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## Insulin resistance, acanthosis nigricans, and hypertriglyceridemia

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### CASE SUMMARY

#### History

A 23-year-old white female was seen in consultation in the Dermatology Clinic at the National Institutes of Health, in Bethesda, Maryland for plaques involving the neck, axillae, and inguinal areas. At 4 months of age, she was noted to have hepatomegaly and hypertriglyceridemia with values as high as 6000 mg/dL. The patient described a ravenous appetite from a young age. Type 2 diabetes mellitus was diagnosed at age 12 and, despite attempts at dietary modification, her blood glucose levels remained poorly controlled. Treatment with metformin was initiated at age 14, followed shortly thereafter by insulin because of continued poor control. Menarche occurred at age 15, and the patient described a history of oligomenorrhea. A liver biopsy at age 18 prompted by elevated transaminases yielded a diagnosis of nonalcoholic steatohepatitis (NASH) with early cirrhosis. The patient's medications at the time of presentation included metformin 850 mg three times a day and U-500 insulin totaling 800 units daily.

#### Physical examination

Physical examination was remarkable for a tall, muscular-appearing woman with prominent forehead and mandible, a systolic ejection murmur, a protuberant abdomen with a liver span 12 cm below the subcostal arch, and an umbilical hernia (Fig 1, A). The patient's muscular appearance was further enhanced by prominent enlarged veins on her

arms and legs. Dermatologic examination identified facial hirsutism as well as prominent terminal hair growth on the central chest and abdomen. Tan velvety plaques were prominent on the neck (Fig 1, C). Thicker tan plaques were visible in the axillary vaults bilaterally and extended onto the anterior shoulders (Fig 1, E). Plaques overlying the proximal medial thighs resulted in a papillomatous texture to the skin in this area. Hyperpigmentation with very fine small papules created a "pebbling" appearance over the joints of the dorsal hands. Numerous discrete exophytic fleshy papules consistent with acrochordons were noted in the axillae.

#### Other significant diagnostic studies

A glucose tolerance test showed a fasting blood sugar of 70 mg/dL and a 2-hour glucose level of 229 mg/dL. HbA1c was 8.7% (normal range, 4.8-6.4%). Other elevated values included: triglycerides, 702 mg/dL (normal range, <150 mg/dL); free testosterone, 63 pg/dL (normal range, 3-19 pg/dL); alanine aminotransferase, 54 u/L (normal range, 6-41 u/L); and aspartate aminotransferase, 40 u/L (normal range, 9-34 u/L). Serum leptin was decreased at 1.44 ng/mL (normal range, >6 ng/mL). Assessment of body composition by dual energy radiograph absorptiometry showed 7.8% body fat (normal range, 22.5-30.8%).<sup>1</sup>

### DIAGNOSIS

- Congenital generalized lipodystrophy (CGL) with prominent acanthosis nigricans.

### FOLLOW-UP

The patient was enrolled in a protocol evaluating the efficacy of recombinant human leptin replacement in patients with lipodystrophy. Within 4 months of initiating therapy, her appetite normalized and a 20-pound weight loss ensued (Fig 1, B). The patient's menstrual cycle became regular and her insulin requirement decreased dramatically. The

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**Fig 1.** **A** and **B**, Prominent muscular appearance with paucity of subcutaneous fat (**A**) and dramatic change in body habitus after one year of leptin therapy (**B**). **C-F**, Prominent acanthosis nigricans on the neck (**C**) and right axilla (**E**) is significantly improved (**D** and **F**) following leptin treatment.

HbA1c decreased from 8.7% to 4.7%, and triglycerides normalized (75 mg/dL). The liver enzymes also normalized. The patient's insulin was discontinued after 4 months of treatment and metformin was withdrawn after 6 months. The acanthosis nigricans also diminished remarkably in concert with the other physical and biochemical changes (Fig 1, *D* and *F*).

