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Case Report

A Visual Diagnosis: Lipodystrophy

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Abstract

Lipodystrophy syndromes are rare metabolic disorders characterized by local or generalized loss of adipose tissue, resulting in insulin resistance, dyslipidemia, and cosmetic disfiguration. The lipodystrophic phenotype is highly variable, with partial lipodystrophy often missed or misdiagnosed as other diseases from a lack of a proper physical examination and low physician awareness. Correct diagnosis is important for optimal treatment and follow-up strategies in these patients. The use of GLP-1 analogs has not been systematically evaluated in lipodystrophy and could be a potential precision medicine therapy. We aim to make the reader, particularly generalists or endocrinologists outside of tertiary referral centers, aware of the presentation and clinical features of partial lipodystrophy, emphasize the role of a full physical examination in diagnosis, and discuss therapeutic options, including GLP-1–based glycemic management illustrated by our clinical case.

Key Words: lipodystrophy, physical exam, GLP-1 analogs, diabetes, insulin resistance, adipose tissue

Abbreviations: FPLD, familial partial lipodystrophy; GLP-1a, GLP-1 analog; T2DM, type 2 diabetes mellitus.

Introduction

The prevalence of obesity in most regions in the United States is 30% to 40% and may exceed 50% in many general internal medicine and endocrinology clinics. As a result of rising obesity rates, rates of metabolic syndrome, type 2 diabetes mellitus (T2DM), and hypertension have increased. Screening for secondary causes of metabolic disease other than primary obesity is not routinely performed and there is no established and cost-effective algorithm for doing so. This can lead either to under- or missed diagnosis of uncommon metabolic diseases, or false-positive testing, causing inappropriate treatment, increased patient anxiety, and financial costs.

In this report, we describe a case of partial lipodystrophy, in which the patient had no clear diagnosis despite years of treatment and evaluation by multiple physicians. This case illustrates a practical approach, particularly for generalists or early-career endocrinologists without prior clinical exposure to lipodystrophy cases and reinforces 2 age-old dictums sometimes difficult to follow in busy modern clinical practices: (1) listening to your patient's concerns and (2) performing a full physical examination. Additionally, we discuss the use of GLP-1 analogs (GLP-1a) in our patient with lipodystrophy, which resulted in significant improvement in her previously poorly controlled hyperglycemia.

Case Presentation

A 54-year-old female with a 15-year history of T2DM, hypertension, and worsening central obesity presented to our outpatient endocrine clinic for a second opinion regarding the underlying cause of her diabetes and obesity, and for optimization of glycemic control.

The patient was diagnosed with T2DM at age 39 years. Despite treatment with different medication regimens over the years, including metformin, sulfonylureas, sitagliptin, and basal-bolus insulin therapy, she exhibited poor and deteriorating glycemic control. The patient had difficulty maintaining optimal weight despite a strict diet and intense physical activity. She was frustrated by the worsening of her abdominal obesity, exacerbated by the addition of insulin to her medication regimen 2 years prior. She did not report signs of hypercortisolemia such as easy bruising, striae, or muscle weakness.

She had seen multiple physicians and had not obtained clarity on her underlying diagnoses. She wanted to know "whether this was 'just' obesity or a more specific undiagnosed metabolic disease." Her family history was notable for T2DM and obesity in both her parents and her sister. She was a nonsmoker and reported minimal alcohol use. She did not have a history of glucocorticoid use. Her hemoglobin A1c level 4 months before presentation to our clinic was 11.4% (15.6 mmol/L); she also had hypertriglyceridemia (496 mg/dL [5.6 mmol/L], normal value < 200 mg/dL [2.26 mmol/L]) and hypercholesterolemia (total cholesterol 267 mg/dL [6.9 mmol/L], normal value <200 mg/dL [5.16 mmol/L]). Current prescription medications included metformin 1000 mg twice daily, basal-bolus insulin (insulin glargine 18 units once daily and variable dose of insulin aspart before meals, with an average total daily dose of 32 units),

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40 mg lisinopril and 25 mg hydrochlorothiazide daily for hypertension.

Diagnostic Assessment

On examination, her vitals were within normal limits. Body mass index was 33.4 kg/m^2. The patient had abdominal obesity (waist circumference, 106.8 cm), in stark contrast to her muscular extremities and gluteal region, which had lipoatrophy (hip circumference, 93.7 cm) (Fig. 1). She noted that her father and paternal uncle had a similar body habitus.

