Differential loss of fat in polycystic ovary syndrome: A welcome or warning sign?

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ABSTRACT

Lipodystrophy syndrome is a rare disorder characterized by selective deficiency of adipose tissue and severe insulin resistance resulting in metabolic complications. Its presentation as polycystic ovary disease (PCOD) is even rarer. We present a 23-year-old woman who came with complaints of oligomenorrhoea and hirsutism. When specifically asked, she accepted noticing loss of fat from some areas of her body. Examination showed loss of fat from the face, buttocks and thighs. Her investigations revealed deranged blood sugars, transaminitis, dyslipidaemia and elevated serum testosterone; ultrasonography showed fatty liver and polycystic ovary. Fat composition measurement revealed loss of fat from lower limbs and increased ratio of trunk-to-leg fat. Based on these findings, a diagnosis of lipodystrophy was made. She was started on metformin, statins and ursodeoxycholic acid. Blood sugars, lipid profile and dyslipidaemia improved over a period of 6 months. We suggest that in lean patients with PCOD, lipodystrophy becomes a differential diagnosis, so attention should be paid to body fat distribution in them. Despite normal body mass index (BMI), these patients tend to develop metabolic complications as in our patient (BMI 21.5). This diagnosis has long-term implications in view of its association with metabolic complications.

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INTRODUCTION

Lipodystrophy syndromes are a group of rare acquired or genetic disorders characterized by selective deficiency of adipose tissue. Its presentation as polycystic ovary syndrome (PCOS) is even rarer. This is categorized based on aetiology (genetic or acquired) and distribution of disease (generalized or partial). It is associated with metabolic complications such as diabetes mellitus (DM), dyslipidaemia, PCOS and non-alcoholic steato-hepatitis.[1] Cardiovascular diseases (myocardial infarction and arrhythmia) are important causes of mortality in them, so timely diagnosis and preventive measures are needed.[2,3] Patients need lifelong follow-up due to the association of PCOS with metabolic syndromes. We present a woman with PCOS who was subsequently diagnosed with lipodystrophy.

THE CASE

A 23-year-old woman presented to the outpatient department of endocrinology with complaints of secondary amenorrhoea for 3 years and hirsutism for 2 years. Initially, she had oligomenorrhoea which progressed to amenorrhoea over 2 years. She also had complaints of excess hair growth over her face, arms and legs for the past 2 years. She noticed loss of scalp hair and darkening of skin at the back of the neck for the past 1 year. On being asked specifically about any change in body composition, she said there was decreased fat mass on her cheeks, upper arms, buttocks and thighs. Her cousin sister had complaints of irregular periods and hirsutism but not of fat loss. There was no history of diabetes or metabolic disorder in her family. Her height was 138 cm and weight 41 kg with a body mass index (BMI) of 21.5. She had decreased subcutaneous fat in the arms, thighs, buccal and gluteal area; and abdominal obesity (Fig. 1) along with acanthosis nigricans on the back of her neck. She had frontal recession, temporal balding and a masculine body. Her modified Ferriman–Gallwey score for hirsutism was 18.

Her ultrasound of the pelvis showed the right and left ovary volume to be 10 ml and 14 ml, respectively with multiple peripherally arranged follicles and thick stroma. Ultrasound of the upper abdomen showed a fatty liver. She was assigned a diagnosis of PCOS with phenotype A as per the consensus of the National Institutes of Health (NIH).[4] Further work-up suggested diabetes mellitus. The cause of deranged liver function tests (LFT) was non-alcoholic steatohepatitis as viral markers and markers of autoimmune hepatitis were negative. Fat

