CASE REPORT

Food-dependent Cushing’s syndrome: from molecular characterization to therapeutical results

N M Albiger, G Occhi, B Mariniello, M Iacobone1, G Favia1, A Fassina2, D Faggian3, F Mantero and C Scaroni
Department of Medical and Surgical Sciences Endocrinology Unit, University of Padua, via Ospedale 105, 35128 Padua, Italy, Departments of 1Endocrine Surgery, 2Pathology and 3Laboratory Medicine, University of Padua, 1-3 Giustiniani, 35128, Padua, Italy
(Correspondence should be addressed to N M Albiger; Email: nalbiger@yahoo.com)

Abstract

Objective: Cortisol secretion in ACTH-independent macronodular adrenal hyperplasia (AIMAH) may be regulated by the aberrant expression of several G-protein-coupled receptors. Bilateral adrenalectomy is the treatment of choice in most cases. We searched for aberrant receptor expression in a patient with AIMAH and evaluated the response to medical and surgical treatment.

Patient: A 35-year-old woman with amenorrhea, hirsutism, and hypertension presented ACTH-independent cortisol secretion with high androgen levels. Abdominal computed tomography showed bilateral adrenal macronodules (4.5 cm right and 1.0 cm left). Scintigraphy with I131-norcholesterol showed bilateral uptake, prevalent on the right side. Several in vivo stimulation tests were assessed before and after treatment and in vitro studies were performed after unilateral adrenalectomy.

Results: Plasma cortisol increased after a standard meal test (60%) and oral glucose loading (147%), and the response was blunted by pretreatment with 100 mg s.c. octreotide. The therapy with long-acting release octreotide (octreotide-LAR) showed an improvement in urinary free cortisol (UFC) levels. Unilateral adrenalectomy was performed and histopathology revealed macronodular AIMAH. Cortisol and androgens increased after perifusion of tumoral tissue with glucose-dependent insulinotropic polypeptide (GIP), and GIP and LH-receptor overexpression was found in both the adrenal nodules and the adjacent cortex. After surgery, UFC and androgen levels normalized followed by clinical improvement.

Conclusions: GIP and LH-receptor expression may coexist in AIMAH, influencing the functional and morphological phenotype. Aberrant hormone receptor expression enables specific pharmacological treatment, but long-term studies are needed to evaluate its real efficacy. Unilateral adrenalectomy may be a safe initial option, particularly for asymmetric bilateral adrenal enlargements.

Introduction

Approximately 10% of adrenocorticotropic hormone (ACTH)-independent Cushing’s syndrome (CS) is secondary to bilateral nodular ACTH-independent macronodular adrenal hyperplasia (AIMAH) (1). A significant proportion of ACTH-independent adrenal tumors or hyperplasia may be under the control of aberrant hormone membrane receptors that may be expressed eutopically or ectopically (2). Hamet et al. (3) described the first case of cortisol production stimulated by food intake in a patient with a unilateral adrenal adenoma leading to CS. Several studies have since demonstrated that the abnormal cortisol response in these cases depends on the expression of glucose-dependent insulinotropic polypeptide receptor (GIP-R), which can be expressed in macronodular adrenal hyperplasia (4–9) and, less frequently, in unilateral adrenal adenoma (10–13). In the majority of reported cases, cortisol is the main steroid secreted in response to food intake, so most of these patients have a clinical appearance of subclinical or overt CS, though some atypical cases with GIP-mediated cortisol and androgen secretion (12), or a cortisol response to both gonadotropin and GIP stimulation (14), have been described.

Since the luteinizing hormone (LH)/hCG receptor was shown to be expressed in the reticularis zone of adrenal glands (15), an aberrant expression of this receptor has also been suggested in some cases of CS (14, 16, 17) and in several cases of pure androgen-secreting adrenal adenoma (18–24) or hyperplasia (25) responding to LH or hCG stimulation in vivo and/or in vitro.

Identifying aberrant receptor expression can prompt new pharmacological alternatives to surgical treatment, particularly when bilateral disease would demand bilateral adrenalectomy and thus carry the consequence of primary hypoadrenalism.

Bilateral adrenalectomy is generally considered the treatment of choice in most patients with ACTH-independent macronodular adrenal hyperplasia,
though a few reports have suggested the feasibility of unilateral adrenalectomy in selected cases (26, 27).