She did not exhibit signs of severe dyslipidemia (palmar xanthomas, xanthelasma), Cushing syndrome (supraclavicular/dorsocervical fat pad, moon facies, violaceous striae, bruising, proximal muscle weakness, hirsutism), acanthosis nigricans, skin tags, or acromegaly. We performed a 24-hour urinary free cortisol (16 mcg/24 h [44.1 nmol/24 h]; normal, 5-40 mcg/24 h [13.8-110 nmol/24 h]) and 1-mg dexamethasone suppression testing (0.77 mcg/dL [21.24 nmol/L], normal <1.8 mcg/dL [<49.6 nmol/L]) to exclude Cushing syndrome.

The clinical history, together with the physical examination and negative laboratory assessment for Cushing syndrome raised concern for partial lipodystrophy. A fasting leptin level was normal (56.6 ng/mL [4.5 nmol/mL]). The patient provided written, informed consent for a natural history study of insulin resistance (NCT00001987) approved by the institutional review board of the National Institutes of Health. Evaluation of body fat mass distribution was performed using X-ray densitometry, which showed a significantly increased trunk-to-lower limb fat percent ratio of 1.74, which was 5 SDs above age- and sex-matched normal ratios. FibroScan revealed hepatic steatosis without evidence of cirrhosis. Genetic testing for common forms of partial lipodystrophy (*LMNA* and *PPARG* mutations) was negative. Whole-exome sequencing results were pending at the time of writing this report.

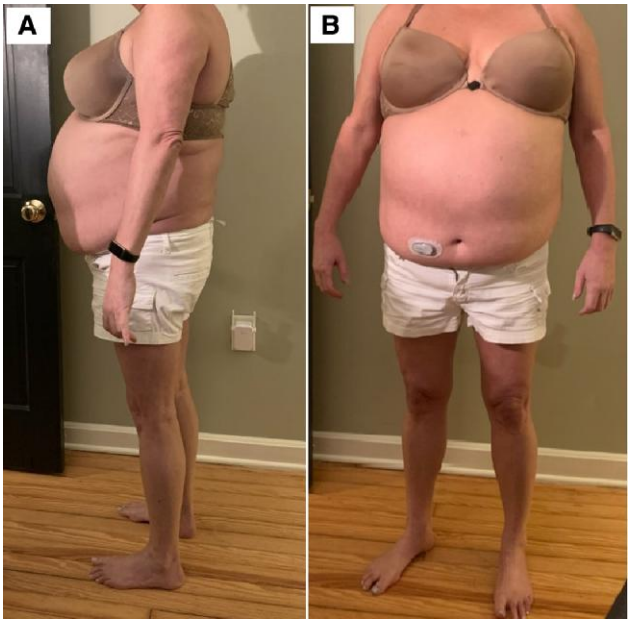

Figure 1. (A) Side profile of the patient demonstrates prominent central adiposity, with significant loss of adipose tissue in the lower extremities (gluteal and thigh region) and upper extremities. (B) Front profile of the patient demonstrates prominent central adiposity, with significant loss of adipose tissue in the lower extremities (gluteal and thigh region) and upper extremities.

We made a clinical diagnosis of familial partial lipodystrophy (FPLD) type 1 based on the patient's physical examination and imaging findings. As the patient had suspected, a previously unrecognized diagnosis of partial lipodystrophy was responsible for both her central obesity and lipoatrophic diabetes. This clarity and unifying diagnosis explaining her constellation of metabolic diseases was a great relief to the patient after years of uncertainty.

Treatment

The patient was initiated on dulaglutide 0.75 mg once weekly and atorvastatin 40 mg daily for the management of diabetes and hyperlipidemia, respectively. She was continued on basal-bolus insulin and metformin. Pioglitazone 15 mg daily was also initiated, but the patient self-discontinued after approximately 4 months of use.

Outcome and Follow-up

The patient had a substantial improvement in hyperglycemia, as assessed by hemoglobin A1c, after initiation of dulaglutide (Fig. 2). Glycemic control continued to improve even with discontinuation of insulin. Furthermore, the patient lost 35 pounds after insulin therapy was stopped. Hyperlipidemia responded well to high-dose atorvastatin (triglycerides, 155 mg/dL [1.75 mmol/L]; total cholesterol, 168 mg/dL [4.34 mmol/L]).

