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CLINICAL CASE SEMINAR

Cyclical Cushing Syndrome Presenting in Infancy: An Early Form of Primary Pigmented Nodular Adrenocortical Disease, or a New Entity?

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Cushing syndrome is uncommon in childhood and rare in infancy. We report the case of a 3-yr-old child who presented with symptoms of Cushing syndrome beginning shortly after birth. Her hypercortisolemia was cyclical, causing relapsing and remitting symptoms, which eventually led to suspicions of possible Munchausen syndrome by proxy. Investigation at the National Institutes of Health excluded exogenous administration of glucocorticoids and indicated ACTH-independent Cushing syndrome. Paradoxical response to dexamethasone stimulation (Liddle's test) suggested a diagnosis of primary pigmented nodular adrenocortical disease (PPNAD).

After bilateral adrenalectomy, both glands showed micronodular adrenocortical hyperplasia, but histology was not consistent with typical PPNAD. DNA analysis of the coding sequences of the *PRKAR1A* gene (associated with PPNAD and Carney complex) and the *GNAS* gene (associated with McCune-Albright syndrome) showed no mutations.

We conclude that hypercortisolemia in infancy may be caused by micronodular adrenocortical hyperplasia, which can be cyclical and confused with exogenous Cushing syndrome. A paradoxical rise of glucocorticoid excretion during Liddle's test may delineate these patients. Infantile micronodular disease has some features of PPNAD and may represent its early form; however, at least in the case of the patient reported here, micronodular hyperplasia was not caused by coding mutations of the *PRKAR1A* or *GNAS* genes or associated with typical histology or any other features of Carney complex or McCune-Albright syndrome and may represent a distinct entity. (*J Clin Endocrinol Metab* 89: 3173–3182, 2004)

CUSHING SYNDROME IN childhood is most often iatrogenic caused by excessive glucocorticoid hormone administration (1–3). Endogenous Cushing syndrome in children is rare (4); in infancy, less than 100 cases have been described worldwide. Most of these patients had Cushing syndrome due to an ACTH-secreting tumor (5–11) or ACTH-independent bilateral adrenocortical hyperplasia (12–14). Occasionally an ACTH-secreting neuroblastoma, paraganglioma, or other neuroendocrine tumor has been found to be causative (15). With the exception of a handful of cases of adrenocortical cancer or unilateral adenomatosis (16), almost all the reported cases of ACTH-independent infantile Cushing syndrome were due to bilateral macronodular adrenocortical disease and represented early presentation of McCune-Albright syndrome (12–14, 17, 18).

A handful of cases of ACTH-independent Cushing syndrome in infancy are due to micronodular adrenal disease (19–27). The youngest patients with a micronodular form of bilateral adrenocortical hyperplasia and Cushing syndrome were two siblings that presented shortly after birth (22) and a 6-month-old infant reported in 1982 (21). An infant reported by Sobel and Taft in 1959 (28) may also have had Cushing syndrome since early infancy (21, 28).

Micronodular adrenocortical hyperplasia and its better-known pigmented variant, primary pigmented nodular adrenocortical disease (PPNAD), are invariably bilateral (24). Familial and sporadic cases of PPNAD have been reported to be associated with germline inactivating mutations of the *PRKAR1A* gene (25–27). Most patients with PPNAD also have Carney complex, an autosomal dominant multiple neoplasia syndrome, which consists of skin lentigines, myxomas, and other nonendocrine and endocrine tumors, and is also caused by *PRKAR1A* mutations (25, 26).

Patients with PPNAD may present with atypical forms of Cushing syndrome such as cyclical or episodic Cushing syndrome (29–32). These unusual patients can have remitting

Abbreviations: CT, Computed tomography; oCRH, ovine CRH; 17OHCS, 17-hydroxycorticosteroid; PPNAD, primary pigmented nodular adrenocortical disease; UFC, urine free cortisol.

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and relapsing symptoms on a cycle ranging from days to years, a phenomenon that remains largely unexplained (33). Although cyclical Cushing syndrome has been reported before in a number of pediatric patients with (34, 35) or without PPNAD (4), it has not been documented in the neonatal period in a patient with micronodular disease.

