ACTH-independent massive bilateral adrenal disease (AIMBAD): A subtype of Cushing’s syndrome with major diagnostic and therapeutic implications

Steven A Lieberman1,2, T Ross Eccleshall1 and David Feldman1

Department of Medicine1, Stanford University, Stanford CA and Medical Service2, Department of Veterans Affairs Medical Center, Palo Alto, CA, USA


A 49-year-old man with classic manifestations of Cushing’s syndrome had undetectable levels of ACTH, lack of suppression of hypercortisolism with dexamethasone in doses of 2, 8, or 16 mg per day, bilaterally enlarged adrenal glands on MRI, and bilateral adrenal uptake of iodocholesterol. Preoperative treatment with ketoconazole lowered blood pressure and serum cortisol and produced symptoms of steroid withdrawal. Bilateral adrenalectomy revealed massively enlarged adrenal glands (left: 199 g; right: 93 g). Sequencing of the gene encoding the stimulatory G protein, Gsα, did not show either of two activating mutations previously reported in patients with McCune-Albright syndrome or acromegaly. Twenty-three previous cases of Cushing’s syndrome due to ACTH-independent massive bilateral adrenal disease (AIMBAD) have been reported. AIMBAD may cause confusion in the differential diagnosis of Cushing’s syndrome as endocrine testing suggests a unilateral, ACTH-independent process while adrenal imaging demonstrates bilateral abnormalities. Bilateral adrenalectomy is curative and appears to carry little risk of Nelson’s syndrome. The pathogenesis of AIMBAD appears to be heterogeneous, as recent reports have demonstrated GIP-mediated hypercortisolism and familial AIMBAD. Transition from Cushing’s disease to ACTH-independence is not supported by the available data. Future cases of AIMBAD should be investigated carefully to further elucidate the pathogenesis of this disorder.

David Feldman, Division of Endocrinology, Dept. of Medicine, Room S-005, Stanford University Medical Center, Stanford, CA 94305, USA

Causes of endogenous Cushing’s syndrome are traditionally divided into adrenocorticotropic hormone (ACTH)-dependent and ACTH-independent processes. In the former (of which Cushing’s disease and ectopic ACTH production comprise the majority), ACTH stimulation produces hyperplasia and hyperfunction of both adrenal glands. In contrast, the major ACTH-independent causes (adrenal adenoma and carcinoma) are unilateral (1). Among the less common pathologic processes that can also cause Cushing’s syndrome are disorders in which nodular adrenocortical hyperfunction of both adrenal glands occurs independent of ACTH stimulation. The elevated level of cortisol suppresses pituitary ACTH secretion, mimicking the hormonal profile of the more common unilateral adrenal neoplasms even though the process is bilateral. In some of these patients a characteristic clinical course, including early age at diagnosis, mild symptomatology, and frequent occurrence of osteoporosis, is associated with adrenal glands that are small-to-slightly enlarged and studded with small, pigmented nodules. This condition has been termed primary pigmented nodular adrenocortical disease (PPNAD) or primary adrenocortical nodular dysplasia (PAND) (2, 3).

Other reports of patients with corticotropin-independent bilateral adrenal hyperfunction describe non-pigmented nodular enlargement of the adrenals variously referred to as ACTH-independent bilateral macronodular adrenal hyperplasia (AIBH (4) or AIMAH (5)), or “massive” (6), “giant” (7) or “huge” (8, 9), macronodular adrenal hyperplasia. Despite the plethora of terms used to describe these patients, analysis of the reported cases reveals a continuum of bilaterally enlarged adrenal glands comprising this distinct diagnostic entity, which we term ACTH-independent massive bilateral adrenal disease (AIMBAD). Herein we report the case history of a patient with Cushing’s syndrome due to AIMBAD, and we present an analysis of the clinical, diagnostic, pathologic, and therapeutic aspects of the 23 similar patients reported in the literature. We also review the evidence regarding the pathogenesis of this disorder.

Patient and methods

Patient

The patient, a 49-year-old man, was found to have an abnormal bleeding time during preoperative evaluation.
for correction of a deviated nasal septum. He had a history of poorly controlled hypertension for six years, erectile dysfunction for five years, and easy bruising for four years. Over the preceding two years he noticed abdominal striae, facial fullness, weakness and loss of muscle bulk in his legs despite gaining 25 pounds.