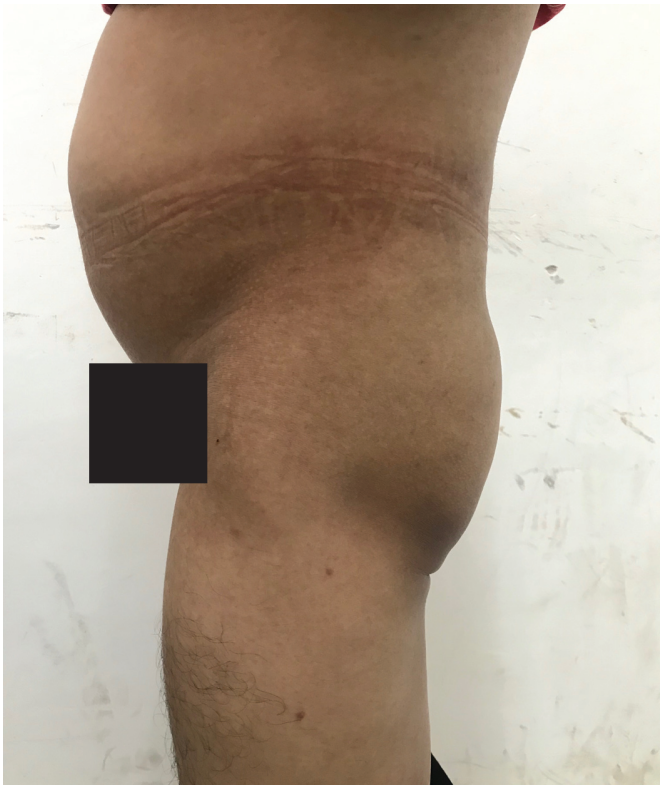

FIG 1. Loss of fat from the gluteal region and thigh, with abdominal obesity

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TABLE I. Relevant investigations of the patient

Investigation	Result (before treatment)	Result (6 months after treatment)	Normal range
Blood sugar fasting (mmol/L)	9.0	5.0	3.8–6.1
Blood sugar post-prandial (mmol/L)	12.1	5.6	5–7.7
Glycated haemoglobin (%)	8	5.46	3.8–5.9
Cholesterol (mmol/L)			
Total	5.31	3.32	3.89–5.18
Low-density lipoprotein	3.36	2.27	0–3.36
High-density lipoprotein	0.85	0.59	0.90–1.42
Triglyceride	8.81	5.12	1.29–5.17
Testosterone basal (nmol/L)	3.39	–	0.2–2.9
Insulin basal (µU/ml)	57.21	–	2.6–24.9
Luteinizing hormone (mIU/ml)	2.56	–	2.4–12.6
Follicle-stimulating hormone (mIU/ml)	4.07	–	3.5–12.5
Thyroid-stimulating hormone (µIU/ml)	2.36	–	0.27–4.2
Prolactin (µg/L)	24.44	–	4.79–23.3
Total bilirubin (µmol/L)	8.21	–	0–17.1
Alanine transaminase (U/L)	180	99	2–40
Aspartate transaminase (U/L)	108	64	2–41
Alkaline phosphatase (U/L)	141	–	42–128
Anti-hepatitis C virus IgG, hepatitis B virus surface antigen	Negative	–	–
Antinuclear antibodies, anti-mitochondrial antibodies, anti-smooth muscle antibody, liver kidney microsomal antibody, anti-parietal cell antibody	Negative	–	–
Urine protein	72 mg/24 hours	–	0–150 mg/24 hours

TABLE II. Classification of lipodystrophy syndrome[8]

Name	Aetiology	Characteristics
Congenital generalized lipodystrophy (Berardinelli–Seip syndrome)	Autosomal recessive	Almost complete lack of fat starting at birth or infancy, prominent muscles, acanthosis nigricans, hepatomegaly, umbilical prominence; usually associated with metabolic complications which may be severe
Familial partial lipodystrophy (Dunnigan variety)	Generally autosomal dominant	Loss of fat from limbs, buttocks and hips; normal fat distribution in childhood, with loss occurring around puberty; metabolic complications are common in adulthood, with increased risk of coronary heart disease
Acquired generalized lipodystrophy (Lawrence syndrome)	Acquired	More common in women (women:men 3:1); may develop at any time in life but appears usually before adolescence, resulting in progressive loss of fat affecting the whole body including palms and soles; metabolic complications are frequent and may be severe; often associated with autoimmune diseases
Acquired partial lipodystrophy (Barraquer–Simons syndrome)	Acquired	More frequent in women (women:men 4:1); begins in childhood or adolescence; fat loss occurs in cranio-caudal trend, progressively affecting the face, neck, shoulders, arms and trunk; metabolic complications are uncommon but association with autoimmune diseases are seen, especially membranoproliferative glomerulonephritis in approximately 20%; because of these associations patients frequently have low serum complement 3 (C3) levels, and some have the presence of C3 nephritic factor

composition measurement (done by Dual energy X-ray absorptiometry) showed loss of fat from the lower limbs and increased ratio of trunk-to-leg fat. Autoimmune work-up ruled out acquired causes of lipodystrophy (Table I).