We present a case of combined adrenal cortisol and androgen production by a food-dependent macronodular adrenal hyperplasia with GIP and LH/hCG-receptor coexpression, in whom medical treatment with a long-acting somatostatin analog improved urinary free cortisol (UFC) levels and unilateral adrenalectomy resulted in long-term remission of hypercortisolism and hyperandrogenism.

Clinical case

A 35-year-old woman was admitted to our institution for endocrinological evaluation due to amenorrhea. She had no family history of endocrine diseases. Menarche was 17 years old. She reported a full-term pregnancy at the age of 28 during which she had major weight gain in the early months. Arterial blood pressure and glucose levels were within the normal range. Postpartum she felt well but had oligomenorrhea (menstrual cycles of 45–60 days). She took oral contraceptives for 2 years. After stopping them, she had no spontaneous bleeding, so estrogen and progesterin treatments were reinitiated. While on this treatment, her blood pressure levels began to increase (150/95 mmHg) and she experienced a progressive gain in weight of 4 kg, acne, and a mild increase in facial hair. Her daily oral medication included calcium channel blockers to control blood pressure levels. During physical examination, she was 1.70 m tall and weighed 60 kg (body mass index, BMI: 21), with a WHR of 0.87. She had a round, plethoric face, increased facial hair (Ferriman–Gallwey score 10) (28), and high blood pressure (140/95 with calcium blockers).

Initial biochemical evaluation revealed high UFC levels of 1100 μg/day (normal: 13.7–75.4 μg/day), morning plasma cortisol 5.7 μg/dl (normal: 5–25 μg/dl), plasma cortisol 6.8 μg/dl (normal: < 3 μg/dl) at 2300 h, morning plasma ACTH 7.9 pg/ml (normal: 5–78 pg/ml), and plasma cortisol after 1 mg dexamethasone 13 μg/dl (normal: < 1.8 μg/dl). Salivary cortisol levels were 0.6 μg/dl at 0800 h and 4.4 μg/dl at 2300 h (normal: 6–13 ng/ml and < 2 ng/ml respectively). Serum DHEA sulfate (DHEAS) levels were 6.6 μg/ml (normal: 0.7–3.9 μg/ml); testosterone 144 ng/dl (normal: 20–90 ng/dl), and androstenedione 2.3 ng/ml (normal: 0.2–3.0 ng/ml). Follicle-stimulating hormone (FSH) was 4.2 mIU/ml, LH 4.8 mIU/ml, and estradiol 12.6 pg/ml in amenorrhea. Sodium, potassium, cholesterol, triglycerides, and glucose levels were within the normal range.

Abdominal magnetic resonance imaging showed macronodular features on both adrenal glands (a non-homogeneous hypodense nodule of 45 mm on the right side and another of 10 mm on the left side). Adrenal scintigraphy with [131I]-norcholesterol showed a bilateral uptake, but prevalent on the right side.

A right unilateral adrenalectomy was performed: the gland measured 7.5 × 5.3 × 3.5 cm and weighed 48.8 g. Histology was typical of a macronodular adrenal hyperplasia (Fig. 1).

Material and methods

In vivo studies

Potentially illegitimate membrane hormone receptors were sought in the patient using a modified version of the clinical protocol previously published by Lacroix et al. (29).

The cortisol response to several stimulation tests was assessed before surgery. All tests were performed after obtaining the patient’s written consent and in accordance with the Helsinki declaration. Before performing the test, the patient had been in a supine position for at least 1 h and had fasted overnight. An i.v. catheter was inserted and permeability maintained with a slow flow of saline solution throughout the tests. Serial ACTH and cortisol measurements were taken at 30-minute intervals for 2–3 h during the tests, which were performed in a sequence lasting several days. LH, FSH, prolactin, thyrotrophin, or GIP were measured at appropriate times.