Past medical history was notable for tonsillectomy in childhood, spinal fusion at L2-3 at age 25, inguinal hernia repair, and recent colon polypectomy. Medications included extended-release nifedipine 60 mg daily, terazocin 2 mg daily, guanfacine 2 mg daily, and triamterene 50 mg + hydrochlorothiazide 25 mg daily. His family history was negative for Cushing’s syndrome.

Physical examination revealed typical Cushingoid features with plethoric moon faces and central obesity. Blood pressure was 170/100. The skin was thin on the extremities with multiple ecchymoses. There were wide violaceous abdominal striae. Head and neck exam revealed supraclavicular fullness and a normal thyroid. Lung and heart exams were normal. The abdomen was protuberant without organomegaly, palpable masses, or tenderness. Genitourinary and rectal exams were normal. The extremities were thin with atrophic musculature in both lower extremities. There was 1+ ankle edema bilaterally. Neurologic exam revealed 4+/5 strength in the shoulder abductors, and 4-/5 strength in the hip flexors.

Routine hematologic examination was normal. A multiphasic chemistry panel was notable for fasting glucose 7.7 mmol/l (138 mg/dl), BUN 9.6 mmol/l (27 mg/dl), creatinine 88 µmol/l (1.0 mg/dl), and cholesterol 5.87 mmol/l (227 mg/dl). Endocrinologic evaluation is detailed in Table 1. Of the seven samples sent for ACTH determination by four reference laboratory methods (three radioimmunoassays, one immunoradiometric assay), only one sample had a detectable level of ACTH. Elevated levels of serum cortisol, urine 17-hydroxycorticosteroids, and urine-free cortisol were not suppressed during 2-day low dose, high dose, or “super-high” dose dexamethasone testing (Table 1). Magnetic resonance imaging revealed bilaterally enlarged adrenal glands. An MRI of the sella turcica was normal. Bilateral suprarenal uptake was present on iodochloroacetate scan.

On the basis of these studies the patient was felt to have ACTH-independent bilateral adrenal-based Cushing’s syndrome and was scheduled for bilateral adrenalectomy. For personal reasons, the patient delayed surgery for 4 weeks, during which time treatment with ketoconazole was instituted. Doses of 400 mg/day reduced morning serum cortisol values to 14 µg/dl and decreased blood pressure to 110–120/70–80, permitting discontinuation of three of the four antihypertensive agents. Edema and bruisability also improved with ketoconazole therapy.

The patient underwent exploratory laparotomy. Both adrenal glands were found to be massively enlarged, and bilateral adrenalectomy was performed. Pathologic findings are discussed below. The patient’s immediate post-operative recovery was uneventful. Serum cortisol was 1.2 µg/dl at 8 AM 2 weeks postoperatively and remained at or below the lower limit of detection in all subsequent measurements. ACTH was <5 ng/l 2 weeks postoperatively and remained undetectable 5 months postoperatively. The patient was treated with 30–35 mg of hydrocortisone daily and required minimal mineralocorticoid supplementation. Within one month after surgery he became normotensive off all antihypertensives.

### G protein analysis

To determine whether constitutive activation of Gs\(_{\alpha}\), the stimulatory guanine nucleotide-binding protein (G protein), was responsible for the autonomous hypercortisolism in our patient, we looked for mutations of the Gs\(_{\alpha}\) gene in DNA from the patient’s adrenal tissue. DNA was isolated from 10 µl slices of paraffin-embedded adrenal tissue as previously described (10). A segment of genomic DNA containing exons 8 and 9 of the Gs\(_{\alpha}\) protein gene was amplified using a nested set of primers under standard polymerase chain reaction (PCR) conditions (11) but using Vent DNA polymerase and buffer conditions suggested by the supplier (New England Biolabs, Beverly, MA). The primer sequences were derived from the Gs\(_{\alpha}\) protein gene sequence (12). The PCR product (346 bps) was cloned into pBluescript II SK(+) (Stratagene, San Diego, CA) and plasmid DNA isolated from a number of transformants. Plasmid inserts were sequenced using a standard protocol (13).