With a history of fat loss from cheeks and buttocks, investigations showing abnormal body fat distribution along with deranged LFT and blood sugars, we made a diagnosis of partial lipodystrophy with metabolic complications of dyslipidaemia, diabetes, non-alcoholic steatohepatitis and PCOS. The patient was advised lifestyle modifications in the form of dietary restriction and physical activity. Metformin 500 mg twice a day was started, which was gradually increased to 1000 mg twice a day. For her deranged LFT, ursodeoxycholic acid and for dyslipidaemia, statins were started. Over a period of 6 months, her LFT, blood sugar and dyslipidaemia improved. She resumed spontaneous menstrual cycles at an interval of 40–50 days, but her balding did not improve.

DISCUSSION

Weight gain is generally seen in PCOS, but a proportion of patients present as lean variants. In all lean PCOS, the pattern of fat distribution should be noted, and if there is any suspicion,

metabolic screening should be done. Lipodystrophy syndrome can be a possibility in them. As in our patient, diagnosing her as lean polycystic ovary disease (PCOD) only would have been incomplete and missing out on the underlying lipodystrophy would have been important due to the long-term complications associated with this pathology. A diagnosis of lipodystrophy can be made on detailed work-up of PCOD.[5,6] It is a rare condition[7] due to which most clinicians are not familiar with the diagnosis and management. The diagnosis of lipodystrophy is based on history and presentation. Although serum leptin level has been proposed as a marker, it is not diagnostic as there is considerable overlap with the general population.[8] There are four main varieties of lipodystrophy (Table II).[8] However, due to heterogeneity of the condition, all subtypes cannot be classified into these categories.[3] Autoimmune markers in acquired causes and genetic testing in familial cases help in the classification. Genetic testing has implications in family members of the proband. Mutation in lamin A/C (LMNA) gene is seen in familial cases.[5,9] Other causes of lipodystrophy should be ruled out such as retrovirus positivity, diabetes on insulin therapy, etc.

Severe insulin resistance is a feature of lipodystrophy which leads to endogenous hyperinsulinaemia having leutenizing hormone-like activity on ovarian theca cells producing increased androgen. Further, hyperinsulinaemia leads to decreased sex hormone-binding globulin increasing bioavailable androgens, leading to hirsutism and menstrual irregularity. Due to non-availability of adipose tissue, dietary fat accumulates in non-adipose tissue such as the liver leading to lipotoxicity, for example, steatohepatitis. Although we did not do a genetic analysis of our patient, we came to the diagnosis of acquired partial lipodystrophy due to the absence of positive family history. Our patient had all the above-mentioned manifestations of metabolic syndrome such as diabetes, dyslipidaemia, PCOS and non-alcoholic steatohepatitis.

There is no curative treatment for lipodystrophy syndrome. Management is directed towards metabolic complications and mitigating morbidity of the condition.[7] Dietary management and exercise is the mainstay of treatment, to prevent accumulation of fat in non-adipose tissue. At present, metreleptin, a synthetic analogue of the hormone leptin, is the only medical treatment approved for this condition.[7] Lipodystrophy also affects the physical appearance of patients, leading to psychological distress in some. Hence, appropriate mental health counselling is needed.

To conclude, in patients with lean PCOS, lipodystrophy becomes a differential diagnosis, so attention should be paid to body fat distribution in these patients. Despite normal BMI, they tend to develop metabolic complications as in our patient (BMI 21.5). This diagnosis has long-term implications in view of its association with metabolic complications.

Conflicts of interest. None declared

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