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Case Report

Cyclic Vaginal Bleeding in an Infant: Surveillance or treatment

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Abstract:

McCune Albright Syndrome (MAS) is a rare genetic disorder characterized by the triad of fibrous dysplasia, café-au-lait skin macules, and endocrinopathies such as precocious puberty. MAS results from post-zygotic mutations in the GNAS gene, leading to mosaic activation of cAMP signaling. Diagnosing MAS can be challenging due to the variability in clinical presentation and the limitations of genetic testing.

Herein, we present a case of a young girl diagnosed with MAS who exhibited cyclic vaginal bleeding since birth, hyperpigmented skin macules and precocious puberty, managed with letrozole therapy. Over the treatment course, the patient exhibited regression of breast development, cessation of vaginal bleeding, normalization of growth velocity, and stabilization of bone age without adverse effects. Letrozole, an aromatase inhibitor, has emerged as a promising treatment option for precocious puberty. We discuss the clinical presentation, diagnostic workup, and treatment approach, highlighting the efficacy and safety of letrozole in this unique context.

Keywords: café-au-lait skin pigmentation; mccune-albright syndrome; peripheral precocious puberty; vaginal bleeding, letrozole

Introduction

McCune Albright Syndrome (MAS) is a rare genetic disorder caused by spontaneous post-zygotic gain-of-function variants at p. Arg201 or p. Gln227 of the alpha subunit of GNAS (Gsα) gene1, which is present in many tissue types, including bone, skin and endocrine tissues1-3. The variant leads to constitutive activation of cyclic adenosine monophosphate (cAMP) signalling, and the severity and clinical manifestation are dependent on the affected tissues and the degree of mosaicism4. The syndrome manifests with a wide range of clinical features, including monostotic or polyostotic fibrous dysplasia, *café-au-lait* skin pigmentation, and various endocrinopathies, such as hyperthyroidism, acromegaly, phosphate wasting, and Cushing syndrome [1-5]. Bone lesions, often presenting as fibrous dysplasia, contribute to abnormal skeletal development and an increased risk of bone fractures3. Peripheral precocious puberty (PPP) is frequently the presenting symptom in girls [1-5]. MAS-associated PP is the result of recurrent, autonomously functioning ovarian cysts leading to intermittent estrogen production5. Girls exhibit episodic manifestations of estrogen exposure, such as breast development and vaginal bleeding, leading to accelerated growth and skeletal maturation6.

The diagnosis of MAS is made by the combination of fibrous dysplasia (FD) and one or more extraskeletal features, OR the presence of two or more extraskeletal features, OR FD and identification of GNAS mutation2. Extraskeletal features include2:

1. *Café-au-lait* skin pigmentation with irregular borders and a distribution that respects the midline of the body;
2. Gonadotropin-independent sex steroid production resulting in precocious puberty;
3. Recurrent ovarian cysts in girls *versus* autonomous testosterone production in boys and men; testicular lesions with or without precocious puberty (PP);
4. Growth hormone excesso;
5. Thyroid lesions consistent with FD/MAS with or without non-autoimmune hyperthyroidism;
6. Neonatal hypercortisolism.

During clinical assessment, elevated estradiol levels, suppressed gonadotropins, and the presence of ovarian cysts on pelvic ultrasound may be observed6. While some individuals may have a mild presentation, the condition typically progresses. If left untreated, it can result in skeletal advancement, central PP, and compromised adult height6.

PP is a common endocrine manifestation, occurring in approximately 80% of affected females [7]. Traditional treatment modalities for precocious puberty include gonadotropin-releasing hormone (GnRH) analogs [8-10], but emerging evidence suggests the efficacy of aromatase inhibitors such as letrozole in this population [11-13].

Case Presentation:

A 9-month-old infant was referred for a pediatric endocrinology consultation due to cyclic vaginal bleeding since birth, occurring approximately once a month in moderate amounts and lasting an average of 2 days. The infant was otherwise healthy and family history was not relevant. The mother was breastfeeding and was under a birth control pill with Desogestrel.

Upon physical examination, a *café-au-lait* pigmentation was observed in the cervical, right thoracic, and right upper limb regions, respecting the midline. Mammary hypertrophy (Tanner stage S2) and fine, straight pubic hair (lanugo) were noted, along with no other changes. An adnexal cystic lesion measuring 29 x 17mm was identified via ultrasound. A pelvic magnetic resonance imaging (MRI) scan revealed a simple cyst measuring 12x10x15mm in the right adnexal region.

Following these findings, Desogestrel was discontinued, and a comprehensive investigation was conducted. Initial analytical studies, including assessments of thyroid, renal, and hepatic function, prolactin, DHEAS, delta4, and SHBG, were within normal limits. Hormonal levels showed FSH at 1.57 ng/mL, LH below 0.1 ng/mL, estradiol below 5 pg/mL, 17OHP at 2.27 ng/mL, and alpha-fetoprotein at 10.9 ng/mL. A pituitary MRI showed no abnormalities. The LHRH test was negative, and phospho-calcium metabolism remained unchanged. The bone age (BA) was advanced by 7 months relative to the chronological age (CA), and subsequent ultrasound assessments revealed regression of the ovarian cyst.