---

**Table 1. Endocrine evaluation.**

<table>
<thead>
<tr>
<th>Dexamethasone (mg/day)</th>
<th>AM cortisol (µg/dl)</th>
<th>ACTH (ng/l)</th>
<th>17OHCS (mg/24h)</th>
<th>Free cortisol (µg/24h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>27, 25, 33</td>
<td>&lt;2.5, &lt;5</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>38</td>
<td>&lt;5</td>
<td>33</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>&lt;5</td>
<td>35</td>
<td>166</td>
</tr>
<tr>
<td>8</td>
<td>32</td>
<td>&lt;5</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>&lt;25</td>
<td>54</td>
<td>360</td>
<td></td>
</tr>
</tbody>
</table>

Summary of the endocrinologic evaluation of a 49-year-old man with clinical manifestations of Cushing’s syndrome. Dexamethasone was administered in divided doses four times daily. Superscripts denote different reference laboratories for radioimunoassay (RIA) or immunoradiometric assay (IRMA) of ACTH: 1 SmithKline Laboratories (RIA, reference range <70 ng/l). 2 Nichols Institute (RIA, reference range 9–52 ng/l). 3 Nichols Institute (RIA, reference range 10–130 ng/l). 4 Mayo Laboratories (RIA, reference range 8–68 ng/l). AM cortisol reference range 7–25 µg/dl, urine 17-hydroxycorticosteroids (17OHCS) reference range 3–15 mg/24 h, urine-free cortisol reference range <50 µg/24 h. All urine collections contained >1.5 g creatinine/24 h.
Literature review

A literature search for similar cases was performed using MEDLINE and extensive cross-referencing. Cases meeting the following criteria were included for analysis: (1) evidence of bilateral adrenal hyperfunction. (2) ACTH independence, and (3) absence of the clinical and pathologic features of PPNAD.

Results

Pathology

On gross examination, the adrenal glands were yellow to tan in color with non-pigmented nodules measuring up to 2 cm in diameter. The left adrenal measured 13 × 6 × 4 cm and weighed 199 g; the right adrenal measured 7 × 8 × 3 cm and weighed 93 g. (Normal single adrenal gland weight is 4–6 g (14).) Light microscopy (Fig. 1) revealed lipid-filled adrenocortical cells organized in numerous well-circumscribed nodules with intervening foci of angiomyelolipomatosis. Areas containing lipid-depleted cells were present, but no areas of atrophy were seen. The nodules varied from nests of cells up to 2 cm in diameter, and many were encapsulated by a fine fibrovascular stroma. Individual cells had clear-to-pink granular cytoplasm and small round-to-oval nuclei.

G protein analysis

Nine cloned inserts containing exons 8 and 9 of the Gsα gene were sequenced to look for the presence of activating mutations. None of these inserts were found to contain a base change, indicating that no such mutations were present. The patient is unlikely to be heterozygous for a dominant negative mutation in exon 8 or 9 as this would have produced a base change in half of the inserts.

Literature review

Our review of the literature revealed only 23 additional cases which met our criteria for AIMBAD: (1) bilateral adrenal hyperfunction, (2) ACTH independence, and (3) absence of the clinical and pathologic features of PPNAD. Of interest, in all cases, the combined adrenal weight was greater than five times normal. Eleven of the reported cases are from Japan (5, 7–9, 15–18). Information on four cases published in foreign languages (3 Japanese (16–18) and 1 French (19)) is derived from summaries in the English literature (6, 9). Characteristics of the 24 cases of AIMBAD are summarized in Table 2. These cases include the “macronodular” (4, 5, 7–9, 20–22) and “massive” (6) adrenal glands previously described. The twenty-three cases in which the adrenal glands were available for examination all showed striking bilateral enlargement. Individual gland weights were reported in 22 of the patients and averaged 96.6 ± 16.7 g, compared to a normal single adrenal gland weight of 4–6 g (14). The left adrenal was larger than the right in 16 of 22 patients. The combined adrenal weight averaged 193 ± 46 g (range: 55–900 g; Table 2). In comparison, combined adrenal weights in patients with pituitary-based Cushing’s disease were reported as 15.6 ± 1.4 g, 16.7 ± 1.3 g, and 33.0 ± 6.8 g for patients with diffuse hyperplasia, micronodular hyperplasia, and macro-nodular (nODULES ≥ 0.5 cm) hyperplasia, respectively (average for all 30 patients: 22.9 ± 3.1 g) (23). Since the weight of the glands in AIMBAD is distributed along a continuum with no apparent modal distribution, rather than making an arbitrary weight cut-off we have included within the AIMBAD designation all cases which meet the criteria outlined above. The essential aspect of AIMBAD is ACTH-independent hyperfunction of both adrenal glands, not adrenal size. While all cases reported to date have a combined adrenal weight greater than five times normal, it is possible that future cases of AIMBAD meeting the criteria outlined above may fall under this level.