## DISCUSSION

CGL is a rare autosomal recessive disorder that is characterized by a dramatic paucity of adipose tissue, extreme insulin resistance, hyperandrogenism, acanthosis nigricans, hypertriglyceridemia, hepatic steatosis, and early-onset diabetes.<sup>2</sup> CGL patients also have voracious appetites, accelerated growth, and low serum leptin levels.<sup>3</sup> Two gene loci exhibiting autosomal recessive inheritance for CGL have been identified. Mutations in some patients with CGL have been localized to the gene encoding 1-acylglycerol-3-phosphate O-acyltransferase2 (AGPAT2) on chromosome 9q34. The AGPAT2 protein is an acyltransferase that catalyzes an essential reaction in the biosynthetic pathway of glycerophospholipids and triacylglycerol in eukaryotes. Perturbations in triacylglycerol synthesis in adipose tissue may lead to triglyceride-depleted adipocytes.<sup>2</sup> Other patients with CGL have a mutation in the Berardinelli-Seip congenital lipodystrophy 2 (BSCL2) gene located on chromosome 11q13. This gene is highly expressed in the brain and testes and encodes a protein of unknown function called seipin.<sup>4</sup> A third group of CGL patients has mutations in neither AGPAT2 nor BSCL2.<sup>5</sup> Our patient was found to have a mutation in the AGPAT2 gene.

Leptin is a hormone or adipocytokine which is produced primarily in white adipose tissue and which signals satiety,<sup>6</sup> curbs appetite,<sup>7</sup> and stimulates oxidation of fat.<sup>8</sup> Because patients with generalized lipodystrophy lack significant adipose tissue, they are consequently deficient in leptin, and have no signal for satiety. Fat accumulation in ectopic areas such as skeletal muscle and liver leads to insulin resistance, diabetes,<sup>9</sup> and steatohepatitis.<sup>10</sup> Leptin replacement reverses the abnormal fat deposition as well as the metabolic abnormalities characteristic of these patients.<sup>11</sup>

We have also observed dramatic improvement in the acanthosis nigricans (AN) of lipodystrophic patients following leptin replacement (Fig 1). There is much speculation about the etiology of AN, and a multitude of systemic diseases have been associated with AN. AN has been ascribed to increased circulating levels of insulin that act on insulin-like growth factor-1 (IGF-1) receptors, inducing fibroblast proliferation.<sup>12</sup> In patients with congenital

partial lipodystrophy, hyperinsulinemia and an increase in the IGF-1/IGF-1 binding protein ratio appear to contribute to an unopposed biological effect of IGF-1 on IGF-1 receptors, leading to the development of AN.<sup>13</sup>

There are numerous reported remedies for obesity-associated acanthosis nigricans, including metformin,<sup>14</sup> isotretinoin,<sup>15</sup> and topical tretinoin and ammonium lactate.<sup>16</sup> We present this case as a demonstration of the effect of leptin treatment on acanthosis nigricans in patients with CGL. We believe that improvement in AN following leptin replacement results from normalization of the metabolic abnormalities characteristic of this syndrome.

## KEY TEACHING POINTS

- CGL is associated with paucity of adipose tissue, extreme insulin resistance, hyperandrogenism, and acanthosis nigricans, hypertriglyceridemia, hepatic steatosis and early-onset diabetes.
- There are two known mutations that cause congenital generalized lipodystrophy: 1-acylglycerol-3-phosphate O-acyltransferase2 (AGPAT2) and seipin (BSCL2).
- The generalized lack of adipose tissue in CGL results in decreased leptin levels, whereas subsequent fat accumulation in ectopic areas such as skeletal muscle and liver leads to insulin resistance, diabetes, and steatohepatitis.
- Leptin replacement in patients with CGL results in remarkable improvement in the physical and endocrinologic manifestations of the disorder, including acanthosis nigricans.

*Editor's note:* Dr Gorden (philg@mail.nih.gov) is a leading authority on lipodystrophies and is actively involved in clinical, therapeutic, and genetic studies of CGL patients at the National Institutes of Health in Bethesda, Maryland.

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