

Case Report**A CASE OF MCCUNE ALBRIGHT SYNDROME IN THE CONTEXT OF AN OVARIAN MASS AND LATE DEVELOPMENT OF CAFÉ-AU-LAIT MACULES**

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Abstract: McCune-Albright syndrome (MAS) is a genetic disorder characterized by polyostotic fibrous dysplasia, precocious puberty, and café-au-lait spots. In this case, a patient presented with precocious puberty in the setting of an ovarian mass and late development of café-au-lait macules, confounding the final diagnosis of MAS. A 3-year-old girl presented with vaginal bleeding. She had a previous episode of vaginal bleeding, breast budding, and a right ovarian cyst at 5 months of age. Work-up at that time showed no abnormal findings, though past medical history was notable for two fractures. Physical exam was significant for increased height (89th percentile), increased weight (99th percentile), bilaterally elevated breast mounds with palpable breast tissue and darkened areolae (Tanner stage 3), and residual blood in the vaginal introitus. Notable labs included low FSH and high ultrasensitive estradiol. Pelvic MRI showed a right ovarian cyst, which, in the context of precocious puberty, raised the suspicion for a juvenile granulosa cell tumor. Follow-up pelvic MRI demonstrated features that instead suggested an ovarian response to hormonal stimulation. On a subsequent visit several months later, the patient had small café-au-lait macules on the chest and right buttock, which were not present on initial evaluation. Further work-up revealed advanced bone age on an x-ray at 6 years 10 months, and multifocal polyostotic fibrous dysplasia involving bilateral femurs and right tibia. It is crucial to identify MAS as a cause of peripheral precocious puberty to guide proper management.

Keywords: pediatric endocrinology, precocious puberty, polyostotic fibrous dysplasia, café-au-lait spots, ovarian cysts, McCune-Albright syndrome

INTRODUCTION McCune-Albright syndrome (MAS) is a rare genetic disorder characterized by the triad of polyostotic fibrous dysplasia, precocious puberty, and café-au-lait spots [1]. The prevalence of MAS is estimated to be less than 1 in 100,000 [1]. In this case, a patient presented with precocious puberty in the setting of an ovarian mass and late development of café-au-lait macules, which confounded the final diagnosis of MAS. Indeed, the presentation of MAS is complicated by a wide range of phenotypic manifestations [2].

CASE PRESENTATION A 3-year-old girl of Caucasian ethnicity presented with vaginal bleeding. She had a previous episode of vaginal bleeding, breast budding, and a right ovarian cyst at 5 months of age. Work up at that time showed no abnormal findings and the ovarian cyst subsequently shrank in size. On this evaluation, the patient's mother noted dark red blood in the undergarments and raised darkened areolae. There was no bleeding from other sites. Mother denied any visual changes, trauma to the breast region, neurological deficits or concerns, history of head trauma, history of brain infections, exposures to lavender oil or estrogen, or any vaginal trauma. Past medical history included a right spiral tibia/fibula fracture and left elbow fracture at 12 months of age. Her family history was noncontributory. Vital signs were within normal limits. Her height was determined to be at the 89th percentile, and her weight at 99th percentile. Physical exam was significant for an elevated breast mound with palpable breast tissue bilaterally and

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darkened areolae, consistent with Tanner stage 3. Residual blood was seen in the vaginal introitus. No foreign body was visualized. There were no rashes, bruising, pubic hair, or axillary hair. The patient was otherwise well and appeared alert and playful. Notable labs included a normal inhibin B (15.6 pg/mL), low FSH (0.030 mIU/mL), and high ultrasensitive estradiol (159.1 pg/mL). Pelvic MRI showed a 4.1 cm x 2.8 cm right ovarian cyst, which in the context of precocious puberty, raised the suspicion for a juvenile granulosa cell tumor. Bone age was not recorded at this time. A subsequent pelvic MRI showed an ovarian cyst of decreased size, with the largest follicle measuring 1 cm and no obvious solid internal enhancement or typical feature of an ovarian neoplasm. This suggested an ovarian response to hormonal stimulation.