The AIMBAD patients average 48.1 ± 4 years (range 37–62) at diagnosis, and are divided roughly evenly among males (N = 13) and females (N = 11). Overall, the clinical presentation is similar to that of Cushing’s disease. The average duration of disease at diagnosis is 4.3 ± 0.6 years. Clinical manifestations, which are described in varying degrees of detail in the case reports, include hypertension (19 of 19 patients in which information is available), weight gain (16 of 16 patients), impaired glucose tolerance or diabetes mellitus (10 of 13 patients), osteoporosis (4 of 8 patients), hypertrophy of the heart, and hypertension.

Fig. 1. Low magnification (40×) photomicrograph of adrenal tissue from a 49-year-old man with ACTH-independent massive bilateral adrenal disease (AIMBAD). Nodules composed of lipid-filled cells are surrounded by areas of smaller, but not atrophic, cells. Foci of angiomyelolipomatosis are apparent.
Table 2. Reported cases of ACTH-independent massive bilateral adrenal disease.

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Age/sex</th>
<th>Clinical features</th>
<th>ACTH* (ng/l)</th>
<th>Dexamethasone suppression (8 mg/d)</th>
<th>Combined adrenal gland weight (g)</th>
<th>Maximum nodule size (cm)</th>
<th>Pathologic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lieberman '93</td>
<td>49/M</td>
<td>HT, DM, HG, MY</td>
<td>undet X 6</td>
<td>non-supp</td>
<td>292</td>
<td>2</td>
<td>small, not atrophic</td>
</tr>
<tr>
<td>Findlay '93 (22)</td>
<td>38/F</td>
<td>HT, DM</td>
<td>NR</td>
<td>non-supp</td>
<td>130</td>
<td>1.3</td>
<td>hyperplastic</td>
</tr>
<tr>
<td>LaCroix '92 (27)</td>
<td>38/F</td>
<td>HT</td>
<td>undet</td>
<td>non-supp</td>
<td>98.5</td>
<td>4</td>
<td>hyperplastic</td>
</tr>
<tr>
<td>Reznik '92 (28)</td>
<td>49/F</td>
<td>HT, MY, PSY</td>
<td>undet</td>
<td>non-supp</td>
<td>55</td>
<td>2.8</td>
<td>hyperplastic</td>
</tr>
<tr>
<td>Alba '91 (5) no. 1</td>
<td>51/M</td>
<td>HT, DM, MY, G</td>
<td>undet</td>
<td>non-supp</td>
<td>NR</td>
<td>NR</td>
<td>atrophic, not compressed</td>
</tr>
<tr>
<td>Ibid. no. 2</td>
<td>52/M</td>
<td>HT, DM, IN</td>
<td>undet</td>
<td>NR</td>
<td>116</td>
<td>NR</td>
<td>atrophic, not compressed</td>
</tr>
<tr>
<td>Ibid. no. 3</td>
<td>45/M</td>
<td>HT, DM, IN</td>
<td>undet</td>
<td>NR</td>
<td>123</td>
<td>NR</td>
<td>atrophic, not compressed</td>
</tr>
<tr>
<td>Ibid. no. 4</td>
<td>37/M</td>
<td>HT, OP</td>
<td>undet</td>
<td>NR</td>
<td>72</td>
<td>NR</td>
<td>hyperplastic</td>
</tr>
<tr>
<td>Zeiger '91 (20) no. 5</td>
<td>49/F</td>
<td>HT, PSY, HRS</td>
<td>4.5 (&lt;4-20)</td>
<td>non-supp</td>