We present the case of a 3-yr-old child, who manifested Cushing syndrome in her first several days of life. Her cyclic symptoms and hypercortisolemia led some clinicians to suspect the parents of Munchausen syndrome by proxy. The patient was eventually diagnosed with ACTH-independent Cushing syndrome, underwent bilateral adrenalectomy, and was found to have micronodular adrenocortical hyperplasia. However, the clinical presentation of the patient, and her tissue and genetic analyses, differentiates this case from classic PPNAD, Carney complex, or McCune-Albright syndrome.

Case report

A female infant was born after a 35-wk gestation. The mother's pregnancy had been complicated by maternal hypertension. Birth weight was 5 lb, 11 oz; birth length 18 in. The placenta was grossly normal but the umbilical cord was small. The patient had apneic episodes and hypothermia during her first day and was transferred to the intensive care nursery. On the third day of life, her blood pressure was as high as 140 mm Hg (systolic) and 90 mm Hg (diastolic) (normal range 60–100 mm Hg and <55 mm Hg, respectively). She had a plethoric face and was edematous (Fig. 1A). A serum cortisol was 54 μg/dl (1490 nmol/liter) (normal range 6–30 μg/dl) with a concurrent ACTH level of less than 5 pg/ml (1.1 pmol/liter) (normal range 9–52 pg/ml). Dehydroepiandrosterone sulfate was also elevated at 794 ng/dl (21.4 μmol/liter) (normal range 5–55 ng/dl). Serum and 24-h urine levels of vanilylmandelic acid, homovanilic acid, and catecholamines were normal; a series of imaging studies, including sonographic examination of the adrenal glands, were also normal. The hypertension was treated with diuretics and β-blockers, and the patient was discharged from the hospital on the 18th d of life. Over the next several months, blood pressure normalized and plethora resolved completely, and all medications were discontinued.

At 25 months of age, the patient began experiencing symptoms of polyuria, plethora, decreased energy, night sweats, leg and back pain, and irritability. She developed a ferocious appetite and experienced rapid weight gain (Fig. 1B). Generalized body hair appeared, although no pubic hair or any other signs of puberty were present. Medical evaluation was delayed until 4 wk after the onset of symptoms, at a time when it was the parents' impression that manifestations were already waning. On examination, systolic blood pressure was 120 mm Hg and diastolic 61 mm Hg. A morning cortisol level was normal at 6 μg/dl (166 nmol/liter), with an ACTH of 11 pg/ml (2.4 pmol/liter). A 24-h urine collection was not obtained. The patient's symptoms continued to resolve and there was rapid weight loss. The patient remained asymptomatic for another 9 months.

At 35 months of age, the patient presented once more with similar symptoms and signs. Evaluation was undertaken within a week after the onset of symptoms. Plethora and obesity were noted on physical examination (Fig. 1C). The growth velocity over the last 10 months had been normal. Systolic blood pressure was 110–120 mm Hg and diastolic pressure measured 60–80 mm Hg. Laboratory evaluation was significant for a cortisol level drawn at 1600 h of 35 μg/dl (966 nmol/liter) (normal range 2.0–11.5 μg/dl); the ACTH level at the same time was 9 pg/ml (2.0 pmol/liter). A 24-h urine free cortisol (UFC) was not obtained. Her symptoms again resolved and body habitus returned to normal over the next 4–6 wk. The parents sought consultation at another institution at which no diagnosis was made. It was during these repeated investigations at different medical facilities that the suspicion of Munchausen syndrome by proxy was raised.

At 42 months of age, rapid weight gain (4 kg over 10 d) and the other symptoms and signs occurred once again. Review of prior growth data revealed normal growth along the 50th percentile since at least 2 yr of age. Bone age was consistent with a skeletal age of 50 months. Physical examination revealed a mildly obese patient with a Cushinoid habitus (Fig. 2A). There were a few scattered comedones on the forehead but no pubic hair and no striae. The 24-h UFC was 2980.7 μg/24 h (normal < 18). Serial serum cortisol levels drawn every 4 h over a 24-h period, during supervised hospitalization, ranged from 32.3 to 44.5 μg/dl (889 to 1228 nmol/liter) with concurrent ACTH levels of 3–5 pg/ml (0.7–1.1 pmol/liter), suggesting ACTH-independent Cushing syndrome. The patient was referred to the NIH, at which she was evaluated during both active and inactive phases of her disease (Fig. 2, B and C).