Based on clinical suspicion of MAS, a targeted genetic study of codons 201 and 227 of the GNAS gene was performed in a peripheral blood sample, with a negative result. This is not unexpected, as variant detection depends on the degree of mosaicism in the tissue and the sensitivity of the technique, with an estimated detection rate of about 20-30% in leukocyte [14]. The detection rate in affected tissues is higher (about 80%), with the notable exception of the skin [15].

Between 9 and 28 months, the infant maintained a regular growth velocity, showed no progression of Tanner stage, exhibited appropriate psychomotor development, and experienced no episodes of vaginal bleeding or advancement of bone age. However, from 28 months onwards, cyclic monthly vaginal bleeding resumed, lasting 2–3 days. An advancement in bone age (~1 year), acceleration of growth velocity (>p97), anemia (Hb 8.9 g/dL), and elevated estradiol (144 pg/mL) with prepubertal LH and FSH were noted at that time. This was consistent with the diagnosis of PP in the setting of MAS.

A multidisciplinary meeting at 32 months led to the decision to initiate Letrozole treatment (2.5 mg once daily). Regular follow-up visits were conducted to monitor clinical response, skeletal maturation, and adverse effects. Over the course of treatment, the patient exhibited no side effects and we could observe regression of breast development, no more episodes of vaginal bleeding, normalization of growth velocity, and stabilization of bone age advancement.

Currently 3 years old, the infant maintains multidisciplinary *follow-up* involving hematology, orthopedics, ophthalmology, otorhinolaryngology, endocrinology and/or genetics. Full body X-ray revealed no apparent bone lesions. No other comorbidities have been identified to date.

Discussion:

The presented case of a 9-month-old infant with peripheral PP (PPP) and MAS prompts several noteworthy discussions.

Firstly, the early onset of cyclic vaginal bleeding in this infant is a characteristic feature of PPP associated with MAS9. In the presence of vaginal bleeding in childhood, an assessment of the clinical characteristics of MAS should be carried out [1-4].

In this case, the diagnosis of MAS is clinical, with the presence of two extraskeletal features (café-au-lait skin pigmentation and PPP), despite a negative genetic test. Genetic testing is crucial in confirming MAS, but the absence of identified mutations does not rule out the clinical diagnosis [2,3]. This discrepancy highlights the complexity of genetic mutations and the limitations of current testing methods2,3. Clinicians should maintain a high index of suspicion for MAS based on clinical features, even when genetic testing yields negative results [2]. In our case report, despite negative genetic testing, the subsequent clinical course, marked by the recurrence of vaginal bleeding (≥ 3 episodes monthly), acceleration of growth velocity (>p97), anemia (Hb 8.9 g/dL) and rise in estradiol (144 pg/mL), with pre-pubertal LH and FSH, led to a multidisciplinary meeting where it was decided to start treatment with Letrozole [11-12].

The management of PPP depends on the underlying etiology and can involve using experimental drugs under specialist guidance and the careful evaluation of their impact on physical and mental health [9,10,16]. Letrozole has demonstrated efficacy in halting pubertal development and is considered a first-line treatment for PPP associated with MAS [11-12]. The management of rarer forms of PPP involves using experimental drugs under the guidance of specialists [17]. The primary goals of therapy with Letrozol are to halt pubertal development and restore sex steroids to prepubertal values to maximize height potential [11-13]. A small pilot study demonstrated beneficial effects, including reductions in skeletal maturation, growth velocity, and vaginal bleeding episodes [12]. Most studies report the use of a single 2.5mg dose of Letrozole once daily until puberty, with few or no adverse effects [11-12]. Possible adverse effects include ovarian enlargement, cyst formation, abdominal pain, and one case of ovarian torsion [11-13]. The successful management of PPP in this case with Letrozole, an aromatase inhibitor, is a critical aspect of the discussion [11,12]. The positive response, evidenced by the absence of vaginal bleeding, the regression of Tanner stage, and the absence of documented adverse effects, underscores the importance of individualized therapeutic strategies in complex endocrine disorders.

Long-term follow-up is critical for comprehensive care, disease monitoring, complication management, and ongoing support for patients and their families with MAS [18,19]. Regular monitoring is essential for better outcomes and improved quality of life3. Monitoring bone age is crucial in assessing the progression of puberty and optimizing interventions2,3. Most clinically significant skeletal lesions are apparent on bone scintigraphy at five years of age, which is why this is indicated from the age of 5, if clinically asymptomatic [20]. Additionally, patients should be monitored for central PP (CPP) and the need to add a Gonadotropin-releasing hormone (GnRH) analogs [12], which is the primary treatment for CPP [8-10].

In our case, we maintained regular endocrinology consultations with a physical examination, assessment of Tanner stage, growth rate and evaluation of scoliosis. Annual screening for endocrine glands (hyperthyroidism, hypophosphatemia and CPP) and advancing bone age was conducted. Bone scintigraphy will be performed at age 5.

Conclusion:

In conclusion, this case highlights the importance of recognizing the clinical manifestations of MAS, the challenges in genetic testing, and the successful management of PP using letrozole therapy. Our findings

underscore the efficacy and safety of letrozole as a treatment option for MAS-associated PP, offering potential benefits in halting disease progression and optimizing long-term outcomes. Further research is warranted to elucidate the optimal dosing regimens, long-term effects, and comparative efficacy of letrozole in this population.

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