Discussion

Obesity is common and typically the result of environmental and polygenic causes. Metabolic diseases such as Cushing syndrome and lipodystrophy, which cause secondary obesity or alter adipose tissue distribution are relatively uncommon. When and how to evaluate for these rare disorders amongst many clinic patients with obesity and/or metabolic syndrome is a challenging decision.

Lipodystrophy syndromes are characterized by generalized or partial absence of adipose tissue, either familial or acquired, despite normal nutritional intake, and results in metabolic dysfunction (insulin resistance, hypertriglyceridemia) and ectopic fat deposition. In FPLD, adipose tissue is typically absent from gluteofemoral depots, and preserved or increased in the head, neck, and trunk. Criteria for the diagnosis of lipodystrophy have not been established [1]. However, experts in the field concur that physical examination is critical in the clinical diagnosis of lipodystrophy. Additional evidence including imaging (abnormal adipose tissue distribution pattern), pedigree analysis, genetic testing, serum complement/autoantibody levels (perilipin antibody, C3 nephritic factor, anti-smooth muscle antibody in acquired lipodystrophy) can help support the diagnosis. Specific forms of lipodystrophy with low leptin levels respond dramatically to leptin therapy.

Diagnosis of a specific cause of metabolic syndrome is important as it can alter the therapeutic plan for patients. For example, patients with lipodystrophy have higher rates of acute pancreatitis, atherosclerotic cardiovascular disease, cardiomyopathy, and steatohepatitis requiring long-term screening.

Performing a full physical examination with at least partial disrobing of a patient is increasingly rare in an era of 15-minute clinic visits. Physical examination thoroughness

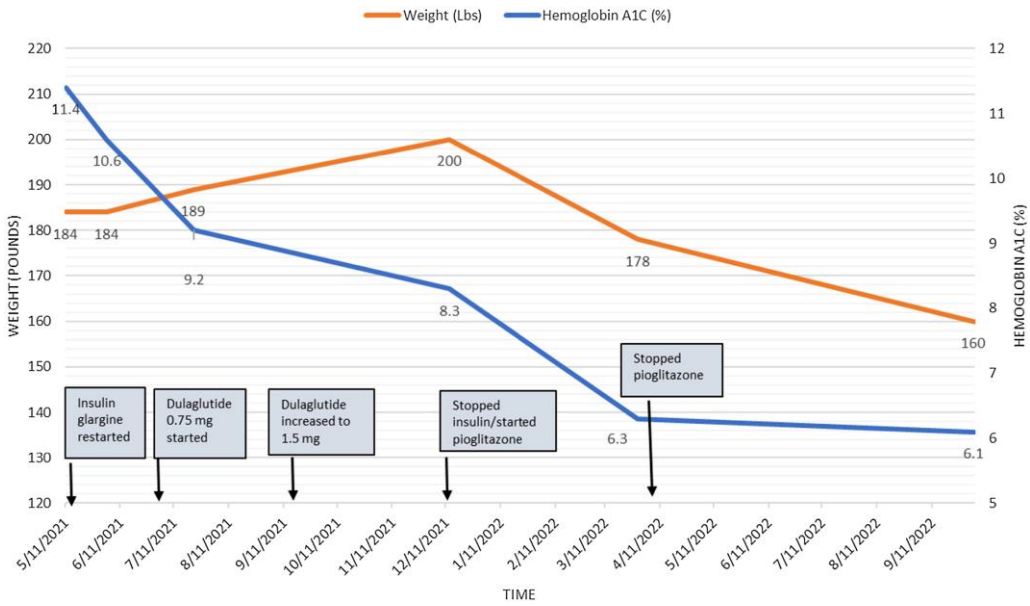

Figure 2. Patient's hemoglobin A1c and weight trend over 1 year shows significant glycemic improvement after initiation of dulaglutide. Weight loss with dulaglutide use was modest but became more prominent after cessation of insulin therapy. Hemoglobin A1c continued to decrease even after stopping insulin therapy.

and quality are dropping, as a result of time constraints, readily available imaging, and a shift toward telemedicine [2]. As our case illustrates, however, a thorough physical examination can quickly reveal a previously unestablished diagnosis.