Clinical Tests

The patient was studied at the NIH Warren Magnuson Clinical Center under protocol 95-CH-0059 after obtaining parental consent. The following studies were obtained for the documentation and etiologic investigation of hypercortisolism: 1) an 0800 h plasma ACTH levels followed by ovine CRH (oCRH) stimulation; 2) diurnal plasma cortisol variation, as previously described (36); 3) magnetic resonance imaging of the pituitary gland and computed tomography (CT) scan of the adrenal glands, as previously described (37, 38); 4) a 6-d Liddle's test, as previously described (37): after 3 d of baseline urinary steroid excretion measurement, low-dose dexamethasone (7.5 μg/kg·dose by mouth every 6 h) was given for 2 d, followed by high-dose dexamethasone (30 μg/kg·dose every 6 h) for the last 2 d of the test. Twenty-four-hour urine steroid excretion was measured daily. UFC was expressed per square meter of body surface area (μg/m^2·24 h) and 17-hydroxycorticosteroid (17OHCS) excretion was expressed per gram of creatinine excreted in 24 h (milligram per gram creatinine per 24 h).

Hormone assays

Plasma ACTH and cortisol were measured, as previously described (36, 37). UFC excretion was measured by direct RIA (39). The intraassay and interassay coefficients of variation were 5 and 10%, respectively (39, 40). Urinary 17OHS

FIG. 1. Cyclical Cushing syndrome. Rapid changes in body habitus exhibited by our patient during three active cycles of her disease (see case report).

excretion was measured by a modification of the colorimetric method of Porter and Silber (40). The intraassay and interassay coefficients of variation were 6 and 11%, respectively (39, 40). HPLC analysis of the urine for the detection of exogenous steroids was also obtained, as described elsewhere (41).

Tissue analysis

Tissue for genetic analysis was obtained at the time of surgery, frozen at −70 C and stored for later use. For light microscopy and immunocytochemistry, tissue was paraffin embedded; sections were then stained with hematoxylin and

FIG. 2. Three different periods of evaluation separated by 4 months. Initial evaluation during an active phase (A) was consistent with ACTH-independent Cushing syndrome. First NIH evaluation (B) was during a quiescent phase and revealed normal levels of 24-h UFC but lack of diurnal variation of cortisol production and a positive Liddle's test. Shortly after her first NIH evaluation, the patient again entered an active phase (C) and returned to the NIH to undergo bilateral adrenalectomy.

eosin and synaptophysin, as previously described (42). For electron microscopy, tissue was obtained at the time of surgery and processed as previously described (43). Preparations of samples obtained at surgery from both adrenal glands and surrounding normal fibrous and fat tissue were processed for genetic analyses (see below).

DNA analysis

DNA was extracted from peripheral lymphocytes by standard methods (44). Tumor DNA was extracted from frozen tissue in a 0.7-ml solution of 50 mM Tris (pH 8.0), 100 mM EDTA, 100 mM NaCl, 1% sodium dodecyl sulfate, and 0.5 mg/ml proteinase K. Samples were subsequently extracted four times in phenol/chloroform, precipitated with ethanol, and resuspended in 1 × Tris/EDTA buffer [50 mM Tris-HCL, 1 mM EDTA (pH 8.0)]. Sequencing of the coding region of the *PRKAR1A* gene was obtained after a protocol that we have described elsewhere (GeneDx, Rockville, MD) (45, 46). Sequencing of the coding sequence of the *GNAS1* gene was also obtained, as we have described elsewhere (47). Sequencing analysis of adrenal tissue-derived DNA was obtained as described elsewhere (48).

