Acanthosis nigricans (AN) is a cutaneous marker for many underlying states such as endocrine abnormality, obesity, certain drugs, and malignancy. Generalized AN is a rare condition and is commonly seen in adults with an underlying malignancy. The type B insulin resistance syndrome, a rare autoimmune disorder, is caused by the autoantibodies to the insulin receptor. Patients typically present with hyperglycemia but also may present with hypoglycemia. We report a rare case of a 36-year-old man with generalized AN and type B insulin resistance syndrome with hypoglycemia.

**Case Report**

A 36-year-old man presented with progressive darkening of the skin and coarsening of features over 6 months before he visited a clinic. The patient also reported intermittent sweating, anxiety, and dizziness at dawn. Hyperpigmentation and thickening of the skin on the periocular and perioral areas, trunk, and extremities were observed on physical examination (Figure 1). Thicker, tan, velvety hyperkeratotic plaques were prominent on the neck and axillae (Figure 2) as well as the groin. The mucous membranes, palms, and soles were not affected.

Histopathologic examination showed hyperkeratosis, mild acanthosis, prominent papillomatosis, and slight hyperpigmentation of the basal layer (Figure 3). A slight perivascular infiltrate of mostly lymphocytes was present in the papillary dermis.

Results of laboratory investigations, including complete blood cell counts and urinalysis, were within reference range. Serum chemistry results were normal, except for the blood glucose level, which was 54 mg/dL (reference range, 70–110 mg/dL). To rule out diabetes mellitus, we performed the oral glucose tolerance test, which did not indicate the disease. On the fasting provocation test, hypoglycemia developed at 3 hours with blood glucose and insulin levels at 24 mg/dL and 19.8 μIU/mL (reference range, 2.0–20 μIU/mL), respectively. We also performed abdominal computed tomography to rule out insulinoma, but no abdominal mass was evident. Other laboratory data included antinuclear antibodies, anti-double-stranded DNA antibodies, antiphospholipid antibodies, antiphospholipid antibodies, lupus anticoagulant, and rheumatoid factor, which were all negative. Thyroid function studies revealed no abnormalities and thyroid autoantibody was within normal range.

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Acanthosis nigricans is characterized by velvety to verrucous, hyperkeratotic, hyperpigmented plaques with grayish brown coloration. The lesions are symmetrically distributed and affect only flexural areas, including the neck, axillae, groin, and antecubital and popliteal areas. On occasion, the eruption may become almost generalized. Generalized AN does not represent a specific type of AN, but it can be seen as a variant or rare manifestation of certain types of AN. It is commonly seen in adults with an underlying malignancy.

Type B insulin resistance syndrome, a rare autoimmune disorder, is caused by the autoantibodies to the insulin receptor. It has been predominantly seen in older black women and frequently is associated with an autoimmune disease, particularly systemic lupus erythematosus. Patients typically present with hyperglycemia but also may present with hypoglycemia if the autoantibodies target the insulin receptor.

The patient was diagnosed with generalized AN and type B insulin resistance syndrome. His AN was treated with 40 mg of oral prednisolone daily to inhibit production of the autoantibodies and 40 mg of oral isotretinoin daily. Serial decrements of the dosage of prednisolone were administered over 14 months and then discontinued because there was no further recurrence of hypoglycemic symptoms. The isotretinoin dosage was maintained for 8 months and then discontinued. For 3 years after treatment, hypoglycemia did not recur and the most recent random blood glucose levels were in the 80 to 150 mg/dL range. Insulin autoantibody was normalized to 6.9%, while the insulin receptor autoantibody was positive. The skin showed partial improvement at 16 months of treatment (Figure 4).

Comment

Acanthosis nigricans involving the periocular and perioral regions (A) as well as the trunk (B).

Thick, tan, velvety hyperkeratotic plaques on the neck (A) and axillae (B).
the responsible immunoglobulins stimulate rather than inhibit the signal transducing activity of the insulin receptor. Acanthosis nigricans is a common feature of type B insulin resistance, and in patients with type B insulin resistance, there is a unique periorcular distribution of AN that is not seen in other forms of insulin resistance.5

Considering the widespread distribution of our patient’s lesions as well as the presence of periorcular AN, he was diagnosed with generalized AN and type B insulin resistance syndrome. Therefore, type B insulin resistance syndrome also can be associated with generalized AN.

Although the mechanism of AN occurrence remains to be elucidated, it has been suggested that hyperinsulinemia causes AN by exerting a toxic effect. Insulin has been demonstrated to cross the dermoepidermal junction to reach keratinocytes. At low concentrations, it preferentially binds to insulin receptors; at high concentrations (as in severe insulin resistance), insulin substantially binds to insulinlike growth factor receptors on keratinocytes.

Figure 3. Hyperkeratosis, mild acanthosis, prominent papillomatosis, and slight hyperpigmentation of the basal layer (H&E, original magnification ×100).

Figure 4. Acanthosis nigricans partially regressed after 16 months of treatment.
or fibroblasts.\textsuperscript{7} Binding of insulin to insulin-like growth factor receptors stimulates the proliferation of keratinocytes and fibroblasts, which in turn leads to AN.\textsuperscript{8,9}

Fareau et al\textsuperscript{10} described a patient with regression of AN associated with the disappearance of circulating anti–insulin receptor autoantibodies in the setting of type B insulin resistance. The patient showed improvement of AN and hypoglycemic symptoms after treatment with prednisolone and isotretinoin.\textsuperscript{10} Retinoids such as isotretinoin have diverse biologic effects. They affect cell growth, differentiation, and morphogenesis, and alter cell cohesiveness.\textsuperscript{11} Oral or topical retinoids have been used in the treatment of AN with varying success.\textsuperscript{12,13} The mechanism of action of isotretinoin, though not studied directly in AN, is probably normalization of epithelial growth and differentiation.\textsuperscript{14} We suggest that this case contributes to the literature on the potential for patients with anti–insulin receptor antibodies to present with generalized AN and hypoglycemia.

REFERENCES