Manifestation of Giant Bilateral Symptomatic Adrenal Myelolipomas in an Adult Patient with Congenital Adrenal Hyperplasia

Yoo-Mi Kim, M.D., Jin-Ho Choi, M.D., Beom-Hee Lee, M.D., Gu-Hwan Kim, Ph.D., Beom-Sik Hong, M.D., Yong-Jun Ryu, M.D. and Han-Wook Yoo, M.D., Ph.D.

Department of Pediatrics, Medical Genetics Center, Departments of Urology and Pathology, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, Korea

Adrenal myelolipoma is an uncommon non-functioning tumor that is composed of variable amounts of mature adipose tissue and scattered islands of hematopoietic elements, including erythroid, myeloid, lymphoid series, and megakaryocytes. Adrenal myelolipoma should be differentiated from other fat-containing adrenal masses, such as teratoma, lipoma, and liposarcoma. This case report describes a 50-year-old adult who was raised as a male and developed giant adrenal myelolipomas that presented as symptomatic adrenal masses, and which were misdiagnosed as liposarcoma on radiologic examination. The patient had been raised as a male despite ambiguous genitalia, and a thorough investigation was never carried out because of his poor socioeconomic status. Physical examination showed profound short stature (< -3.0 standard deviation score), hyperpigmentation, and a micropenis without palpable gonads. Both a uterus and ovaries were evident in the pelvic cavity on abdominopelvic computed tomography. Adrenocorticotropic hormone stimulation tests confirmed adrenal insufficiency. Steroid replacement therapy was initiated before bilateral adrenalectomy and the histologic findings indicated myelolipoma. The patient's karyotype was 46, XX and mutation analysis of the CYP21A2 gene identified compound heterozygosity consisting of p.I173N and p.Q319*. The patient was treated with once-daily 0.5 mg dexamethasone and once-daily 0.1 mg fludrocortisone. Because the subject had been raised as a male, additional procedures such as an oophorohysterectomy are currently under consideration. We here describe an adrenal myelolipoma in this case that was complicated by a 21-hydroxylase deficiency. We conclude from our analysis that patients with congenital adrenal hyperplasia should be screened for incidental adrenal masses to avoid unnecessary surgical procedures.

Key Words: Adrenal glands; Myelolipoma; Congenital adrenal hyperplasia; hydroxylase deficiency; CYP21

Introduction

Adrenal myelolipomas are usually found incidentally and are uncommon non-functioning tumors that are composed of mature adipose cells and hematopoietic elements, including myeloid, erythroid, and lymphoid cells. These lesions are not associated with extramedullary hematopoiesis or hematologic disorders, which is their most important diagnostic feature. The estimated incidence of adrenal myelolipomas varies from 0.08–0.4%, according to previous autopsy series reports. This accounts for 3–5% of all primary adrenal tumors, and
myelolipomas are considered the most common adrenal fatty tumor\(^1\text{-}^3\). The pathogenesis of adrenal myelolipomas remains to be discovered. Some evidence suggests that prolonged adrenocorticotrophic hormone (ACTH) hypersecretion may play a role in the development of these tumors in patients with uncontrolled congenital adrenal hyperplasia (CAH). Cushing syndrome, and chronic stress conditions including obesity, diabetes mellitus, chronic inflammatory processes, and even malignancy\(^6\text{-}^7\). The treatment modality depends on the size and symptoms of the lesion. An asymptomatic adrenal myelolipoma of < 4 cm does not require surgical removal. However, a symptomatic, complicated, and hormonally active myelolipoma of > 7 cm that is at risk of spontaneous bleeding or rupture should be resected\(^1\text{-}^6\).

We here report a case of a giant bilateral adrenal myelolipoma associated with untreated 21-hydroxylase deficiency.

**Case Report**

A 50-year-old phenotypic male presented at our emergency department complaining of abdominal pain. The patient was born following 40 weeks of gestation by an uncomplicated normal delivery with a birth weight of 3 kg from non-consanguineous parents. Ambiguous genitalia were noted at birth, but a thorough investigation was not performed because of the low socioeconomic status of the parents. At that time also, newborn screening for 21-hydroxylase deficiency had not been initiated in Korea. The subject had been raised as a male and there was no family history of adrenal disease or death during infancy. Regarding his past medical history, the patient reported that secondary sexual characteristics, such as growth spurts, virilization, acne, and the deepening of his voice appeared early and that he reached his final adult height in early elementary school. He had no previous history of acute adrenal crisis, but complained of chronic fatigue and hyperpigmentation. He had received four penis augmentation surgeries in primary urology clinics by 20 years of age.