<td>149</td>
<td>diffuse hyperplasia</td>
<td></td>
</tr>
<tr>
<td>Ibid. no. 6</td>
<td>51/F</td>
<td>HT, PSY</td>
<td>4.8 (&lt;4-20)</td>
<td>non-supp</td>
<td>69</td>
<td>3</td>
<td>NR</td>
</tr>
<tr>
<td>Ibid. no. 7</td>
<td>61/M</td>
<td>HT, PSY</td>
<td>undet</td>
<td>non-supp</td>
<td>94</td>
<td>3.8</td>
<td>NR</td>
</tr>
<tr>
<td>Malchoff '89 (4)</td>
<td>47/M</td>
<td>HT, DM, OP, HG, G</td>
<td>undet</td>
<td>non-supp</td>
<td>86</td>
<td>&gt;0.5</td>
<td>small, not atrophic</td>
</tr>
<tr>
<td>Cugini '89 (7)</td>
<td>43/M</td>
<td>HT, DM, IN</td>
<td>10 (10-80)</td>
<td>non-supp</td>
<td>900</td>
<td>NR</td>
<td>not atrophic</td>
</tr>
<tr>
<td>Makino '89 (8)</td>
<td>51/M</td>
<td>HT, DM, G</td>
<td>undet</td>
<td>non-supp</td>
<td>150</td>
<td>NR</td>
<td>atrophic</td>
</tr>
<tr>
<td>Cheitlin '88 (26)</td>
<td>62/M</td>
<td>HT, HG, PSY</td>
<td>undet X 2</td>
<td>NR</td>
<td>760</td>
<td>4</td>
<td>hyperplastic</td>
</tr>
<tr>
<td>Hashimoto '86 (9)</td>
<td>51/M</td>
<td>HT, IGT, HG</td>
<td>undet</td>
<td>non-supp</td>
<td>130</td>
<td>4</td>
<td>normal or compressed</td>
</tr>
<tr>
<td>Miura '84 (17)</td>
<td>62/F</td>
<td>NR</td>
<td>14-20 (10-80)**</td>
<td>non-supp</td>
<td>108</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Murayama '83 (18)</td>
<td>49/F</td>
<td>NR</td>
<td>10 (10-80)**</td>
<td>non-supp</td>
<td>150</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Krivitzyk '80 (19)</td>
<td>39/F</td>
<td>NR</td>
<td>10 (10-80)**</td>
<td>non-supp</td>
<td>110</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ishihara '77 (16)</td>
<td>51/M</td>
<td>NR</td>
<td>10-20 (10-80)**</td>
<td>non-supp</td>
<td>226</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hidal '75 (15)</td>
<td>47/M</td>
<td>HT, OP, MY</td>
<td>NR</td>
<td>non-supp</td>
<td>161</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Choi '70 (34)</td>
<td>44/F</td>
<td>HT</td>
<td>undet</td>
<td>non-supp</td>
<td>NR</td>
<td>0.7</td>
<td>hyperplastic</td>
</tr>
<tr>
<td>Kirschner '64 (25)</td>
<td>40/F</td>
<td>DM, OP, HRS, IN</td>
<td>NR</td>
<td>non-supp</td>
<td>94</td>
<td>3.5</td>
<td>atrophic</td>
</tr>
</tbody>
</table>

*ACTH normal ranges appear in parentheses.
**per Hashimoto (9).


non-supp = non-suppressible, undet = undetectable, NR = data not reported.

patients), and easy bruising (7 of 7 patients). Hypogonadism and gynecomastia are reported in 4 and 3 of 12 males in which information is available, while hirsutism is reported in 3 of 8 females. Psychiatric disturbances, proximal myopathy, and infection are reported in 6, 4, and 4 patients, respectively.

