Late-onset Congenital Adrenal Hyperplasia with Cushing Syndrome

Gurbuz Erdogan, Recai Pabuccu, Sibel Ertek, Shoshana Israel, Banu Yilmaz, Hilal Yilmaz and Gamze Caglar

Abstract

Although hirsutism is classically part of the clinical presentation of polycystic ovarian syndrome (PCOS), congenital adrenal hyperplasia and Cushing’s syndrome (CS), CS associated with underlying late-onset congenital adrenal hyperplasia (LCAH) in an adult has not been previously reported. We herein present the case of a 25-year-old woman who was followed for PCOS for seven years. After undergoing detailed tests described within the text, she received the diagnosis of LCAH and was found to have point mutations. Interestingly, she later had diagnosis of endogenous CS that regressed following excision of an adrenal adenoma found on MRI. The present patient thus exhibited the coexistence of two paradoxical endocrine pathologies.

Key words: congenital adrenal hyperplasia, adrenal adenoma, hirsutism, Cushing syndrome, polycystic ovary syndrome

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Introduction

Idiopathic hirsutism, polycystic ovary syndrome (PCOS) and late-onset congenital adrenal hyperplasia (LCAH) are common causes of adult hyperandrogenemia and/or hirsutism. The underlying pathology in hirsutism may also be Cushing’s syndrome (CS) or an androgen-secreting tumor. Since most hyperandrogenemic patients display irregular menstruation and polycystic ovaries, an inaccurate evaluation of the patient can result in misdiagnosis. Unless the possibility of LCAH is explored, patients admitted with these signs and symptoms are easily mistreated for PCOS. We herein present a case of LCAH treated as PCOS for seven years in which after receiving the correct diagnosis of LCAH, the patient was treated with dexamethasone and developed CS symptoms with adrenal adenoma. This case is the first in the literature to involve both CS and LCAH.

Case Report

A 25-year-old patient who had received treatment for secondary amenorrhea in another city for seven years was admitted to Gynecology Department of Ufuk University in August, 2008. Her age of menarche was 14 years. Shortly thereafter, she was admitted to a gynecologist with complaints of oligomenorrhea, hair loss and hirsutism. Based on an initial diagnosis of PCOS, she was prescribed oral contraceptives that she did not use regularly. Unfortunately, one year later, serum 17-OH P level of 22 ng/mL in the early follicular phase were underestimated and spironolactone therapy (100 mg/day) was added to the oral contraceptive treatment (Visit 1, Table). The patient subsequently experienced 10 kg weight gain over seven years, and her hirsutism worsened. Physical examination revealed Ferriman Gallway score of 16, clitoromegaly (2x2 cm) and polycystic ovaries on an ultrasound evaluation. There were no other signs of virilization or a CS-like appearance. Treatment with oral...
months. She subsequently consulted Endocrinology Depart-
ment) did not result in any change in symptoms within three
contraceptive pills combined with ciproterone acetate (100
mg/day, 10 days/cycle) and metformin (850 mg, twice a
treatment was stopped, and combined oral contracep-
tives with ciproterone acetate was initiated. Because she had no intention to become pregnant, the
steroid treatment was stopped, and combined oral contracep-
tives with ciproterone acetate was initiated. Because she had no intention to become pregnant, the
thought to have an excess accumulation of exogenous ster-
months after the initiation of steroid treatment, she was
posterior axial spine. Since she displayed CS symptoms
she received the diagnosis of glaucoma and osteoporosis
plethora, spontaneous ecchymoses and edema. In addition
three spontaneous menstruations, however she also devel-
veloped a moon face appearance, buffalo hump, weight gain,
and fertility, spontaneous ecchymoses and edema. In addition
she received the diagnosis of glaucoma and osteoporosis
with a bone mineral density T score of -3.6 in the antero-
ior axial spine. Since she displayed CS symptoms
months after the initiation of steroid treatment, she was
thought to have an excess accumulation of exogenous ster-
oids. Because she had no intention to become pregnant, the
steroid treatment was stopped, and combined oral contracep-
tives with ciproterone acetate was initiated.

