Familial partial lipodystrophy misdiagnosed as type 1 diabetes: ensuring accurate diagnosis: a case report

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Br J Diabetes 2026;ONLINE AHEAD OF PUBLICATION
https://doi.org/10.15277/bjd.2026.501

Key words: familial partial lipodystrophy (FPLD), severe insulin resistance, metreleptin therapy, misclassification of diabetes, hypertriglyceridaemia

Abstract

Familial partial lipodystrophy (FPLD) is a rare, inherited disorder characterised by selective loss of adipose tissue, often affecting the limbs and gluteal region, and concurrent fat accumulation in the face, neck and intra-abdominal areas. This redistribution leads to profound insulin resistance, dyslipidaemia and fatty liver disease. It may be misdiagnosed clinically as type 1 diabetes (T1DM), particularly in patients with lean body habitus, or type 2 diabetes (T2DM) due to insulin resistance. We report a case of a young woman who was initially treated for presumed T1DM but was ultimately diagnosed with FPLD.

Introduction

The lipodystrophy syndromes are a heterogeneous group of disorders characterized by complete or partial loss of adipose tissue. They may be either congenital or acquired.[1] Although familial partial lipodystrophy (FPLD) is relatively common, it is still not widely recognised or appropriately diagnosed. Affected individuals frequently present with metabolic abnormalities, including severe hyperglycaemia without ketosis, profound insulin resistance accompanied by acanthosis nigricans and hypertriglyceridaemia with eruptive xanthomas. Genetic testing is available and can aid in confirming the diagnosis of FPLD. Multiple pathogenic variants have been described; FPLD type 3 is associated with mutations in the peroxisome proliferator-activated receptor-gamma (PPARG) gene.[2] We report a case of a young woman who was initially treated for presumed T1DM but was diagnosed with FPLD after genetic testing.

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Case report

A 32-year-old Caucasian woman was referred to the lipid clinic following the incidental finding of eruptive xanthomas and markedly elevated triglyceride levels (67 mmol/L) on routine blood testing. Her HbA_{1c} was 94mmol/mol. She admitted to excess alcohol intake (40–50 units/week), which may have contributed to her severe hypertriglyceridaemia. No history of pancreatitis or liver disease was noted. Family history included a mother with T2DM treated with oral agents, but no clear phenotypic features of lipodystrophy were reported.

She weighed 61 kg (BMI 20.7 kg/m^2). Examination revealed prominent deltoid and trapezius musculature, reduced subcutaneous fat in the limbs, and no acanthosis nigricans or hirsutism.

She was presumptively diagnosed with T1DM given her lean phenotype, osmotic symptoms and high HbA_{1c}, and she was commenced on a basal–bolus insulin regimen. Over a period of weeks, her insulin doses escalated to >150 units/day.

Diagnostic assessment

Diabetes autoantibodies (GAD, IA2, ZnT8) were negative. Fasting C-peptide was elevated (2496 pmol/L; reference >600), indicating preserved endogenous insulin. C-peptide is usually measured after several years of diabetes but in this context it clarified the misclassification.

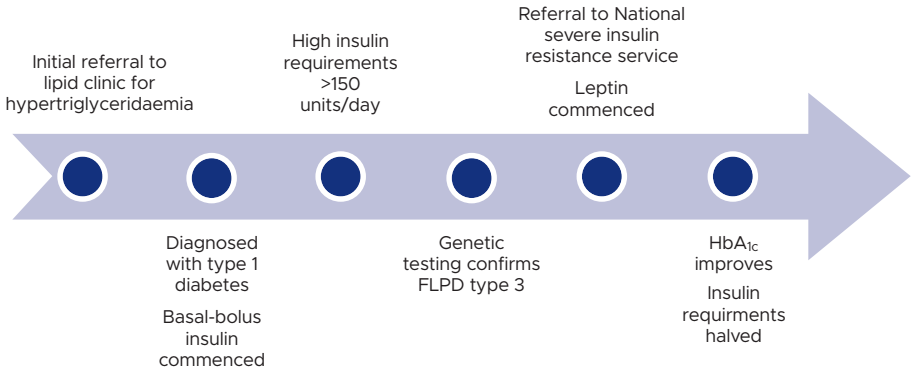
A dexamethasone suppression test was performed because of the high insulin requirement and elevated C-peptide, to exclude occult Cushing's. The result was normal.