As with other causes of Cushing's syndrome (24), morning cortisol levels are not very helpful in establishing the presence of hypercortisolism in AIMBAD (13 of 21 patients had at least one value in the normal range). In contrast, evening cortisol levels (N = 12), the 1 mg overnight dexamethasone suppression test (N = 3), and the 2-day low-dose dexamethasone suppression test (N = 7) all indicated abnormal cortisol production. The 24-h urine free cortisol was elevated in 9 of 10 patients in which it was reported. The failure to suppress cortisol by either the 8 mg overnight dexamethasone suppression test (N = 1) or the 2-day high-dose (N = 20) or 'super-high' dose (4 mg every 6 h, N = 5) dexamethasone suppression tests indicated cortisol hypersecretion due to a non-pituitary cause in all patients so tested. ACTH levels were below the limit of detection in 14 patients and were at or near the lower limit of normal in 7 patients. In one patient in whom ACTH was not reported, melanocyte stimulating hormone, a co-product of ACTH biosynthesis, was below the normal range (15). ACTH was not reported in two further cases which are nonetheless included as cases of AIMBAD because of marked bilateral adrenal enlargement and absence of Nelson's syndrome 17 (22) and 30 (6, 25) years following bilateral adrenalectomy. In 5 patients, pituitary-independence of hypercortisolism was demonstrated by a low ratio of ACTH between the inferior petrosal sinus and peripheral blood in the basal state (N = 5) and following CRH administration (N = 4) (20, 26, 27). Taken together, lack of dexamethasone suppressibility, low or undetectable ACTH levels, and low central/peripheral ACTH ratios
during inferior petrosal sinus sampling indicate that hypercortisolism in AIMBAD is independent of ACTH secretion.

However, the adrenal cortex remains responsive to ACTH and in some cases is hyperresponsive. All thirteen patients administered ACTH as a bolus or infusion had normal or supranormal responses in serum cortisol or urine metabolites. Among patients with specific values reported for a short ACTH stimulation test, the increase in cortisol averaged 212% (N = 4) and the average post-ACTH cortisol level was 75 ± 30 μg/dl (N = 4). Two additional patients were subjectively reported as having a cortisol “hyperresponse” to ACTH (16, 18). per Hashimoto et al. (9)).

Radiographic imaging of the adrenals was undertaken in 19 patients. Computerized tomography (CT) or magnetic resonance imaging (MRI) demonstrated bilateral adrenal enlargement in all 16 patients studied. Radiographs following retroperitoneal air insufflation showed bilateral suprarenal masses in one patient (25) and unilateral enlargement with equivocal contralateral findings in another (15). Angiography, performed in one patient (Findlay et al. (22); patient no. 1), revealed a unilateral adrenal mass. Bilaterality of adrenocortical hyperfunction was demonstrated by iodocholesterol scintigraphy in 12 patients. In summary, there was unequivocal radiographic or scintigraphic evidence of bilateral adrenal involvement in 20 of the 24 cases, with CT and MRI having 100% sensitivity. Although neither of the two patients with evidence of unilateral disease was studied by iodocholesterol scanning, CT, or MRI, both had bilaterally enlarged adrenals at surgery ((15) and Findlay et al. (22), patient no. 1). Two patients did not undergo adrenal imaging.

Total bilateral adrenalectomy was performed in 22 patients (one refused operation (28) and one died before surgery (7)). Among those operated, there are no reports of recurrence of Cushing’s syndrome, with a mean follow-up of 60 months (range: 3 months to 30 years).

Histopathologically, the glands were described as yellow to yellow-brown or tan with large nodules distorting the normal cortical architecture. Rare pigmented foci were reported in 4 cases. Maximum nodule size ranged from 0.7 to 4 cm (average 2.9 ± 0.4 cm) among the 10 cases in which it was reported (Table 2); in others, nodules were described by terms such as “huge” and “grossly nodular”. Of note, the pathologic description in one patient (Zeiger et al. (20), patient no. 5) was diffuse bilateral hyperplasia. With the exception of extracapsular infiltration by cortical cells in the four patients reported by Aiba et al. (5), there was no evidence of invasion or malignancy on microscopic examination. In many of the reports, attention was directed to the appearance of the internodular adrenal cortex. The presumption has been that an atrophic internodular cortex implies autonomous cortisol production by the cells comprising the nodules with suppression of ACTH and resultant atrophy of the intervening cortex, while a hyperplastic internodular cortex presumably results from stimulation of both nodular and internodular cells by an adrenocorticotropic agent (as seen in Cushing’s disease (14, 23)). Fourteen of the case reports addressed the histology of the internodular regions: 5 were reported as atrophic, 5 as hyperplastic or hypertrophic, and 4 as not atrophic. Whether this heterogeneity carries implications with regard to pathogenesis is unknown.