Table. Hormonal Test Results of the Patient on Successive Visits

<table>
<thead>
<tr>
<th></th>
<th>Normal range</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4*</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH (mIU/mL)</td>
<td>3.5-12.5</td>
<td>1.17</td>
<td>-</td>
<td>-</td>
<td>5.78</td>
</tr>
<tr>
<td>LH (mIU/mL)</td>
<td>2.4-12.6</td>
<td>0.10</td>
<td>-</td>
<td>-</td>
<td>13.1</td>
</tr>
<tr>
<td>Estradiol (pg/mL)</td>
<td>12.5-166</td>
<td>5.0</td>
<td>-</td>
<td>-</td>
<td>40.9</td>
</tr>
<tr>
<td>Progesterone (ng/mL)</td>
<td>0.2-1.5</td>
<td>0.60</td>
<td>-</td>
<td>-</td>
<td>2.37</td>
</tr>
<tr>
<td>17-OH P (ng/mL)</td>
<td>0.15-1.1</td>
<td>22</td>
<td>17.92</td>
<td>23.00</td>
<td>7.3</td>
</tr>
<tr>
<td>DHEA-SO4 (μg/mL)</td>
<td>98-340</td>
<td>-</td>
<td>90.64</td>
<td>-</td>
<td>31.89</td>
</tr>
<tr>
<td>Prolactine (μg/mL)</td>
<td>8.66</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>ACTH (pg/mL)</td>
<td>10-120</td>
<td>17.5</td>
<td>78.01</td>
<td>&lt;1</td>
<td>91.3</td>
</tr>
<tr>
<td>Cortisol (pg/dL)</td>
<td>5-25</td>
<td>16</td>
<td>21.84</td>
<td>25.96</td>
<td>17.8</td>
</tr>
<tr>
<td>Testosterone total (ng/mL)</td>
<td>0.06-0.82</td>
<td>0.19</td>
<td>-</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Testosterone free (ng/mL)</td>
<td>0.29-3.18</td>
<td>2.52</td>
<td>-</td>
<td>2.49</td>
<td></td>
</tr>
<tr>
<td>TSH (mIU/mL)</td>
<td>0.2-4.0</td>
<td>0.82</td>
<td>-</td>
<td>0.64</td>
<td></td>
</tr>
</tbody>
</table>

*Visit 4 is test results on day 16 of menstruation, whereas others are on follicular phase.

Another five months later the test results obtained on the
control visit were as shown on Table, Visit 3. She subse-
sequently underwent an additional 1 mg dexamethasone sup-
pression test, and the morning plasma cortisol level was not
found to be suppressed at 28.7 μg/dL. We then conducted 2
days 2 mg dexamethasone suppression test which showed
the cortisol level to be 32.5 μg/dL without suppression, with
a midnight cortisol level of 28.7 μg/dL. The patient under-
went bilateral adrenal magnetic resonance imaging (MRI)
which revealed a left adrenal adenoma presenting as a solid
mass with a regular margin measuring 31x16 mm in size
(Figure). In May 2011, left adrenalectomy was performed
the histopathology of which demonstrated adrenocortical
adenoma and myelolipoma. Histologically, there were sepa-
rated nests of adenomatous cells with abundant lipid vacu-
oles and a granular eosinophilic cytoplasm, without areas of
mitosis or necrosis, separated by fibrous septae, with a
myelolipoid component containing adipocytes and myeloid
tissue with erythrocytes, lymphocytes and megakaryocytes.

A diagnosis of LCAH was confirmed based on a genetic
analysis of progesterone 21-hydroxylase (CYP21) which re-
vealed a point mutation in exon 7 (V281L) and stop codon
in exon 8 (Q318X). Peri-operative prednisolone replacement
therapy was gradually halted over two months. At the end of
the two months, the patient demonstrated significant im-
provement in symptoms and loss of CS features and hirsu-
tism, the recovery of spontaneous menstruation, and a
plasma cortisol of 5.8 μg/dL. On a physical examination re-
gression of hirsutism (Ferriman Gallwey score:8) and a de-
crease in the size of the clitoris were noted. However, an ul-
trasonographic evaluation revealed polycystic ovaries. The
patient was found to be menstruating regularly; however her
cycles were anovulatory (day 19 progesterone: 3.66 ng/mL,
day 21 progesterone: 2.47 ng/mL, day 24 progesterone: 1.61
ng/mL).