The tests included the i.v. administration of 100 μg gonadotrophin-releasing hormone (Gn-RH) (Relefact, Gonadorelin, Aventis, Germany) and 200 μg i.v. TRH (thyrotropin-releasing hormone TRH UCB, S.A. UCB N.V., Bruxelles), 500 μg i.v. terlipressin (Glipressina,
Ferring, Italy). 1 mg i.m. glucagon, 10 μg i.v. desmopressin (Minirin/DDAVP, Ferring S.p.A., Milano, Italy), 10 mg metoclopramide orally (Plasit, Gruppo Lepetit SpA, Italy), and 100 μg i.v. ovine CRH (CRE, Clinalfa, Merck Biosciences AG). The postural test was also performed, with 2 h in the supine position followed by 2 h of ambulation. A standard mixed meal challenge was performed, and a 75 g oral glucose tolerance test (OGTT) to confirm the findings. Ocreotide (Sandostatin, Novartis, Italy) 100 μg s.c. was subsequently administered 60 min before a second standard mixed meal test to assess the effect of octreotide on GIP secretion and cortisol response.

After surgery, an OGTT was repeated and in addition an hCG test (Gonasi HP AMSA Srl, Italy: 5000 UI i.m. with samples obtained every 30 min for 3 h) was performed.

A test result was arbitrarily considered as a negative response when the increase in plasma cortisol levels was < 25% of the baseline after the stimulus, as a partial response with an increase between 25 and 49%, and as a positive response with an increase ≥ 50%. If a partial or positive response was found, the test was repeated to confirm the data.

**In vitro studies**

**Tissue collection** Adrenocortical tissue specimens were obtained immediately after surgery and stored in RNAlater (Ambion, USA) at −20 °C until nucleic acid extraction. During surgery, a fragment of the patient’s tumor was immersed in DMEM (Life Technologies, Grand Island, NY, USA) and taken rapidly to the laboratory for perifusion studies. One normal adrenocortical sample was obtained after surgery for renal transplantation, normal adult pancreas was obtained after surgery of a pancreatic tumor, and tumoral tissue from two patients with non-GIP-dependent CS and bilateral macronodular adrenocortical hyperplasia were also evaluated.

**Perifusion experiments** The tumor tissue was diced into small pieces (1–2 mm), rinsed with fresh DMEM, and transferred to perifusion chambers supplied with the same medium. The temperature in the chambers was maintained at 37 °C and pH at 7.4. Before beginning the test, the tumor pieces were allowed to stabilize for 2 h at a constant flow rate (300 μl/min), then the substances were dissolved in DMEM and infused at the same flow rate.

Effluent fractions were collected at 5 min intervals and kept at −20 °C until assay. Gastric inhibitory polypeptide was purchased from Sigma–Aldrich.

**RNA extraction and RT-PCR** The tissues were homogenized and RNA was isolated with 1 ml Trizol (Invitrogen) according to the manufacturer’s protocol, using a Polytron homogenizer (Ultra-Turrax T8, Ika Labortechnik, Staufen, Germany). Briefly, the RNA was precipitated with 0.5 ml isopropl alcohol in the aqueous phase. The RNA pellet was washed once in 70% ethanol, dried, and resuspended in 50 μl RNase-free water and kept at −80 °C until use. RNA yield and integrity were determined with a BioPhotometer (Eppendorf, Italy).

A 20 μl RT mixture containing 0.5 μg total RNA, 0.5 mM dNTPs, 4.5 ng/μl random hexamers, 5 mM dithiothreitol, 20 U RNase OUT, and 100 U Super Script III (Invitrogen) was incubated at 50 °C for 1 h followed by 15 min at 70 °C.

RT-PCR was performed in 12.5 μl volumes containing 0.4 units Taq polymerase (Amplitaq Gold, Applied Biosystems, Monza, Italy), 25 ng cDNA, 5 pmol of each oligonucleotide primer (R-GIP-6-7F 5′-GAGTTTGTT-CAGGCGGCTAC-3′, R-GIP-8R 5′-GCAAGTGAATGAG-GAAATGG-3′), 2.5 mM MgCl2, and 0.2 mM dNTPs. Amplification was carried out on a 2700 GeneAmp PCR system (Applied Biosystems) under the following conditions: 94 °C for 10 min followed by 35 cycles of 94 °C for 30 s, 57 °C for 30 s, and 72 °C for 30 s. Aliquots of the amplified products were separated by 1.5% agarose gel electrophoresis and stained with ethidium bromide.

