Case Report with Review of Literature

Polycystic ovarian syndrome in patients with lipodystrophy: Report of 2 cases with review of literature

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ABSTRACT

Lipodystrophy is a clinical disorder characterized by maldistribution of body fat. Hyperinsulinemia, insulin resistance, and abnormalities of glucose homeostasis are commonly described among these patients. Hyperinsulinemia is also involved in the pathogenesis of polycystic ovarian syndrome, a condition, described rarely in patients with lipodystrophy. Here, we describe 2 females of partial lipodystrophy who presented with features of polycystic ovarian disease. Both had severe hyperinsulinemia and irregular periods, one had hyperandrogenism and hirsuitism while the other was non-hirsuite.

Key words: Polycystic ovarian syndrome, lipodystrophy, phenotype

Introduction

Lipodystrophy is a rare disorder, characterized by dystrophy of fat cells. A number of endocrine alterations have been described in patients with lipodystrophy, and this has been attributed to adipocyte malfunction and rare coding mutations in the genes responsible for adipogenesis.[1-3] Hyperinsulinemia, metabolic syndrome, fatty liver, and dyslipidemia are frequently described in patients with lipodystrophy. Ovarian dysfunctions including subfertility and polycystic ovarian syndrome have also been reported in these patients.

Polycystic ovarian syndrome (PCOS) is characterized mainly by hyperandrogenism and oligoanovulation. Hyperinsulinemia plays an important role in the pathogenesis of both these features.[4,5] There are only a few case reports of PCOS in patients with partial lipodystrophy. Here, we describe 2 cases of lipodystrophy presenting with a variable phenotype of PCOS.

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Case Reports

Case 1

A 22-year-old female presented to the endocrinology unit with complaints of irregular periods since menarche and hyperpigmentation of face and neck for the past 5 years. There had been acneform eruptions on the face since the last 3 years, but she denied any hirsuitism. She had noticed changes in her physical appearance, with face and neck getting fuller and muscles of hands and legs getting more prominent.There was no history of diabetes mellitus, PCOS or similar physical appearances in any of the family members.

On examination,she was of average built with height – 160.8 cm and weight – 52.8 kg, and BP – 110/60 mmHg. Hypertrophy of calves, biceps, and triceps was noted. There were changes in the fat distribution pattern in her body, with loss of subcutaneous fat in the abdominal and gluteal region and accumulation of fat in the face,neck, and in the paraumbilacal region.Acanthosis nigricans was present on the face (tip of the nose was spared), neck, axilla, and pubic

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region. Hypertrophy of labia was noted. Asymmetry in her breast size was present, with left being bigger in size than the right one. Acneform eruptions were present on the face with minimal hair on the chin.There were no significant findings on cardiovascular/CNS and chest examination.

Lab evaluation revealed normal hemogram, liver function, and kidney function tests. Urine examination was normal.There was no cardiac abnormality evident on echocardiography. Response to glucose tolerance test was impaired (0 hr. - 97 mg/dl, 1 hr. – 197 mg/dl, 2 hr. –157 mg/dl.) and basal and post-glucose insulin levels were high (0 hr – 40.05 μIu/ml, 1 hr. – 882.67 μIu/ml and 2 hr.- 281.94 μIu/ml), respectively. High triglycerides and low HDL levels were noted (T. Cholesterol: 168 mg/dl, HDL – 29 mg/dl, LDL – 96 mg/dl, VLDL – 43 mg/dl, and triglycerides:213 mg/dl). Hormonal profile revealed normal TFT, FSH, and LH values (T3 - 3.66 pg/ml, T4 - 1.10 ng/ dl, TSH - 4.10mIU/L, LH - 5.22 mIU/ml, FSH - 7.43 mIU/ml, respectively). Total testosterone was 0.658 nmol/L (0.198 - 2.67 nmol/L), free testosterone was 0.649 pg/ml(0.4 - 4.18 pg/ml), DHEAS - 0.72 μg/ml (0.48 - 2.75 μg/ml), and 17 OHP - 1.44 ng/ ml (0.2 - 1.3 ng/ml) levels were normal.

Ultrasound abdomen and adnexae revealed- hepatomegaly with diffuse fatty infiltration, and both the ovaries revealed multiple small follicles in peripheral distribution with increase in stromal echogenicity suggestive of polycystic pattern of ovaries (right ovary measured – 3.2 × 1.9 × 1.7 cms with a vol of 5.5 cc. and left ovary measured– 2.7 × 1.8 × 1.5 cms with a volume of 4.1 cc) [Figure 1]**.** Non-enhanced computed tomographic scan of the neck, chest, and abdomen revealed excessive accumulation of face and neck with marked reduction of fat in the chest and abdomen [Figures 2 and 3]. There was a loss of fat from the breasts with preserved muscle bulk with fibroglandular tissue within the breasts. Peritoneal fat was preserved, and excessive deposition of fat was also noted in the perineal region and labia majora. These findings were suggestive of partial lipodystrophy associated with polycystic ovarian disease.