The most recent laboratory findings obtained in January
2012 are as shown in Table, Visit 4 (16th day of the men-
strual cycle). Due to the high possibility of a glucocorticoid
reserve deficiency, the patient remains under close follow-
up.

Discussion

LCAH is an autosomal recessive disease characterized by
oligomenorrhea, hirsutism, acne and hair loss (1-3). In
adults, PCOS and idiopathic hirsutism are considered in the
differential diagnosis. In patients with LCAH, androgen ex-
cess may result in PCOS-like phenotype with all manifesta-
tions of PCOS, including an elevated luteinizing hormone
(LH) level and a polycystic ovarian appearance potentially
being observed (4-7). The frequency of PCOS has been re-
ported to be 1-19% in patients with LCAH (8, 9). In LCAH
patients, unlike those with PCOS, signs of virilism such as
citoromegaly may develop. Symptoms of hyperaldoster-
nism and hypercortisolism related to 21- hydroxylase deficiency can also be observed (10).

ACTH stimulation test constitutes the gold standard test for obtaining an accurate diagnosis of LCAH (7, 11). After measuring the serum 17-OH P and 11 deoxycortisol levels, a single dose (0.25 mg) of ACTH injection is performed. In patients with 21- hydroxylase deficiency, the serum 17-OH P level increases by 30 nmol/L. In contrast, in those with 11 beta hydroxylase deficiency, the 11 deoxycortisol level increases by threefold of the 95th percentile observed in controls after 30-60 minutes (12). Therefore, in patients with hyperandrogenism, in order to provide optimal management and avoid misdiagnosis, alternative diagnostic tests to ACTH stimulation tests were under investigation. In a study by Avivi and colleagues, the results of ACTH stimulation tests were compared before and after six months of cyproterone acetate and etinil estradiol treatment (13). The authors detected significantly lower levels of 17-OH P and progesterone in the LCAH patients. Furthermore, the authors suggested that correlating the results of ACTH stimulation tests with the human leukocyte antigen (HLA) typing increases both the sensitivity and specificity (13).

In a Turkish population with PCOS, the rate of 11 beta hydroxylase deficiency was reported to be 8.4% (12). Another study found 21- hydroxylase deficiency to be present in 33% of patients with PCOS and hirsutism (14). The largest study (n=205) from Turkey reported a frequency of LCAH of 9.75% among patients with hirsutism (15). In the literature, the rate of LCAH in those with hirsutism ranges from 6% to 12% with a genetic expression of 21- hydroxylase deficiency of between 0.015 and 0.057 (5). Based on these studies, the frequency of LCAH emphasizes the need to obtain differential diagnosis in patients with suspected PCOS presenting with oligomenorrhea, hair loss, acne and hirsutism. PCOS is the most common endocrinopathy in women of reproductive age (6-8%), and other pathologies with androgen excess and anovulation can mimic the features of PCOS (16, 17). Another endocrine disorder that interferes with PCOS symptoms is CS. Although weight gain, hirsutism, acne, and irregular menstruation are common findings in both disorders, the detection of accompanying truncal obesity, buffalo hump, striae and osteoporosis favors a diagnosis of CS (16, 18-20). Occasionally, LCAH and CS can be confused due to their similarity in signs and symptoms. In the literature, there are several cases of iatrogenic CS in patients treated with corticosteroids for LCAH (21, 22). In addition, a case of LCAH associated with physical findings of CS has been reported (23).

A decade ago, researchers suggested that adrenal tumors are capable of changing their enzymatic activity (24). Previously, 21- hydroxylase and 11 beta hydroxylase deficiencies were explored in a study consisting of 48 cases of adrenal incidentaloma and 10 cases of subclinical CS (24). In that study, the results of ACTH stimulation tests showed an exaggerated response in adrenal incidentaloma cases, in which the increase in the 17-OH P and 11 deoxycortisol levels was significantly higher in the subclinical CS patients (24). Among the participants of that study, the 17-OH P levels declined to normal levels in seven of eight patients treated with surgery. In addition, the adrenal incidentaloma patients exhibited enzymatic diversity with alterations in enzymatic pathways being a phenomenon mostly associated with glucocorticoid autonomy (24). The results of that study showed that the possible effects of changes in stereoideogenetic pathways on adrenocortical tumor formation can be documented using molecular analysis. In the present case, a point mutation in CYP21 resulted in a higher level of 17-OH P whose conversion to 11-deoxycortisol was decreased due to 21-hydroxylase deficiency, causing LCAH. Pathophysiologically, this phenomenon constituted the basis of treatment strategy for LCAH, cortisol treatment decreases the ACTH level and therefore decreases excess androgen synthesis and hirsutism in affected patients. However, our patient presented with a high cortisol level and dynamic test results without suppression suggesting excess adrenal cortisol production, with CS symptoms. Therefore, both genetic tests and hormonal studies, together with a postoperative pathological evaluation, revealed the presence of simultaneous
LCAH and an adrenal adenoma causing CS in this unique case.