The patient’s height was 140 cm (< -3.0 standard deviation score [SDS]), his weight was 48.1 kg (-1.1 SDS), and his body mass index (BMI) was 24.5 kg/m\(^2\) (1.2 SDS). His blood pressure was 120/67 mmHg, his pulse was 98 beats/minute, and his respiratory rate was 20 breaths/minute. Large abdominal masses were palpable on both flank areas. We did not observe symptoms of moon face, buffalo hump, abdominal striae, or headache. His Tanner stage was B1 P4, and his penile length was 2 cm. His gonads were not palpable in either the scrotal or inguinal areas. Laboratory findings were as follows: Na, 137 mEq/L; K, 4.6 mEq/L; Cl, 102 mEq/L; dehydroepiandrosterone-sulphate (DHEA-S), 68.4 g/dL (normal, 5–57 g/dL), plasma renin activity, 27.6 ng/mL/hr (normal, 0.68–1.36 ng/mL/hr); aldosterone, 75.0 ng/dL (normal, 3.57–24 ng/dL); ACTH, 32.2 pg/mL (normal, 10–60 pg/mL); and cortisol, 10.7 ug/dL (normal, 5–25 ug/dL). His serum 17-hydroxyprogesterone was not measured. The findings of the urine assays were as follows: urine vanillylmandelic acid, 5.6 mg/day (normal, 0.7–6.9 mg/day); urine epinephrine, 46.1 ug/day (normal, 3–38 ug/day); urine metanephrine, 50.2 ug/day (normal, 52–341 ug/day); urine normetanephrine, 280.7 ug/day (normal, 110–720 ug/day). Short ACTH stimulation tests were done before surgery. The basal cortisol level was 10.7 ug/dL and the peak cortisol level was 13.3 ug/dL. The results of the ACTH stimulation test indicated adrenal insufficiency. Abdominal computed tomography (CT) further demonstrated heterogeneous fatty-enhanced masses in both adrenal glands. The maximal diameter was 8.5 cm for the right mass and 16 cm for the left mass (Fig. 1). The patient underwent laparoscopic bilateral excision of the adrenal masses with a preoperative diagnosis of liposarcoma. Before surgery, the patient was parenterally administered stress doses of hydrocortisone. There were no complications during surgery, and sampled fresh-frozen tissues did not show any signs of malignancy.

The right tumor weighed 182 g and measured 12×9×4.5 cm, and the left tumor weighed 914 g and measured 21×15.5×9 cm (Fig. 2). Macroscopically, the tumor tissue

**Fig. 1.** Adrenal computed tomographic images of the patient. (A) Coronal section showing a 16-cm-sized mass in the left adrenal gland (white arrow) and an 8.5-cm-sized mass in the right adrenal gland (black arrow). (B) Axial view showing myelolipomas in the left (white arrow) and right (black arrow) adrenal glands. Note the heterogeneous fatty-enhanced masses in both adrenal glands.
consisted of mixed brownish and yellowish areas, and on gross section comprised adipose tissue. Microscopic examinations revealed mature adipose tissue intermixed with abundant hematopoietic tissue, including all 3 hematopoietic elements. The tumor was a lobulating mass that was 15% necrotic. After the diagnosis was histologically confirmed as adrenal myelolipoma, further investigations were performed to evaluate the CAH. The patient’s karyotype was 46,XX, and he
was negative for the SRY gene. Mutation analysis of CYP21A2 identified compound heterozygous mutations: c.518T > A (p.I173N) and c.955C > T (p.Q319*) (Fig. 3). Subsequently, 0.5 mg dexamethasone treatment was initiated at bed time and 0.1 mg 9α-fludrocortisone was administered daily. Follow-up endocrinologic findings with medication for 1 month included the following: ACTH 166 pg/mL (normal, 10–60 pg/mL); 17α-hydroxyprogesterone, 0.77 ng/mL (normal, 0.2–4.7 ng/mL); testosterone 0.05 ng/mL (normal, 0.01–0.55 ng/mL), luteinizing hormone (LH) 0.52 mU/mL (normal, 1–12 mU/mL), follicle stimulating hormone (FSH) 3.3 mU/mL (normal, 2–13 mU/mL), androstenedione 0.3 ng/mL (normal, 0.6–2.2 ng/mL), and estradiol 10 pg/mL (normal, 30–120 pg/mL). Because the patient has been raised as a male, additional procedures such as an oophorohysterectomy are currently under consideration.