On a visit several months later, the mother reported a café-au-lait macule on the right buttock. She denied any worsening bleeding or enlargement of breast tissue. At that time, the patient had a small café-au-lait macule on the chest and right buttock that were not present on the initial evaluation. Further work-up to identify the source of the hormonal hyperstimulation showed advanced x-ray bone age at 6 year 10 months, and multifocal polyostotic fibrous dysplasia involving bilateral femurs and the right tibia, with no impending pathologic fractures on MRI. After the diagnosis of MAS was established, interventions included follow up with orthopedic surgery for monitoring of fibrous dysplasia and endocrinology for monitoring of precocious puberty.

DISCUSSION Precocious puberty is defined as the onset of secondary sexual characteristics before the age of eight years in girls and nine years in boys [3]. Precocious puberty can broadly be classified into two categories: central precocious puberty or peripheral precocious puberty [1]. MAS is an etiology of peripheral precocious puberty, and thus girls with MAS can present with vaginal bleeding secondary to ovarian enlargement [1]. This can create a diagnostic challenge when other features of MAS are not present upon initial examination, as this presentation can be mistaken for granulosa cell tumor, for which management involves oophorectomy [4].

The similarities in the precocious puberty mediated by granulosa cell tumors and McCune-Albright syndrome has led some to previously hypothesize that the underlying etiologies for both diseases involve similar activating mutations [5]. MAS is caused by an activating mutation of

GNAS1, which encodes the alpha subunit of the G-protein involved in intracellular signaling. This mutation results in a loss of GTPase activity that subsequently leads to an abnormal accumulation of intracellular cyclic adenosine monophosphate and unregulated cell proliferation [1]. Study of pathologic specimens from juvenile and adult granulosa cell tumors found no mutations in either the G α or the FSHR fragments studied [5].

Early recommendation of oophorectomy is a known issue in the early management of girls with MAS, as many are presumed to have ovarian tumors responsible for their symptomatology [4]. A case series of nine girls revealed that half of these patients underwent salpingo-oophorectomy. Surgical pathology later revealed benign ovarian cysts of those four patients [4]. Given that the average age of these patients was only 3.2 years [4], there is a need for increased awareness of this disease among pediatricians and pediatric surgeons. Café-au-lait spots and fibrous dysplasia are signs of MAS that differentiate it from other causes of precocious puberty [4,6]. Café-au-lait macules notably precede the other symptoms of the MAS triad, though fibrous dysplasia and precocious puberty may rarely occur before the development of these cutaneous findings [7]. Furthermore, these skin findings may not be present in many cases of MAS, given that one-third of patients do not have any café-au-lait spots [7].

Recent cases in the literature suggest that a timely diagnosis of MAS utilizing these telling signs would have prevented unnecessary oophorectomy. One such case described a 3-year-old girl with an ultrasound-identified cystic ovarian mass as well as café-au-lait spots and fibrous dysplasia [6]. Another case described an 11-year-old girl with an irregular pelvic mass (9.74 x 9.01 x 7.30 cm), who was found to have café-au-lait spots and fibrous dysplasia after her oophorectomy [8]. MAS may rarely be confounded with other malignant diseases, such as in the case of a 9-year-old girl admitted for ataxia who was found to have lytic lesions in the long bones [9]. Following referral to pediatric oncology for suspected Langerhans cell histiocytosis or metastatic tumor, the patient was found to have MAS with co-existing postinfectious cerebritis [9].

Failure to include MAS in the differential diagnosis has led to unnecessary oophorectomy in this patient population [10]. Presentation of café-au-lait spots, fibrous dysplasia, or precocious puberty should raise suspicion for MAS. In

addition to these signs, one author suggested that recurrent bleeding due to hormonally active cysts may suggest MAS [11]. The same author noted that these cysts may persist but may be further differentiated from a neoplasm via its fluid character on ultrasonography [11]. These benign cysts should not be managed surgically due to the risk of likely recurrence and loss of fertility. In our patient, the late development of cutaneous findings contributed to the complexity of the diagnosis. Therefore, it is crucial to identify MAS as a cause of peripheral precocious puberty in order to guide proper management.

DISCLOSURES: No animal or human studies were carried out by the authors for this manuscript.

PROTOCOL: IRB approval was not needed for case report per institutional guidelines.

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