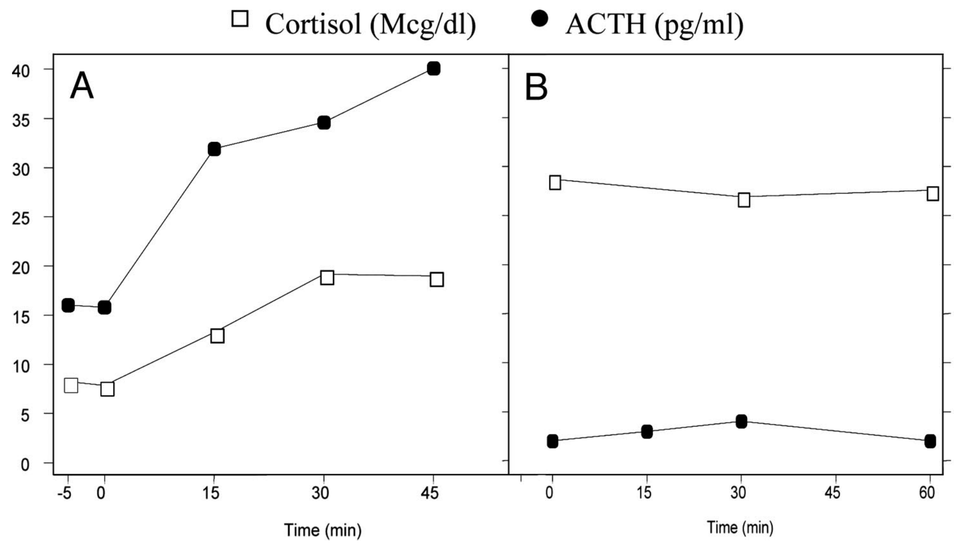

FIG. 3. An oCRH stimulation test. Baseline ACTH and cortisol levels were obtained (−5 and 0 min) followed by 1 μg/kg oCRH iv administration. Both ACTH and cortisol show the expected rise during inactive, normocortisolemic phase (A). However, during the active, hypercortisolemic phase (B), ACTH stays suppressed and cortisol remains high during stimulation, consistent with ACTH-independent Cushing syndrome. (Unit conversion: Cortisol: μg/dl × 27.6 = nmol/liter; ACTH: pg/ml × 0.22 = pmol/liter).

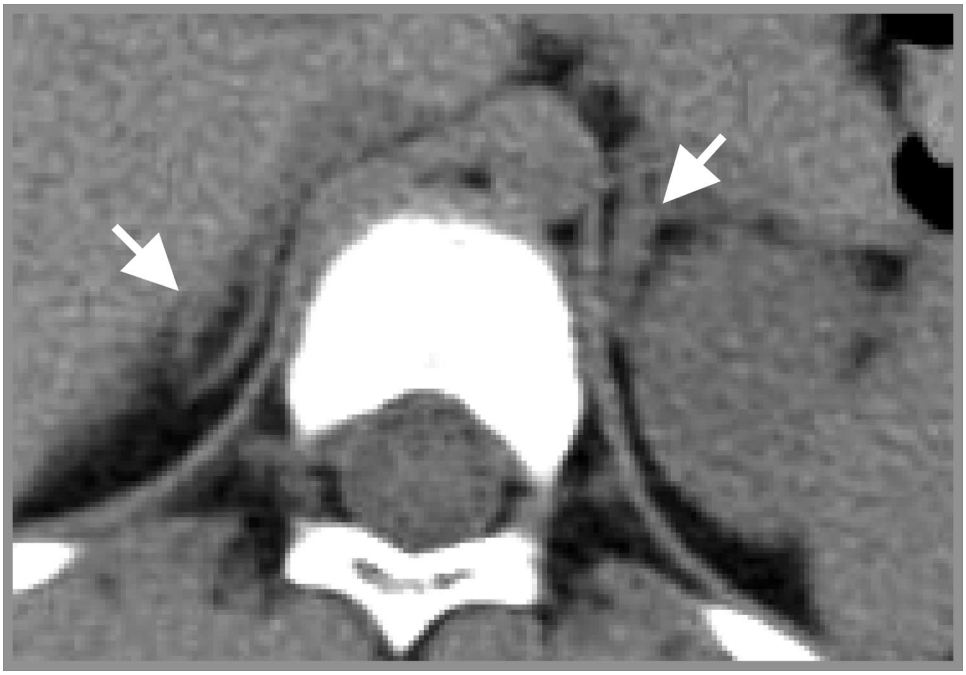

FIG. 4. Normally shaped (but hyperplastic for age, especially *left*) adrenal glands of our patient on CT (*arrows*).

Results

Clinical diagnosis and treatment

The patient was evaluated over a 4-month period during periods of both high and low cortisol excretion. Determination of steroid excretion by HPLC at several occasions during this observation period failed to show any exogenous steroids (data not shown). Despite total normal UFC and 17OHCS excretion, the patient had no diurnal serum cortisol variation, an abnormality that was also present when she was evaluated during hypercortisolemia. ACTH and cortisol responses to oCRH were appropriate during normocortisolemia (Fig. 3A) and absent during hypercortisolemia (Fig. 3B). These tests suggested cyclical endogenous cortisol excess but did not indicate the source. Imaging studies were not diagnostic, although they did exclude a large pituitary mass (data not shown) and adrenocortical tumors; CT did show moderate thickness of the adrenal contour bilaterally (Fig. 4), which was supportive of an endogenous cause for Cushing syndrome in this patient. Liddle's test showed a greater than 50% increase in both UFC and 17OHCS excretion during the last day of urine collection (Fig. 5); this response was considered diagnostic for PPNAD (40), and the patient underwent bilateral adrenalectomy. An iodocholesterol scan was not performed because it was felt that enough information was available for an ACTH-independent bilateral adrenocortical process as the cause of Cushing syndrome in this patient.