Although patients with CAH have a higher incidence of adrenal incidentalomas compared to the normal population, accompanying endogenous hypercortisolism is rare. In the medical literature, two cases of Cushing’s disease with 21-hydroxylase deficiency have been reported (25). However, with the exception of a single case report (26) of the autopsy of an 8-week-old infant in 1964, the case reported here is the first in the literature to involve both CS and late-onset congenital adrenal hyperplasia.

In the present case, the patient’s signs and symptoms of CS regressed following the cessation of steroid treatment for LCAH, then later re-appeared. ACTH secretion was likely suppressed during the steroid treatment and perhaps also due to excess endogenous cortisol. The recurrent overproduction of ACTH following steroid cessation may have also played a role in this case, however, since an endogenous source was still present, we believe that this phenomenon presented a transient period of high ACTH. The rapid suppression of the ACTH level following 0.5 mg/day dose of dexamethasone may also reflect the additional effects of endogenous cortisol. Following the cessation of dexamethasone, the patient’s autonomous adrenal cortisol secretion continued without the need for ACTH stimulation. In addition, an abnormal dexamethasone suppression test result was observed prior to surgery of the adrenal mass, and the diagnosis of endogenous steroid excess was confirmed when the patient’s cortisol level declined and her symptoms regressed following excision of the adrenal adenoma found on MRI. Furthermore, the diagnosis of LCAH was confirmed using a genetic analysis highlighting the uniqueness of this case with respect to the coexistence of two paradoxical endocrine pathologies.

Moreover, myelolipomas generally exhibit a variable growth rate (27), and myelolipomatous foci can be present in association with other pathological conditions of the adrenal glands, such as hyperplasia or adenoma (28). Adenomas are hormonally active and usually have smaller size, with differing growth rates, whereas myelolipomas are generally silent and asymptomatic and although rarely exceeding 5 cm in diameter, they can reach up to 34 cm in size (29). Since the present patient had neoplasm with two different components, the growth rate of the lesion could not be estimated.

This case emphasizes the importance of making the differential diagnosis of hirsutism and applying dynamic diagnostic tests with inter-disciplinary follow-up in patients with hormonal diseases.

The authors state that they have no Conflict of Interest (COI).

References

13. Avivi I, Pollack S, Gideoni O, Linn S, Blumenfeld Z. Overdiagnos- 
sis of 21-hydroxylase late onset congenital adrenal hyperplasia: correlation of corticotropin test and human leukocyte antigen typ- 
15. Unluhizarci K, Kula M, Dundar M. The prevalence of non-classic adrenal hyperplasia among Turkish women with hyperandro-
22. Campos SP, MacGillivray MH. Preclinical Cushing syndrome due
to an adrenocortical adenoma mimicking late-onset congenital ad-
23. Loh V, Krishnan B, Prentice M, Panahloo A, Seal L. Late onset
congenital adrenal hyperplasia masquerading as subclinical Cus-
24. Dall’Asta C, Barbetta L, Libé R, Passini E, Ambrosi B. Coexis-
tence of 21-hydroxylase and 11 beta-hydroxylase deficiency in ad-
hormonal profile of two women with Cushing’s disease and mild
adrenocortical hyperplasia with Cushing’s syndrome. JAMA 187:
27. Han A, Brunett AL, Fishman EK, Marshall FF. The natural treat-
ment and history of adrenal myelolipoma. J Urol 157: 1213-1216,
1997.
ipoma and testicular interstitial tumor in a man with congenital

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http://www.naika.or.jp/imonline/index.html