Differential diagnoses of partial lipodystrophy in our patient included Cushing syndrome and acromegaly. These were excluded clinically and with laboratory assessment. Lipodystrophy and Cushing syndrome can cause overlapping phenotypes with respect to adipose distribution (predominantly central), which can be difficult to distinguish. In our case, the severe central obesity with extremity sparing together with the absence of other signs of Cushing syndrome strongly favored lipodystrophy.

In our patient, genetic testing for *LMNA* and *PPARG* pathogenic variants (the most common forms of familial partial lipodystrophy) was negative. The clinical phenotype of central adiposity with deficiency of fat in the gluteal region and extremities in our patient most closely matched FPLD type 1 (Köbberling-type lipodystrophy) [3, 4]. FPLD type 1 is characterized by abdominal and neck lipohypertrophy together with lipoatrophy in the extremities, with areas of transition to lipoatrophy forming a ledge, notable on examination [3]. FPLD type 1 is typically seen in women. No specific genetic mutation has been identified for FPLD type 1; genome-wide association studies point to a likely polygenic inheritance pattern [5]. Measurement of the Köb index (ratio of subscapular: calf skinfolds) has been proposed as a diagnostic tool to establish the diagnosis of FPLD type 1 (cutoff value, 3.477; sensitivity, 89%; specificity, 84%) [4]. In our case, we made a clinical diagnosis of FPLD type 1, supported by fat distribution ratios on densitometry; however, future assessment of skin-fold measurements can be further helpful. Skin-fold testing can be more cost-effective in the general practice, compared with densitometry.

Our patient's leptin level was normal. The primary utility of measuring leptin is to identify leptin-deficient patients who might benefit from metreleptin therapy [6]. Leptin levels neither establish nor rule out lipodystrophic syndromes [1].

Because both diabetes and hypertension, seen in patients with FPLD type 1, are risk factors for cardiovascular events, screening for cardiovascular disease should be considered in this population. Treatment recommendations for partial lipodystrophy include dietary modifications, metformin, and insulin therapy, which did not provide optimal glycemic and weight management benefit in our patient. However, the use of GLP-1a in our patient provided robust improvement in glycemia, and permitted discontinuation of insulin, thus avoiding its contribution to weight gain.

The use of GLP-1a in lipodystrophy is not well studied but supported by animal studies and human case reports [7]. Specific mechanisms underlying the benefits of GLP-1a in lipodystrophy are unclear. Possibilities include the known effects of GLP-1a on improving insulin sensitization, fat redistribution, and hepatic steatosis; all of which are pathological characteristics of lipodystrophy. More specifically, treatment of obese mice with GLP-1a was found to promote leptin sensitivity [8] . In addition, patients with FPLD type 2 were found to have elevated levels of dipeptidyl peptidase-4, which catabolizes endogenous GLP-1 [9]. A case reported by Banning et al described impaired first-phase insulin secretory response on a euglycemic clamp in a patient with FPLD type 2 [10]. That patient responded dramatically to liraglutide. Although our patient did not have FPLD type 2, the similarity of an excellent glycemic response to a GLP-1a suggests GLP-1a should be considered early in the treatment of partial lipodystrophy. Future studies in patients with FPLD type 1 can examine these possibilities by evaluating these parameters following treatment with GLP-1a vs other medications.

Our patient noted significant weight loss after initiation of GLP-1a; however, most of it occurred after stopping insulin therapy (Fig. 2). Insulin therapy is associated with weight gain because of increased adipogenesis and can potentially exacerbate body image concerns in patients with lipodystrophy.

Thus, the use of weight-neutral/weight loss–promoting diabetic therapies might be more favorable.

Learning Points

- Evaluation of secondary causes of metabolic syndrome should include a comprehensive physical examination and laboratory evaluation for Cushing syndrome.
- Lipodystrophy is a clinical diagnosis and requires a high degree of suspicion. Physical examination with minimal clothing is needed to observe the lipodystrophic phenotype.
- Leptin levels are not diagnostic of lipodystrophy but can help identify hypoleptinemic patients who might benefit from leptin replacement therapy.
- Diabetes mellitus in some lipodystrophy variants can respond particularly well to GLP-1a, and use of these agents should be systematically explored in patients with lipodystrophy.

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Contributors

S.Z.B., R.J.B., and R.R.B. were involved in the diagnosis and management of the patient and in the writing and submission of the manuscript.

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Disclosures

The authors have no conflicts of interest to declare.

Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient.

Data Availability Statement

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

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