Histopathology, electron microscopy, and DNA studies

The right adrenal gland measured 3.4 × 2 × 0.3 cm and weighed approximately 5 g. The cut surface had a golden color with focal punctate dark brown areas. The left adrenal

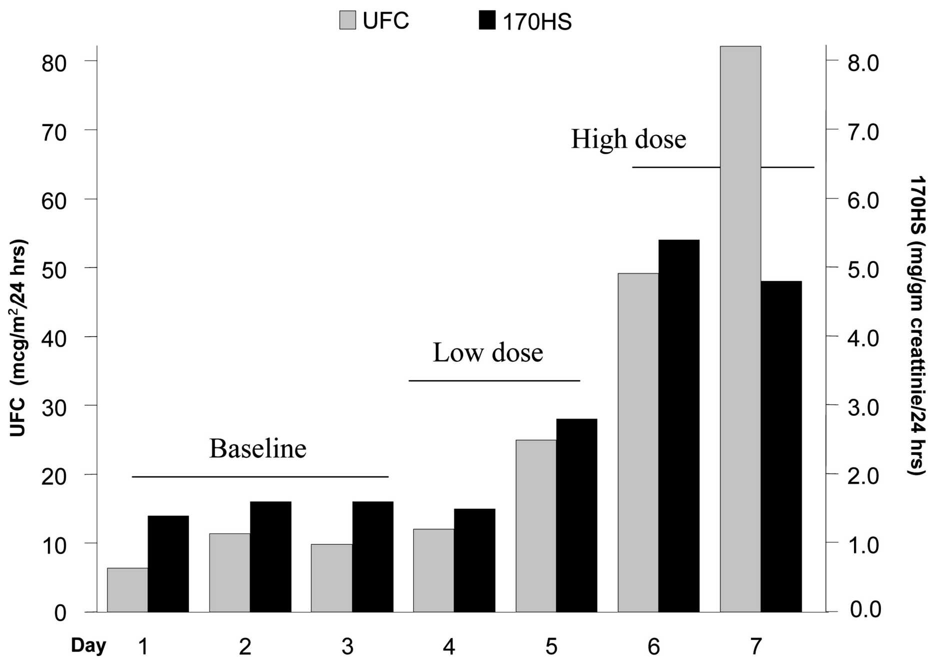

FIG. 5. Liddle's test. After several days of baseline UFC and 17OHS measurement, low-dose dexamethasone (7.5 μg/kg per dose every 6 h) is given for 2 d, followed by high-dose dexamethasone (30 μg/kg per dose every 6 h) for 2 d. The patient shows the paradoxical increase in cortisol excretion in response to dexamethasone, a characteristic of PPNAD (see also Ref. 40).

gland measured 3.5 × 2.5 × 0.3 cm and weighed 4 g. The cut surface had a uniform yellow-brown appearance without nodules. Microscopically, the glands were similar histologically. The cortex was 1 mm or slightly more in thickness. The zonation pattern normally seen was not as distinct as usual. Intracapsular aggregates of cells and cortical excrescences in the periadrenal fat were prominent. The cortical cells seemed smaller than normal. There were occasional variably shaped cell aggregates, round, irregular, or linear, in which the cells were larger than the remainder of the cortex. Only one nodule had deeply pigmented cytoplasm. Nuclei were generally normal sized, but a few were larger than normal. These features were consistent with micronodular adrenal hyperplasia (Fig. 6, A and B), but the absence of pigmentation made the diagnosis of PPNAD uncertain. Synaptophysin stained the nodules (Fig. 6C). Electron microscopy, on the other hand, showed pigment granules consistent with lipofuscin accumulation, giant and round mitochondria, dilated smooth endoplasmic reticulum, lipid accumulation, and other features that have previously been seen in PPNAD (43) (Fig. 6D).