Given her phenotype, high insulin requirement and biochemical profile, lipodystrophy was suspected. Genetic testing confirmed FPLD type (PPARG variant).

Therapeutic intervention

She was referred to the National Severe Insulin Resistance Service. Baseline leptin concentration was low (2.1 ng/mL; reference >4.0), meeting NICE criteria for metreleptin initiation.[3] Metreleptin therapy halved her insulin requirement, improved satiety and reduced hunger.[3,4] HbA_{1c} fell to 68mmol/mol within three months. The clinical timeline is shown in figure 1. Triglycerides improved to 4.89 mmol/L (Figure 2) and the eruptive xanthomas resolved. She was commenced on a statin–fibrate combination to further address residual dyslipidaemia. ApoE phenotyping was considered but not performed, as

Figure 1 Clinical timeline for this case



triglyceride improvement with leptin and lipid therapy suggested secondary dyslipidaemia.

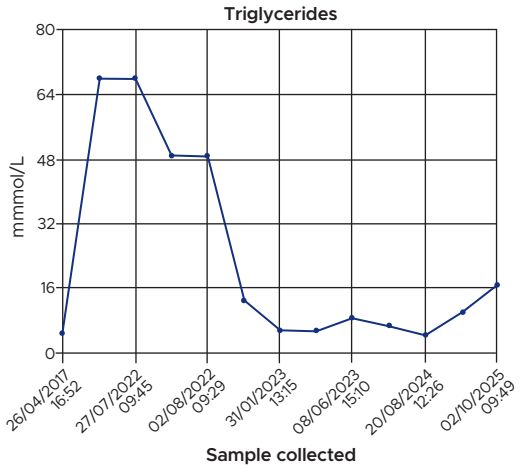
Follow-up and outcome

She initially tolerated metreleptin but started to develop itching, nausea, vomiting and lumps at injection sites (but no rash) six months after starting injection. She was unable to continue taking the metreleptin and her insulin requirement continued to increase, with a carbohydate ratio of 1 unit for 1g in addition to a basal insulin requirement of 100 units degludec U200. Her triglyceride level deteriorated.

She was started on dapagliflozin and her time in range increased from 7% to 60%. She was happy to continue with this despite polyuria.

The diagnosis of FPLD was made 18 months after initial presentation. She and her family received genetic counselling. One of her two sons screened positive.

Figure 2. Following the cessation of metreleptin, her triglyceride levels rebounded to 17.21 mmol/L, representing a marked deterioration from the metreleptin treated nadir of 4.89 mmol/L



Discussion

This case highlights the pitfalls of diabetes misclassification. Studies suggest that up to 7–15% of patients labelled with T1DM may be misclassified.[2,5] Contrary to the typical abrupt-onset clinical features of T1DM, the patient's high HbA_{1c} on diagnosis suggests a period of insidious hyperglycemia, likely driven by the extreme insulin resistance characteristic of familial partial lipodystrophy. Features warranting review include unexpectedly high insulin requirements (>2 units/kg/day), preserved C-peptide, negative autoantibodies and disproportionate fat distribution. Autoantibody testing should be considered in all new diagnoses of T1DM.