**Discussion**

Untreated patients with CAH are at risk of developing adrenal tumors such as myelolipoma, pheochromocytoma, or adenoma. This is the first report of a bilateral giant myelolipoma in a Korean patient with CAH. The first case of myelolipoma in a patient with 21-hydroxylase deficiency was reported in 1975. To date, approximately 30 such cases have been reported. Most of these cases were found to be associated with a 21-hydroxylation deficiency, whilst 5 patients reported in the literature were diagnosed with a 17α-hydroxylase deficiency and one case was diagnosed with an 11β-hydroxylase deficiency. The mean age at diagnosis of myelolipoma of the 30 previously reported cases of CAH was 48 (range, 28–82 years). Most of these cases (88.5%) were undiagnosed or left untreated due to loss on follow-up examinations. Untreated CAH with prolonged excessive ACTH stimulation might contribute to diffuse or nodular adrenocortical hyperplasia, which could later cause myeloid metaplasia in the adrenal cortex.

There are several hypotheses regarding the development of adrenal tumors, including the notion that the embryonic bone marrow rests in the adrenal tissues, the establishment of bone marrow in adrenal gland by embolization, and metaplastic changes in adrenal cortical tissue. In addition, Sely et al. induced adrenal myelolipoma in rats by injecting extracts from the anterior pituitary gland. A recent study has described the occurrence of adrenal myelolipoma by reviewing 31 patients with uncontrolled CAH. Adrenal myelolipoma usually presents later in adult life. Hence, there may be undiagnosed patients with incidental adrenal tumors among patients with CAH. There were 13 reported cases of myelolipoma in patients with CAH from 1975–1997. However, over the past 15 years, more than 20 cases have been reported. This suggests that the incidence of myelolipomas in CAH might have been previously underestimated. A recent study reports a high incidence of myelolipoma in patients with CAH (6%) compared with the normal population (1.5–8% of adrenal incidentalomas). Diagnosis of adrenal myelolipoma is based on radiologic imaging, with ultrasonography, computed tomography, and magnetic resonance imaging, which are effective methods for this purpose in > 90% of cases. However, if the diagnosis is in doubt or symptomatic, surgical excision should be performed. Interestingly, all patients were able to live without adrenal crisis until the diagnosis of CAH and had just complained of chronic fatigue and hyperpigmentation. These patients were short in stature and experienced early puberty due to excessive androgen release from the adrenal glands. However, there were no reported incidents of severe symptoms or emergent events.

In our current case, surgical excision was required due to the huge size of the tumor and the patient’s symptoms. Because myelolipomas are usually benign, unnecessary surgical removal should be avoided. Our patient was diagnosed with CAH by molecular analysis because the endocrinologic data collected following bilateral adrenalectomy were uninformative, such as the low levels of 17-hydroxyprogesterone and androstenedione despite a high ACTH level. However, the patient’s ACTH level was within normal range when he visited our hospital at first. It is assumed that his normal preoperative ACTH level was caused by measuring ACTH level using blood drawn at midnight, as well as steroid medication from primary clinic. Hence, the possibility of CAH should be taken into account when evaluating incidental adrenal tumors, especially in patients with mild symptoms such as chronic adrenal insufficiency and early puberty.

**References**

양측성 거대 부신 골수 지방종으로 발현된 선천성 부신증식증

김유미1, 최진호1, 이범희1, 2, 김구환2, 홍범식3, 류영준4, 유한욱1, 2
울산대학교 의과대학 서울아산병원 소아청소년과1, 의학유전학과2, 비뇨기과3, 진단병리과4

부신성 골수 지방종은 지방 조직과 조혈세표들로 구성된 종양으로 비기능성이나 크기가 7 cm 이상이거나 증상을 동반할 경우 수술적 절제가 필요한 종양이다. 다른 기형종과 지방종, 지방육종과의 감별이 필요하며 초음파, CT, MRI, 등의 영상학적 검사로 진단할 수 있다. 지사는 50세까지 남자로 살아오다 양측성 거대 부신 골수 지방종으로 인해 뒤늦게 선천성 부신 증식증을 진단받은 증례를 경험하여 이를 보고한다. 환자는 복강내 여성생식기 및 애매한 외부 생식기로 선천성 부신 증식증이 의심되었으나 양측 부신 절제술 시행 이후 시행된 내분비검사에서 뚜렷한 증거를 찾지 못해 유전자 검사를 통해 확인할 수 있었다. 현재까지 치료받지 않은 선천성 부신 증식증에서 부신 골수지방종이 동반된 보고가 30례 정도였으며 우연히 발견되는 부신 증상에서 선천성 부신 증식증은 반드시 감별되어야 하겠다.