Sequencing analysis of the coding regions of the *PRKAR1A* and *GNAS* genes from peripheral blood and tumor DNA, respectively, failed to show any mutations (data not shown).

Clinical follow-up

A year after the diagnosis of Cushing syndrome was originally made, and almost a year after adrenalectomy, the patient is doing well on hydrocortisone and fludrocortisone replacement (10 mg/m^2·d and 100 μg/d, respectively). Signs of Cushing syndrome have completely disappeared, hypercortisolemia has resolved, and there has not been development of signs of Carney complex or McCune-Albright syndrome; extensive imaging studies for the exclusion of these conditions have been negative.

Discussion

Cushing syndrome in infancy is extremely rare. In the most recent comprehensive epidemiologic study, the incidence of Cushing syndrome due to adrenocortical causes over an 11-yr follow-up of the entire population of Denmark was 0.8/million·yr, which yielded a total of only 48 patients (49). There were no infants in these series, the youngest patients being two 3-yr-olds who had an adrenocortical carcinoma and an adenoma, respectively (49).

Infantile Cushing syndrome may be rare, but it is usually not difficult to recognize. Several factors contributed to the delay in diagnosis in the case presented in this report, the most striking being the erratic pattern of clinical symptoms and hypercortisolemia. Cyclical hypercortisolemia is one of several atypical presentations of Cushing syndrome (4, 34, 39). Although uncommon, cyclical Cushing syndrome is actually seen more commonly in children than adults (34), and in the rare cases of adrenocortical hyperplasia, it is almost the norm (50–52). In our experience, it is even not uncommon for such patients to go through phases of relative adrenocortical insufficiency. The latter may last for as long as it takes for endogenous ACTH secretion to recover from the suppression caused by the preceding high glucocorticoid secretion phase (our unpublished observation). Our patient represents an extreme example of this phenomenon, for which there is no apparent or obvious pathophysiologic or molecular explanation.

In this case, when Cushing syndrome was suspected, the etiology was difficult to identify. oCRH testing showed inconsistent results reflecting the incomplete suppression of the hypothalamic-pituitary-adrenal axis during short periods of hypercortisolemia. Imaging studies were also not very helpful, other than for the exclusion of large lesions in the pituitary and adrenal glands. The lack of adrenocortical atrophy supported endogenous Cushing syndrome (41, 53),