PCR product identity was confirmed by direct DNA sequencing analysis using the BigDye dyeoxy terminator (Applied Biosystems Manza, Italy) on an ABI 3100 DNA sequencer (Applied Biosystems). Chromas 1.5 software (TechneLysium, Helensvale, Australia), and the LASERGENE (DNA Star Inc., Madison, WI, USA) package of computer programs (DNASTAR) were used to edit and assemble sequences.

**Real-time PCR** Primers for amplification of the target sequences were based on published sequences for human LH/hCG-R and human GAPDH. The primer set used for LH/hCG-R consisted of forward: 5′-TCCTGGA-AAGATGCACAATGGA-3′ and reverse: 5′-GCTGCC-AATTTGTTGGAAGA-3′, and for GAPDH forward is 5′-CCTCCTGCTCTCTGCTGAGC-3′ and reverse is 5′-TGAAGCGATGTGGCTCGCT-3′.

Real-time PCR was performed in a total volume of 30 μl per reaction using the reaction parameters recommended by the manufacturer, using a power SYBR Green PCR Master Mix (2×; Applied Biosystems), 50 nM of each primer, and 20 ng cDNA. All reactions were performed for LH-R and the housekeeping gene (GAPDH) at the same time. Data were obtained as Ct values according to the guidelines (the cycle number at which logarithmic PCR plots cross a calculated threshold) and used to determine ΔCt values (ΔCt = Ct of the target gene minus Ct of the housekeeping gene). The equation 2−ΔΔCt was used to calculate the fold changes in gene expression between the patient and controls. Measurements were taken at least thrice for each sample.

**Immunohistochemistry (IHC)** IHC was performed with an automatic immunostaining device (Vision BioSystems ‘Define’ Polymer Detection System, Vision www.eje-online.org
BioSystems, Newcastle, UK), using a Bond-maX immunostainer (Vision Biosystems), on 5 μm thick sections from formalin-fixed paraffin-embedded tissues. Sections were transferred to adhesive slides and dried at 62 °C for 30 min. Anti-LH/choriogonadotropin receptor antibody (L 6792, Sigma–Aldrich Inc.) was diluted at 1:200. Bond primary antibody diluent was used. Sections were pretreated with Bond enzyme 1 for 10 min and stained with primary antibodies for 30 min, post-primary antibodies for 20 min, polymer for 30 min, and diaminobenzidine Define for 10 min, then counterstained with hematoxylin. The sections were dehydrated in alcohol, cleared in xylene, and mounted with DPX. As a negative control, the primary antibody incubation step was omitted, and placentas were employed as positive controls.

**Hormonal assays**

Plasma and urinary cortisol were measured by RIA (DIA-Sorin Diagnostics, Saluggia, Italy) with intra- and inter-assay coefficient of variation (CV) values of 5.4 and 9.6% respectively, and plasma ACTH levels by IRMA (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA) with intra- and inter-assay CV values of 4.3 and 8.7% respectively. Serum DHEA-S concentrations were measured by RIA (DPC Diagnostic Products Corporation, Los Angeles, CA, USA) with intra- and inter-assay CV values of 8.1 and 5.3% respectively. Serum and perifused samples for 17-OH progesterone were determined by an enzyme immunoassay (DRG International Inc., DRG, Marburg, Germany) with intra- and inter-assay CV values of 5.5 and 6.8% respectively, and testosterone levels were determined by a chemiluminescence immunoassay (Roche Elecsys). Cortisol levels on perifused samples were determined in all fractions by RIA (Radim, Pomezia, Italy) with intra- and inter-assay CV values of 4.2 and 8.5% respectively.

**Results**

**In vivo studies**

A positive cortisol response (60% above the baseline) was prompted by the standard mixed meal, and this response was inhibited by the administration of 100 μg s.c. octreotide 60 min before the meal (Fig. 2a and b). Plasma cortisol response was confirmed after an OGTT test (147% above the baseline; Fig. 2c). The patient’s treatment began with 20 mg octreotide-LAR, and subsequently increased to 30 mg, every 28 days for 5 months. A significant reduction in UFC levels was seen with treatment, but cortisol levels remained slightly above normal (Fig. 3). There was a modest improvement in clinical signs of CS during treatment.

**Figure 2** In vivo studies. Variations in (A) cortisol and (B) GIP levels after a standard meal without (– –) or with ( – –) octreotide treatment (100 μg s.c.) 1 h beforehand. (c) Variations in cortisol levels after an OGTT without (– –) or during ( – –) a long-acting somatostatin analog treatment.

