

Acanthosis nigricans in association with congenital adrenal hyperplasia: resolution after treatment Case report

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A case is described of a three-day-old female with salt wasting type of 21-hydroxylase deficient congenital adrenal hyperplasia who presented with acanthosis nigricans of both axillae. Following corticosteroid and mineralocorticoid therapy for disease, the acanthosis nigricans resolved. It is believed that this is the first reported case of acanthosis nigricans occurring in association with congenital adrenal hyperplasia, a phenomenon that resolved after treatment. We speculate that the acanthosis nigricans resulted from hyperandrogenemia or other unknown factors in our patient.

Key words: acanthosis nigricans, congenital adrenal hyperplasia, newborn.

Acanthosis nigricans (AN) is characterized by hyperpigmented, velvety, hyperkeratotic plaques that are most often localized to the neck, axillae, inframmary areas, groin, inner thighs, and anogenital region. The histologic changes are those of papillomatosis and hyperkeratosis rather than acanthosis or excessive pigment formation. AN has classically been associated with obesity; drugs such as nicotinic acid; endocrinopathies, including diabetes mellitus, Addison disease, Cushing's syndrome, acromegaly, hypo- and hyperthyroidism, Stein-Leventhal syndrome, and hyperandrogenic or hypogonadal syndromes; and many other genetic syndromes such as Bloom's Crouzon's or Rud's syndromes. Occasionally, it may be familial with autosomal dominant inheritance. AN was present in 71% of the 1,412 children in an unselected population. It is rarely found in the neonatal period, but has been reported in this period in association with some syndromes such as Beare-Stevenson syndrome, congenital lipodystrophies, bone dysplasia and Leprechaunism¹⁻⁴. However, AN has not been reported in patients with congenital adrenal hyperplasia (CAH).

A case of AN associated with salt wasting type of 21-hydroxylase (21-OH) deficient CAH is presented. To our knowledge this is the first such association reported in the literature.

Case Report

This case was referred to the Endocrinology Service at three days of age because of ambiguous genitalia. The child's weight at birth was 3300 g and length was 51 cm after an uneventful pregnancy followed by a spontaneous vaginal delivery at term. It was the sixth pregnancy of a 24-year-old healthy mother. There was first-degree consanguinity between mother and father. There was no history of disease and no use of drugs before or during pregnancy. The fifth child is a healthy three-year-old boy. However, the first four boy infants died at birth, two months of age, four months of age and one month of age, respectively; no diagnosis had been made in any of the cases. In our patient, physical examination showed ambiguous genitalia. The genital tubercle measured 2x1 cm, the urethral opening was at the perineum, and two gonads were not palpable within a bifid scrotal structure (Fig. 1). The genitalia, areola and axilla were markedly hyperpigmented, and there were hyperkeratotic plaques. In particular, the axillary skin had a velvet texture and a grayish-brown pigmentation with marked grayish-red papillomatous vegetations (Fig. 2a). Bone age was 38 weeks by knee X-ray. The infant's blood pressure was 60/45 mmHg. Blood was drawn for electrolytes, androgen levels, and karyotype. Serum sodium concentration was decreased

(109 mEq/L) and serum potassium concentration was elevated at 8.7 mEq/L. Metabolic acidosis (serum bicarbonate concentration was 8.5 mmol/L) was also present. The therapy for salt wasting was started. Serum concentrations of adrenal steroids and their precursors before the first dose of hydrocortisone were abnormal. 17-hydroxyprogesterone (17 OHP) was 150 ng/ml (normal: 0.4-2 ng/ml), 11-deoxycortisol was 11.56 ng/ml (normal: 0.1-1.5 ng/ml), dehydroepiandrosterone sulfate (DHEA-S) was 2938 ng/ml (normal: 50-110 ng/ml), androstenedione was 34.76 ng/ml (normal: 0.06-0.68 ng/ml), total testosterone was 1859 ng/dl (normal: 75-400 ng/dl), free testosterone was 74.68 pg/ml (normal: 1.5-31 pg/ml), adrenocorticotropic hormone (ACTH) was 114 pg/ml (normal: 0-60 pg/ml), and cortisol was 6.52 µg/dl (normal: 2.8-23 µg/dl). Ureterogram showed a normal uterus. Echocardiographic study showed patent foramen ovale with a diameter of 3 mm. Ultrasonography revealed bilateral adrenal hyperplasia. The karyotype was 46,XX. The

patient had presented with a combination of aldosterone and cortisol deficiency and androgen excess. Thus, she was diagnosed as salt wasting type of 21-OH-deficient CAH. CAH due to 21-OH deficiency was diagnosed according to published criteria⁵. Diagnosis was based on elevation of 17-OHP, supported by clinical presentation and serum electrolyte abnormalities, and by genital ambiguity. After the acute manifestations were under control, the patient required chronic replacement therapy for her aldosterone and cortisol deficiencies. Glucocorticoid (hydrocortisone: 20 mg/m²) and mineralocorticoid (Florinef 0.1 mg daily) were given perorally. The androgens and 17-OHP were suppressed after one-month of treatment. Because the skin changes were unusual, AN was suspected. A diagnosis of AN was made after skin biopsy (Fig. 3). Fasting insulin, leptin, and glucose were measured. The glucose/insulin ratio calculated as a measure of insulin resistance was 6.2 (normal value, ≥ 6) and leptin level was normal. Following treatment for CAH, the skin pigmentation and AN resolved (Fig. 2b).