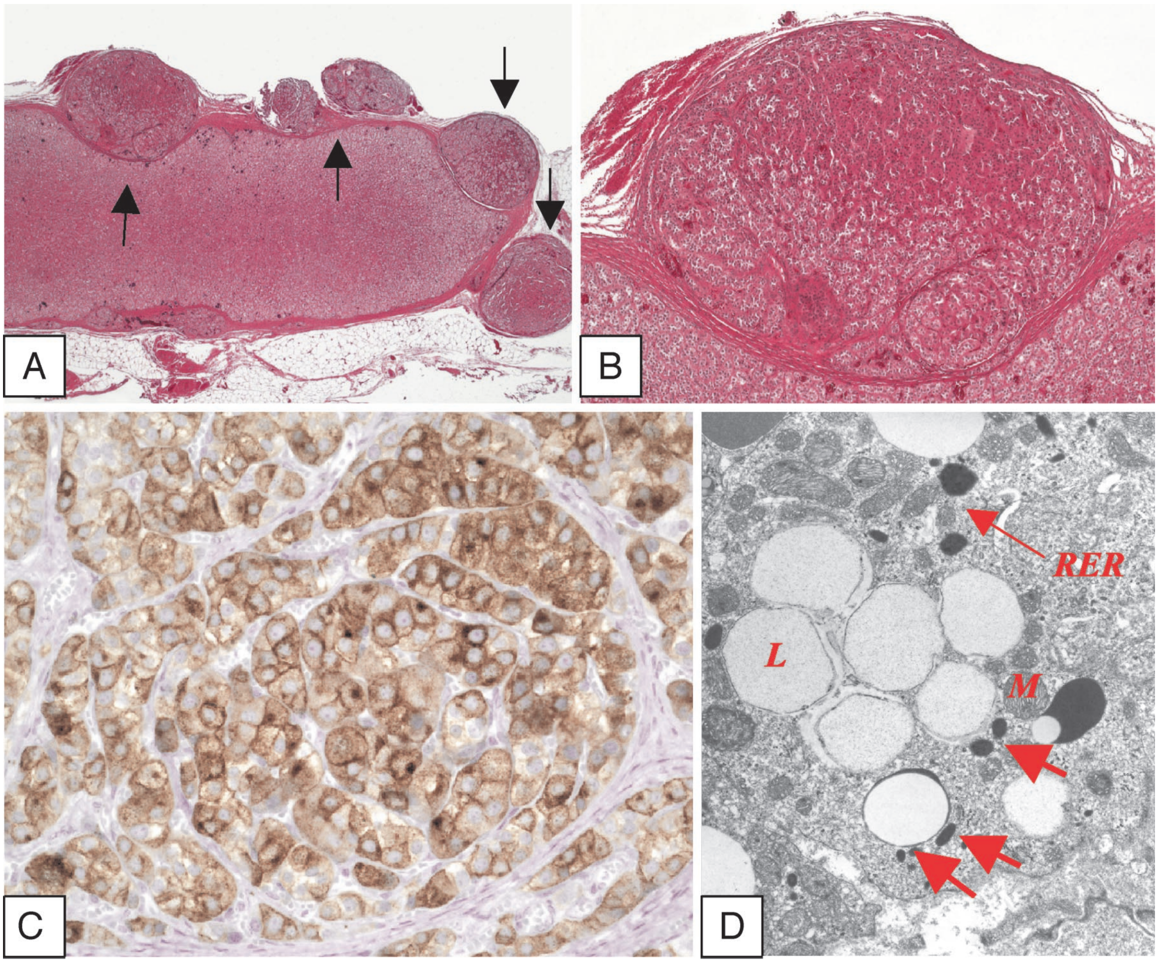

FIG. 6. Patient's adrenals, showing adrenocortical hyperplasia with several nodules pointed by the *arrows* (A) (magnification, ×10); one of these nodules is shown (B) (magnification, ×20). Staining with synaptophysin was positive (C), and electron microscopy showed some characteristics of PPNAD including accumulation of lipid (L) and pigmented granules (*large arrows*), rough endoplasmic reticulum (RER), and several round mitochondria (M) with features of increased steroidogenic activity (D).

although the source was uncertain due to measurable ACTH levels.

Because of the atypical presentation in this case, the suspicion of exogenous administration of cortisol was raised. There are several clinical presentations of Munchausen syndrome by proxy in infancy, but none includes Cushing syndrome according to our most recent survey of the literature and recently published experience (54–56). On the other hand, there are several reported cases of factitious Cushing syndrome in young and older adults (41, 57–60). It is well known that atypical, periodic, or mild cases of Cushing syndrome are often difficult to diagnose, and factitious and pseudo-Cushing syndrome states should always be included in the differential diagnosis (41). In our case, the elevation of dehydroepiandrosterone and androstenedione concurrent with elevated cortisol on different occasions and the determination of steroid excretion by HPLC were not consistent with exogenous steroid administration. Subsequent adrenal gland pathology conclusively ruled out Munchausen syndrome by proxy.

Most infantile cases of Cushing syndrome reported to date are due to ACTH-secreting tumors (5–11) or bilateral macronodular adrenocortical hyperplasia associated with McCune-Albright syndrome (12–18). Several children with micronodular hyperplasia or PPNAD have been reported but none as early as at birth (19–28); a 6-month-old with a micronodular form of bilateral adrenocortical disease and Cushing syndrome was reported in 1982 (21). There have been no other infants since, and we certainly did not encounter any such cases in our most recent retrospective analysis of 88 PPNAD cases among 338 patients with Carney complex (26). In these series, patients with PPNAD presented mostly late in childhood or in young adulthood (26). Only occasionally PPNAD manifested with sudden onset of hypercortisolemia and Cushing syndrome in the older patient; in these cases, their late diagnosis reflected the difficulty with which a chronic, congenital disorder with a mild phenotype can be suspected (50, 51, 61–64).