**Figure 3** UFC levels during 5 months of therapy with a long-acting somatostatin analog (SSA). Values are expressed in μg/24 h (normal: 37–75 μg/24 h).
with octreotide-LAR, and OGTT was repeated with no cortisol response to the stimulus (Fig. 2c).

There was no cortisol response to desmopressin, terlipressin, TRH, and the postsurgical test before treatment. Only a partial response of ACTH (29% above the baseline) to CRH stimulation was observed. A negative cortisol response was also observed during Gn-RH stimulation test, but the increase in LH levels (baseline: 4.8 mIU/ml, peak: 9.2 mIU/ml) was only modest. No androgen measurements were taken during these tests.

**In vitro studies**

**Perifusion study** The kinetics of the responses of perifused tissue to a pulse of GIP (10⁻⁷ M, 20 min) are shown in Fig. 4A. GIP administration induced a brisk but transient increase in cortisol secretion that reached a maximum of 262.0 ± 3.0 ng/dl. Moreover, GIP stimulation also induced an increase in 17-hydroxyprogesterone and testosterone levels of 127.0 and 86.0% respectively.

**mRNA receptor expression** RT-PCR analysis for GIP-R mRNA expression showed a band of 320 bp in the normal adult pancreas, and in the adrenal macronodules and adjacent adrenal cortex in this patient, but not in the adrenal cortex of a normal subject or in the macronodular adrenal hyperplasia of two patients with non-GIP-dependent CS (Fig. 4B).

In our patient, mRNA expression of the LH/hCG-R gene, evaluated by real-time PCR, was about 94 times higher (∆Ct = 8.44) in tumoral tissue and 26 times higher (∆Ct = 10.54) in peritumoral tissue (Table 1, GIP +) than in control tissues of normal adrenal cortex (∆Ct = 15.00). The same mRNA analysis for LH/hCG-R was performed in two other patients with macronodular adrenal hyperplasia but non-GIP-dependent CS (Table 1, GIP−). Patient 2 had no LH/hCG-R mRNA expression in either tumoral or peritumoral tissue, whereas patient 3 showed a mild increase only in tumoral tissue (∆Ct = 12.57). In vivo evaluation of these two patients demonstrated a negative cortisol response to the Gn-RH test.

**Immunohistochemistry** Immunohistochemical data for LH/hCG-R performed in the tissue sample of our patient supported the real-time data. LH/hCG-R showed staining in placenta used as positive control and a moderate staining was observed in cells throughout the tumor sample (Fig. 5A and B).

**Postoperative follow-up**

After surgery, the patient began replacement therapy with acetate cortisone at 25 mg/day because of low cortisol levels (3.1 μg/dl) and she was then maintained with half this dose. Androgen levels returned to normal after surgery (testosterone: 11 ng/ml and DHEA-S: 0.5 μg/ml). Acetate cortisone therapy was tapered off after 7 months of follow-up. Clinical signs and symptoms of CS disappeared completely, the patient’s menstrual cycle normalized, her weight dropped to 56.0 kg, and her blood pressure levels were normal in the absence of antihypertensive therapy. After 20 months of follow-up, she had normal UFC (51.0 μg/24 h) and plasma cortisol levels (9.7 μg/dl) and regular cortisol suppression after 1 mg dexamethasone overnight (0.6 μg/dl). ACTH levels were 33 pg/ml. Neither cortisol (baseline: 9.7 mmol/l, 30 min: 8.4 mmol/l, 60 min: 8 mmol/l, 90 min: 7 mmol/l, 120 min: 6.5 mmol/l) nor testosterone responses were observed after repeating the OGTT, we

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<th>GIP-R+</th>
<th>GIP-R−</th>
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<tr>
<td>Adrenal macronodules</td>
<td>94.34</td>
<td>6.88</td>
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<td>Adjacent adrenal cortex</td>
<td>26.13</td>
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ND, not done.
In our case, GIP-dependent CS was suggested by the in vivo cortisol response to food intake and the oral glucose challenge and was confirmed by in vitro studies. The GIP receptor had previously been demonstrated to be an ectopic or illicit receptor because no in vitro cortisol response to GIP was found in normal adult or fetal adrenal cells (6). It is not clear why the GIP receptor is expressed in these cases, considering that no mutations of either the full-length GIP-R or the promoter region were found in the affected adenomas or macronodular adrenal hyperplasias studied (9, 31).