Case 2

A 26-year-old female from Nepal presented with the complaints of irregular periods from the age of 14 yrs. She had noticed hair growth on face and chin, which started from the age of 22 yrs, with hair getting coarser over the years. She had similar complains of changes in her looks like in the case 1, with muscles over the limbs getting more prominent with fullness over face and chin. Her maternal grandmother was diabetic and hypertensive. She has been on metformin for about 6 months, but she denied any change in appearance/hirsuitism with the medication.

On examination, – the patient was lean, with weight - 50.9 kgs., height – 148.5 cms., and BMI – 23.24 kg/m^2. Muscles of legs and arms and abdomen were hypertrophied, and less subcutaneous fat was noted. Acanthosis nigricans was present in the axillary region and around the neck. Clitoromegaly or labial hypertrophy was absent. Ferriman Gallawey hirsuitism score was 19. There were no acneform eruptions.

Lab evaluation revealed normal hemogram and biochemistry. Metformin was stopped for 1 week and GTT and other hormones evaluated. 1 and 2 hour glucose values were marginally high (0 hr - 85 mg/dl, 1 hr - 163 mg/dl, and 2 hr - 141 mg/dl) and were associated with a rise in both basal and post-glucose insulin levels (0 hr – 21.15 μIU/ml, 1 hr - 717.9 μIU/ml, 2 hr. – 717.9 μIU/ml).Her lipid profile demonstrated low HDL and a high triglyceride levels (Total cholesterol - 254 mg/dl, HDL cholesterol- 42 mg/dl, LDL cholesterol - 176 mg/dl, VLDL cholesterol - 36 mg/dl, triglycerides - 178 mg/dl). Hormonal profile revealed normal TFT, LH, FSH, and prolactin levels respectively

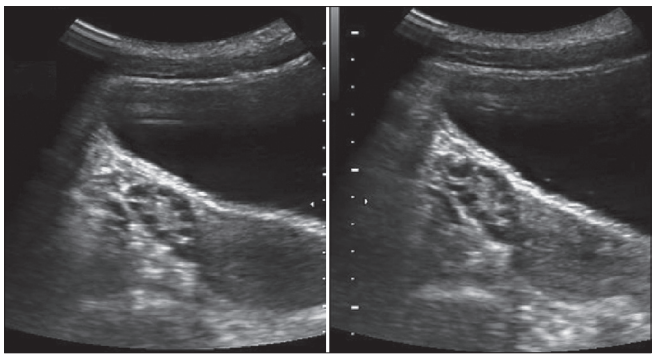

Figure 1: Transvesical ultrasound reveals polycystic ovaries with typical peripheral distribution of follicles (Case 1)

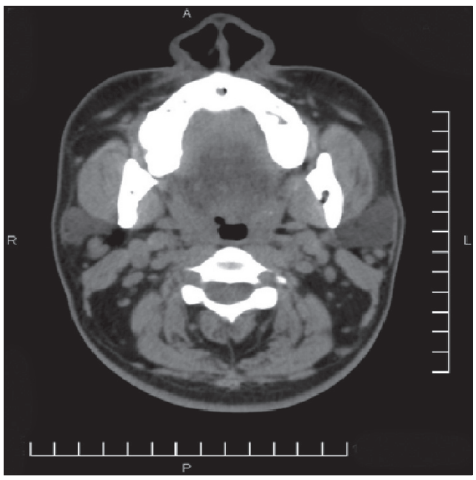

Figure 2: Axial non-enhanced CT at the level of maxilla reveals excessive accumulation of facial subcutaneous fat (Case 1)

(TSH - 1.8mIU/L, FT4 - 1.0 ng/dl, FT3 - 4.0 pg/ml, LH - 4.5 mIU/ml, FSH – 5.5 mIU/ ml,prolacin - 11.1 ng/ml). Total testosterone -3.34 nmol/L(0.198 -2.67 nmol/L) and DHEAS - 3.71 μg/ml (0.48 - 2.75 ug/ml), free testosterone -7.11 pg/ml (0.04 - 4.18 pg/ml)and 17 OHP - 3.01 ng/ml (0.2 -1.3 ng/ml) levels were elevated.

Ultrasonography adnexae revealed multiple cysts arranged along the periphery with echogenic stroma. (Right ovary measured to be 3.3 × 2.8 × 1.8 cm with a volume of 9.1 cc, and the left ovary measured 3.2 × 3.1 × 2.4 cms with a volume of 13.4 cc) [Figure 4].

Discussion

Lipodystrophy is a diverse clinical disorder with a complete or partial lack of adipose tissue (lipoatrophy) and / or lack of adipose tissue in certain body areas, with excess of adipose tissue (lipohypertophy) elsewhere.[6] Lipodystrophic patients manifest a group of unique features such as hyperlipidemia, insulin resistance, progressive liver disease, and increased metabolic rate. Patients with lipodystrophy have primarily a loss of mature, functional adipocytes as opposed to an absence of lipids in otherwise normal adipocytes.[1-3] The underlying defects could be associated with failure of adipogenesis,adipocyte apoptosis, or a failure to store triglycerides in existing adipocytes because of ineffective lipogenesis or excessive lipolysis.