Establishing the diagnosis of PPNAD can indeed be a difficult task. The associated hypercortisolism usually develops slowly over several years, and the clinical manifestations may be subtle (50, 51, 65, 66). Radiologic imaging can be either normal or indistinguishable from the subtle nodularity that is often present in normal controls (especially in older age) (24, 40, 52). In addition, plasma ACTH levels may not be suppressed, especially in the cases of mild or periodic Cushing syndrome (40, 50, 51). Earlier reports had mentioned a paradoxical increase of glucocorticoids in response to various doses of dexamethasone in patients with micronodular forms of adrenocortical hyperplasia (40, 50, 51, 63). This phenomenon is reproducible *in vitro* and is associated with an increased expression of the glucocorticoid receptor in PPNAD tissue (67). Recently diagnostic criteria using the administration of low- and high-dose dexamethasone as first suggested by Liddle (68) were established for the differentiation of PPNAD patients from other forms of adrenal causes of Cushing syndrome (40). Our patient had a positive Liddle's test, meeting the published criteria for the diagnosis of PPNAD.

Histologically, however, the observations were not diagnostic of PPNAD (65, 66). The main findings were a cortex of approximately normal thickness with indistinct zonation, multiple intracapsular cell aggregates, and cortical excrescences in the periadrenal fat, generally small cells with occasional foci of larger cells and a single pigmented nodule. The capsular aggregates and the cortical excrescences, which have been seen before in other cases of pediatric micronodular adrenocortical hyperplasia (69, 70), suggested some proliferative activity in the peripheral zona fasciculata, but the cells involved did not look active: they were not large and they did not have eosinophilic cytoplasm. Immunohistochemistry showed intense staining of the nodules with an antibody to synaptophysin, a feature of PPNAD (42). Electron microscopy also showed some features of PPNAD, such as abundant mitochondria with giant forms, dilated smooth endoplasmic reticulum, and lipofuscin pigment granules (43, 68–71).

Molecular analysis did not support a diagnosis of PPNAD but did not conclusively rule it out. In most cases, PPNAD in its sporadic or isolated forms as well as when it is associated with Carney complex, is caused by inactivating mutations of the *PRKAR1A* gene, encoding the regulatory subunit type-Iα of the cAMP-dependent protein kinase A (26, 27). In our patient, the coding sequence of the *PRKAR1A* gene was normal. The other form of neonatal Cushing syndrome was also excluded: both germline and tumor DNA from the patient's blood and adrenal glands, respectively, showed no coding mutations of the *GNAS* gene that would be suggestive of McCune-Albright syndrome.

Activating adrenal autoantibodies have also been proposed as the explanation for PPNAD (72–74). However, several PPNAD patients with antibodies (72) have subsequently been found to have germline mutations of the *PRKAR1A* gene. There is no known role of this gene in the regulation of immunity; on the other hand, the possibility of *PRKAR1A* autoantibodies in these patients has not been adequately investigated.

Reviewing the histopathologic features of pediatric patients with PPNAD (19–28, 43), we encountered a statement that may offer a reasonable hypothesis for the uncertain nature of the adrenocortical findings of our case: Travis *et al.* wrote that "the most subtle pathological manifestations were seen in one of the youngest patients, whereas the most dramatic and florid involvement was seen in the oldest patient" (43). The authors suggested that the "spectrum of pathological changes may vary with the age of the patient and the duration of disease." However, the same investigators made another observation that is suggestive of an alternative hypothesis: they saw the most unusual morphologic features of the adrenal cortex, the ones consistent with classic PPNAD, in the single patient with familial disease (43). This patient was later investigated by our group and was found to have a germline *PRKAR1A*-inactivating mutation (del c.578TG) (45, 46).

Thus, the lack of characteristic PPNAD findings in our patient could be due to either her young age or the fact that she did not have germline or tumor *PRKAR1A* mutations; she does not, in other words, belong to the majority of PPNAD cases reported to date that are familial or have Carney complex (26, 27, 45, 46). Aiba *et al.* (70) suggested that infantile or very early pediatric cases of primary adrenocortical micronodular dysplasia may be a different disorder and should be differentiated from PPNAD. Consistent with this hypothesis is the recent report by Barat *et al.* (75), who reported a child with congenital Cushing syndrome, no mutations of the *GNAS* or *PRKAR1A* genes, and profound neurological delay. A different syndrome may in fact be associated with additional clinical manifestations, such as the ones reported by Barat *et al.* (75), which are unlikely to be caused by Cushing syndrome alone. It is possible that another gene, yet elusive, may underlie the genetics of a distinct group of bilateral micronodular adrenocortical hyperplasias in childhood. It has been suggested that this gene is on chromosome 2 (76), but more extensive genetic heterogeneity would not be a surprise (26, 46).

Acknowledgments

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