Fig. 1. Patient showing ambiguous genitalia.



(a)



(b)

Fig. 2. a) Acanthosis nigricans involving the axilla region prior to treatment.
b) Six months after treatment, the acanthosis nigricans is markedly diminished.



Fig. 3. Histopathologic changes consistent with acanthosis nigricans: the epithelium shows papillomatosis, hyperkeratosis, acanthosis and keratin plaques. There is an orthohyperkeratotic stratum corneum overlying a mammillated hyperplastic epidermis. There is no significant inflammatory infiltrate.

Discussion

Congenital adrenal hyperplasia due to 21-OH deficiency is an autosomal recessive condition in which deletions or mutations of the cytochrome P450 21-hydroxylase gene result in glucocorticoid and/or mineralocorticoid deficiency or excess, respectively. This leads to increased secretion of ACTH, adrenal hyperplasia, and increased production of androgens and steroid precursors before the enzymatic defect. Current treatment is to provide adequate glucocorticoid and, when necessary, mineralocorticoid substitution to prevent adrenal crises and to suppress the abnormal secretion of androgens and steroid precursors from the adrenal cortex⁶⁻⁸. In our patient with ambiguous genitalia, clinical and endocrinologic evaluation at presentation revealed that she had the salt-wasting type of classic 21-OH deficiency. The patient with CAH presented with a darkening of the skin of the axilla and areola and of the oral and genital mucosa. Her axillary skin was especially marked in particular was by a grayish-brown pigmentation. Because it was characterized by the appearance of papillomatosis with hyperpigmented and hyperkeratotic plaques with a velvet texture and a grayish-brown coloration, AN was suspected in the patient with CAH. The underlying usual diseases could not be determined at the initial screening, and diagnosis was confirmed with biopsy. Acanthosis nigricans appears to be a dermatological manifestation of the severe hyperinsulinemia and hyperandrogenism⁹. Although the factors that induce acanthosis nigricans development have not been fully elucidated, insulin, insulin-like growth factor

(IGF)-I, epidermal growth factor, and testosterone have been implicated. Thus, Cruz and Hud¹⁰ recently categorized AN into two types: (1) AN associated with increased insulin binding to IGF receptors, and (2) AN due to other causes. It can be speculated that elevated androgens and/or perhaps their precursors might contribute to the development of AN in the patient.

Increased pigmentation of the skin should always alert the clinician to the possibility of adrenocortical insufficiency. This manifestation occurs in those conditions in which there are a deficiency of cortisol and excessive secretion of corticotropin, as in primary adrenal hypoplasia, familial glucocorticoid deficiency, adrenoleukodystrophy, and Addison disease. When adrenal disease is severe, as in CAH due to cortisol synthetic enzyme defects, adrenal hemorrhage, or congenital absence of the adrenals, disturbances in serum electrolytes with hyponatremia and hyperkalemia or ambiguous genitalia may provide diagnostic clues. Hyperpigmentation may also provide the clue to CAH with increased ACTH levels. Pigmentation may be first apparent on the face and hands and is most intense around the genitalia, umbilicus, axillae, nipples, and joints. Scars and freckles may be especially pigmented^{11,12}. The interesting points of our case were presentation with AN and response to treatment. Significant improvement in skin of the axilla was noted after corticosteroid and mineralocorticoid therapy. This further enforces the correlation between the adrenal hyperplasia process and the skin changes in the patient. This finding is consistent with knowledge in

the literature where skin changes regressed or disappeared following treatment of hyperandrogenemia, as was observed in HAIR-AN syndrome and polycystic ovary syndrome^{13,14}. However, the presence of AN in these conditions is a significant clue that indicated insulin resistance. Therefore, elevated androgen levels may have contributed to the development of acanthosis in our patient. The mechanism of this correlation and indeed the mechanism of CAH-induced AN are not clear. We suggest that AN is probably caused by excess of adrenal androgens that may stimulate keratinocytes and dermal fibroblasts at the cell receptor level.

Previous researchers have reported that hyperandrogenism caused by an inborn error of adrenal steroidogenesis could produce insulin resistance in females with 21-hydroxylase deficiency¹⁵. Furthermore, a recent study report that children with classic CAH have significantly higher serum leptin and insulin concentrations and increased insulin resistance index, compared with their healthy counterparts¹⁶. The skin lesions appear to be a manifestation of insulin resistance. The clinical severity and histopathologic features of AN correlate positively with the degree of hyperinsulinism. It has been hypothesized that insulin resistance, with compensatory hyperinsulinism, leads to insulin binding to and activation of IGF receptors, promoting epidermal growth¹⁷⁻²¹. An association between AN and CAH could be coincidental, although the fact that hyperandrogenism regressed together with AN after the CAH treatment would suggest some relationship between these diseases. After the treatment, endocrinological abnormalities and cutaneous manifestations of AN markedly improved in the patient. Perhaps in the intrauterine period, both elevated leptin and insulin concentrations played a role in the development of AN. We could not document insulin resistance and increased leptin at the time of diagnosis, but in an effort to identify the pathogenetic mechanisms of AN in these patients, insulin resistance might be documented in the prenatal period. In addition, we speculate that small amounts of tissue insulin (despite normoinsulinemia) may transducer proliferative effects in skin cells, leading to AN.

In conclusion, while the underlying pathophysiologic mechanism remains unknown, AN can be associated with CAH as identified in our patient. To our knowledge, there is no report in the literature of AN associated with CAH.

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