Evaluating aberrant membrane receptor expression in adrenal tumor tissues has been proposed as an alternative to determining the physiopathological mechanisms involved in these rare forms of CS, but also as an opportunity to identify new therapeutic options. In previous reports, chronic s.c. octreotide administration thrice daily resulted in a transient decrease in UFC levels in patients with food-dependent CS due to the well-known inhibitory effects of somatostatin analogs on GIP levels (7, 8). In our patient, treatment with a long-acting somatostatin analog reduced UFC levels and inhibited cortisol response to OGTT, but UFC levels remained slightly above normal range and this could be explained by a different stimulation possibly due to the expression of other aberrant receptors. A long-term follow-up would be necessary to ascertain the real efficacy of this therapy over time.

Our patient also had an increase in androgen levels that make the case particularly interesting. Cortisol and androgen secretion by the adrenal glands is usually seen in patients with CS due to pituitary adenoma, while patients with adrenal adenomas may present a dissociation in cortisol and androgen secretion because of ACTH suppression due to high levels of cortisol being secreted irrespective of the pituitary stimulus. However, benign adrenal adenomas can secrete both cortisol and androgens (33), suggesting that stimuli other than ACTH can also regulate adrenal androgen synthesis (15).

In our case, we demonstrated in vitro the concomitant release of adrenal androgens and cortisol from adrenal tissue perfused with GIP. This situation has been previously described in a patient with an adrenocortical adenoma leading to hirsutism and subclinical CS (12). However, Bertherat et al. (14) identified two patients with CS due to adrenal hyperplasia that responded to both gonadotropin and GIP stimulation, demonstrating that ACTH-independent adrenocortical tissues may simultaneously express multiple illegitimate membrane receptors.

Early studies suggested that gonadal tissue in the adrenal glands might be implicated in androgen secretion in adrenal tumors responding to LH or hCG stimulation with an increase in androgen levels (34, 35). In situ hybridization studies have demonstrated LH/hCG-receptor mRNA transcripts in human
clearly indicative of macronodular adrenal hyperplasia, was discharged because histological findings were adenoma with a contralateral adrenal incidentaloma remission after surgery. The likelihood of adrenal scintiscan sufficed in our patient to achieve long-term of the larger gland with the prevalent uptake at ommended in selected cases(26, 27). Adrenalectomy sia, but unilateral adrenalectomy has been rec-

choice in patients with macronodular adrenal hyperpla-

adrenal tissue is open to debate.

could have influenced the onset of hyperplastic/tumoral castrated transgenic mice (39). Whether the patient's high levels of circulating hCG during her pregnancy could have influenced the onset of hyperplastic/tumoral adrenal tissue is open to debate.

Bilateral adrenalectomy is considered the treatment of choice in patients with macronodular adrenal hyperplasia, but unilateral adrenalectomy has been rec-

recommended in selected cases (26, 27). Adrenalectomy of the larger gland with the prevalent uptake at scintiscan sufficed in our patient to achieve long-term remission after surgery. The likelihood of adrenal adenoma with a contralateral adrenal incidentaloma was discharged because histological findings were clearly indicative of macronodular adrenal hyperplasia, adrenal scintigraphy with $^{131}$I-norcholestero showed a bilateral uptake, and LH/hCG and GIP receptors were also expressed in the cortical tissue surrounding the macronodule, suggesting the probability of bilateral lesions. The patient needed therapy with acetate cortisone for several months at a low dosage, probably because the remaining adrenal did actually secrete some, but not enough, cortisol, which would be in agreement with the hypothesis that these GIP-dependent hyperplastic adrenal tissues have a low secretion rate. These data confirm that unilateral adrenalectomy can be a safe alternative in some selective patients with adrenal hyperplasia, avoiding the need for lifelong glucocorticoid and mineralocorticoid replacement therapy. A long-term follow-up is indicated, however, due to the possibility of an asynchronous progression of nodule formation (27).

In some patients, the presence of aberrant hormone receptors enables a specific pharmacological treatment, but long-term studies are warranted to evaluate the real efficacy of medical treatment in such cases.

References


