang P, Mei L, Niu X, Cui T. McCune-Albright syndrome diagnosed from the ovarian tissue of a 5-year-old girl: a case report. Gynecol Pelvic Med 2023;6:8.

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