Discussion
The current report describes a case of Cushing’s syndrome due to massive enlargement and hyperfunction of both adrenal glands with undetectable levels of ACTH, which we term ACTH-independent massive bilateral adrenal disease (AIMBAD). This disorder differs from the three common causes of endogenous Cushing’s syndrome (Cushing’s disease, ectopic ACTH syndrome, and adrenal neoplasm) in that hypercortisolism results from adrenocortical hyperfunction which is both independent of ACTH stimulation and bilateral. It is distinguished from another type of nodular adrenal hyperplasia, primary pigmented nodular adrenocortical dysplasia (PPNAD), by the massive and non-pigmented enlargement of the adrenal glands, the absence of associated tumors or other endocrinopathies, and the older age at which AIMBAD is diagnosed. PPNAD has been the subject of two comprehensive reviews (2, 3).

Difficulty in the diagnosis of AIMBAD may arise because a subset of patients with pituitary-based Cushing’s disease have bilateral nodular enlargement of the adrenals which is visible on radiographic studies. The term “macronodular hyperplasia” has been applied both to the latter group (23, 29) as well as to patients with AIMBAD, thus causing considerable confusion in the literature. Further uncertainty in the diagnosis of AIMBAD derives from the poor sensitivity and specificity of radiologic studies in the differential diagnosis of Cushing’s syndrome: falsely negative MRIs occur in up to 50% of patients with Cushing’s disease (30), while hormonally silent tumors are common in both the pituitary (31) and the adrenal glands (32). Confidence in distinguishing AIMBAD from Cushing’s disease with bilateral macronodular adrenal enlargement derives from clear demonstration of an ACTH-independent process and allows surgery to be appropriately directed toward the adrenal glands.

The pathogenesis of AIMBAD is unclear. An early hypothesis held that chronic stimulation of the adrenal cortex in long-standing Cushing’s disease ultimately resulted in autonomous adrenal cortisol production (23, 25). Smals et al. (23) examined Cushing’s disease patients with macronodular hyperplasia (arbitrarily defined as nodules >0.5 cm), micronodular hyperplasia, or diffuse hyperplasia and concluded that
long-standing adrenal stimulation by ACTH resulted in larger adrenal glands, macronodule formation, and greater autonomy of adrenal function. In contrast to Smals' patients, those with AIMBAD have a shorter duration of disease and a normal or exaggerated cortisol response to ACTH. Other authors have proposed a transition from pituitary- to adrenal-based hypercortisolism (33) or dual pituitary/adrenal control of cortisol secretion (34). However, the rarity of Nelson’s syndrome following bilateral adrenalectomy in patients with AIMBAD (only one case (34) among 24 patients, while twelve patients in whom information was available had no evidence of Nelson’s syndrome during 6 months to 30 years of follow-up (4, 8, 9, 15–19, 22, 25, 26)) argues against transition from ACTH-dependence to ACTH-independence as a pathogenetic mechanism in AIMBAD and emphasizes the apparent safety of bilateral adrenalectomy in the management of this disorder.

The possibility that stimulators of the adrenal cortex other than ACTH may play a role in the pathogenesis of AIMBAD is suggested by the results of dynamic testing in several of the case reports. Increased corticosteroid secretion occurred without a detectable increase in ACTH levels in subsets of patients tested with CRH (2 of 9 patients tested), insulin (3 of 3 patients tested), or metyrapone (3 of 17 patients tested). In an attempt to explain this finding, Hashimoto et al. treated isolated cortical cells from their patient with AIMBAD with several hormones (ACTH, angiotensin II, insulin, vasopressin, norepinephrine, or epinephrine) but found an increase in cortisol release only with ACTH (9). Whether the ACTH-independent response to CRH, insulin, or metyrapone (4, 5, 8, 9, 18) is caused by an unidentified adrenocortical stimulator or by adrenal hypersensitivity to fluctuations in ACTH below detection limits is unknown. The latter cannot entirely be excluded in light of the hyperresponsiveness to ACTH stimulation in some of the patients as described above.