Figure 3. Eruptive xanthoma over elbow

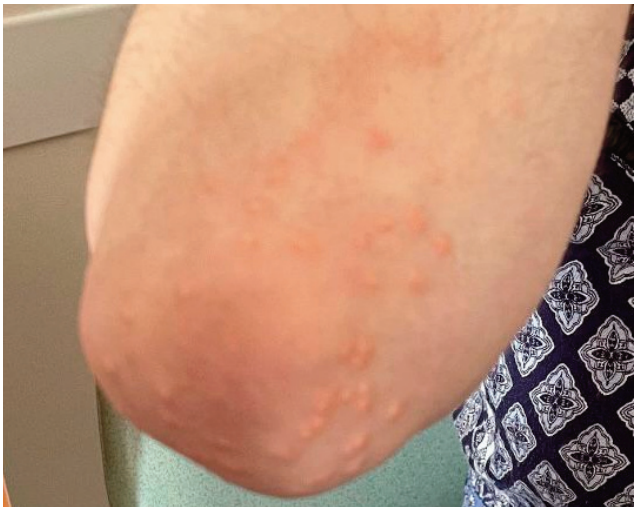


Figure 4. Eruptive xanthoma on upper legs

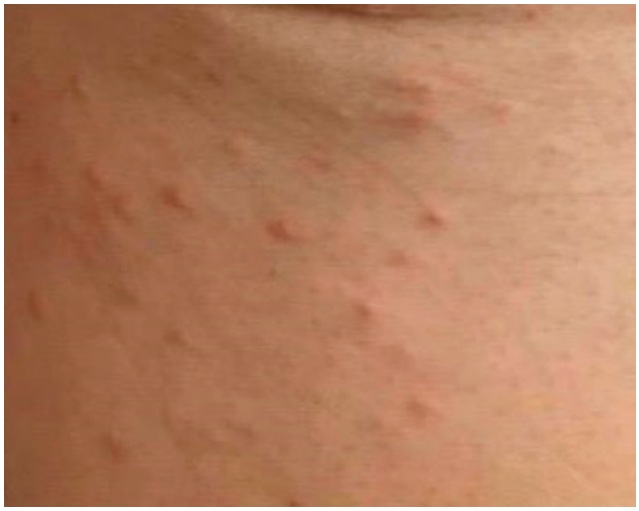
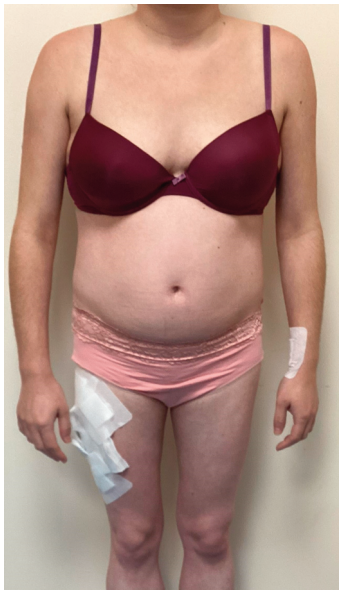


Figure 5. Clinical photograph showing loss of limb subcutaneous fat with relative central adiposity, characteristic of familial partial lipodystrophy



Eruptive xanthomas (Figures 3 and 4) were also noted at presentation, which later resolved with metabolic control. The figures illustrate these hallmark phenotypic features, underscoring the diagnostic value of detailed physical examination.

FPLD is often under-recognised due to heterogeneity of presentation; subtle phenotypes may be missed in the absence of careful physical examination.[6,7] Loss of limb fat and relative central adiposity are important clinical clues (Figure 5). The photographs (with patient consent) illustrate the classical phenotype (Figure 5) and in figures 3 and 4 the initial eruptive xanthomas can be seen. The psychological burden of altered body habitus can be profound and warrants multidisciplinary support.

Metreleptin replacement has transformed management of lipodystrophy, addressing both metabolic and symptomatic burden.[3-5] Some patients are unable to take metreleptin due to allergy, which can further complicate management. Residual dyslipidaemia often requires pharmacological therapy, and additional lipid disorders such as ApoE2 homozygosity should be considered in those with severe hypertriglyceridaemia.[8]

Key messages

- Consider FPLD in lean patients who have severe insulin resistance and dyslipidaemia
- Early physical examination and C-peptide testing aid correct diabetes classification
- Metreleptin improves metabolic control but its use may be limited by tolerability
- Genetic counselling is essential for family risk assessment

Patient perspective

The key outcome of discussions with the patient revealed how important it was to her and her family that clinicians in the field have an awareness of familial partial lipodystrophy, its presentation, diagnosis and appropriate management.

Conflict of interest None to declare.
Funding None.
Patient consent The patient consented for this case report to be published. All details have been kept anonymous.

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