Although the mediator(s) of these ACTH-independent effects are unidentified, two recent reports not only validate the concept of hypercortisolism stimulated by factors other than ACTH, but also illuminate a novel pathogenetic mechanism for the disorder. Lacroix et al. (27) and Reznik et al. (28) simultaneously and independently reported two patients with gastric inhibitory polypeptide (GIP)-induced Cushing’s syndrome characterized by low fasting and elevated postprandial cortisol levels, undetectable ACTH levels, non-suppressibility with standard high dose dexamethasone testing, increased cortisol secretion following oral feeding but not intravenous glucose infusion, significant correlation of plasma cortisol with plasma GIP levels (28), and elevation of plasma cortisol in response to infusion of GIP (27). These elegantly demonstrated cases of GIP-mediated food-dependent Cushing’s syndrome are believed to result from ectopic expression of GIP receptors by adrenocortical cells (27, 28). These cases clearly meet the criteria for AIMBAD (Table 2); however, the presence of fasting hypercortisolemia in most of the cases we reviewed excludes this mechanism as a common cause of AIMBAD.

Another recent report further expands the spectrum of AIMBAD. Findlay et al. (22) described Cushing’s syndrome in a mother and daughter, both of whom meet the criteria for AIMBAD. With the exception of PPAN, which often follows an autosomal dominant pattern (3), and the recent report of Cushing’s disease in two family members with multiple endocrine neoplasia type 1 (35), Cushing’s syndrome is otherwise non-familial (22).

Bilateral adrenal hyperfunction independent of ACTH in our patient recalled the pattern seen in patients with McCune-Albright syndrome, in which activating mutations of the stimulatory G protein, Gsα, in affected tissues may produce hypercortisolism and other endocrine hypersecretory states (36). We analyzed adrenal tissue from our patient for mutations in the Gsα gene at the two locations (arginine-201 and glycine-227) affected in patients with McCune-Albright syndrome and in a subset of patients with acromegaly (37). Sequencing of the PCR-amplified DNA revealed no mutations in the examined portions of exons 8 and 9 of the Gsα gene. Whether other G protein mutations may play a role in the pathogenesis of AIMBAD is unknown.

In summary, AIMBAD is an uncommon cause of Cushing’s syndrome characterized by bilateral massive enlargement and hyperfunction of the adrenal glands without suppression of ACTH secretion. Endocrine testing indicates an ACTH-independent cause of hypercortisolism, and adrenal imaging with CT or MRI demonstrates bilateral abnormalities in all cases, usually with evidence of massive adrenal enlargement. Bilateral adrenalectomy is the treatment of choice as it is curative and appears to carry little, if any, risk of Nelson’s syndrome. The pathogenesis of AIMBAD is unknown in most cases but appears to be heterogeneous. We predict that a variety of mechanisms will ultimately be found to underlie adrenal stimulation in different subgroups of these cases. Future cases of AIMBAD should be investigated carefully to further elucidate the pathogenesis of this disorder.

Acknowledgments. The authors thank I. Ross McDougall, M.D. for performing the iodocholesterol scan, Michael Hendrickson, M.D. for assistance with the pathological specimens, and Lawrence Crapo, M.D. for critically reviewing the manuscript.

References


10. thermostable
18. stranded
17. Sci
Kosawa
Saiki
San
embedded
a
Cushing's
Murayama
nodular
Miura
Ishihara
due
hyperplasia
Doppman
Pathol
Aiba
et
Malchoff
years
(1980;32:1659-64)


Lamberts SWJ, Bos N, Bruining HA. Different sensitivity to adrenocorticotropic of dispersed adrenocortical cells from patients with Cushing's disease with macronodular and diffuse adrenal hyperplasia. J Clin Endocrinol Metab 1984;58:1106-10
Gross MD, Shapiro B. Clinically silent adrenal masses. J Clin Endocrinol Metab 1993;77:885-8
Gaitan D, Loosen PT, Orth DN. Two patients with Cushing's disease in a kindred with multiple endocrine neoplasia type I. J Clin Endocrinol Metab 1993;76:1580-2

Received November 16th, 1993
Accepted March 14th, 1994