Lipodystrophy is classified into generalized and partial both, these are further subdivided into congenital and acquired forms. Partial lipodystrophy is characterized by selective regional fat loss and is often associated with hypertrophy of adipose tissue in non-atrophic areas. The inherited forms could be face-sparing (dunnigan variety) or could be restricted to the extremities (Kobberling type).

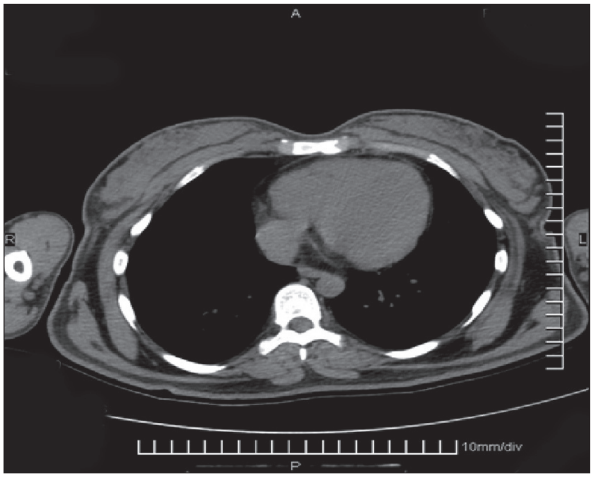

Figure 3: Unenhanced transverse CT scan at the level of mid abdomen shows sparing of the peritoneal fat (Case 1)

Other types of partial lipodystrophies may be due to mutations in genes like PPARG mutations (FPLD3,AKT2, and CAV1).[7] Acquired partial lipodystrophy show a female dominance and is characterized by fat loss that progresses in cephalocaudal fashion.[8,9] Excessive fat accumulation is seen over the lower abdomen, gluteal region, thighs, and calves.

Polycystic ovarian disease, a common endocrine disorder of reproductive age group, is characterized by oligo-amennorhea and hyperandrogenism, resulting in acne and hirsuitism and obesity. Insulin resistance and hyperinsulinemia play an important role in the pathogenesis of PCOS. Insulin synergizes with LH to stimulate theca cell steroid production from the ovaries.[4,5] Insulin also inhibits hepatic production of sex hormone binding globulin, thereby increasing free testosterones levels.Post-receptor binding defects in insulin signaling have been described in fibroblasts, adipocytes, and skeletal muscle cells of women with PCOS.[10,11] Insulin responsive transcription factor involved in fat and glucose metabolism has been shown to upregulate testosterone forming gene 17 βHSD type V. Since both insulin and testosterone enhance each other's action, it is controversial which of the two is primary and which is secondary.

Women with severe insulin resistance due to insulin receptor antibodies or due to genetic abnormalities of the insulin receptor have severe hyperandrogenism and virilization. Since lipodystrophy is a rather rare disorder, there are only a few cases of polycystic ovarian syndrome described in patients with lipodystrophy. According to Joy *et al*., 4 of the 25 patients with FPLD had PCOS in comparison with 14 of the 3,326 control subjects. They concluded that women with genetically confirmed FPLD have an increased risk for PCOS.[12] Vantyghem *et al*. reported that the mean number

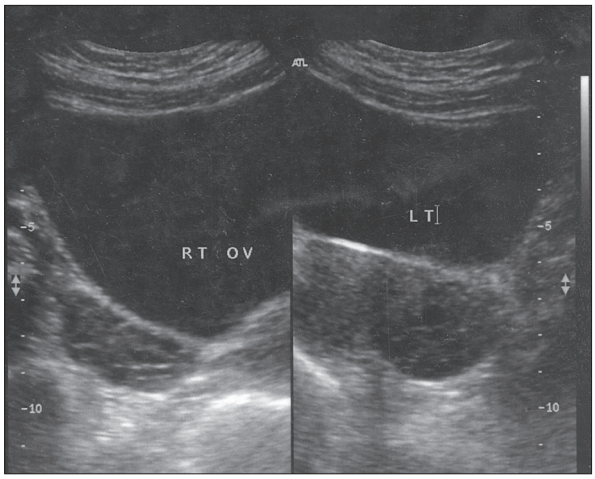

Figure 4: Transabdominal ultrasound in Case 2 shows bilateral enlarged ovaries with mild increase in stromal echogenicity and multiple small subcentimeter follicles arranged along the rim of the ovaries, consistent with polycystic pattern of ovaries

of live children per woman was 1.7 in LMNA-related FPLD affected patients vs. 2.8 in non-affected relatives. In this study, 54% of LMNA-mutated women exhibited a clinical phenotype of PCOS. 28% suffered from infertility, and 50% experienced at least one miscarriage.[13]

Both our patients had polycystic ovarian disease on ultrasound and also had very high insulin levels (above 700 μIU/ml post-glucose load) and impaired glucose tolerance, in spite of lean phenotype. One was hirsuite with high androgen levels, whereas the other had normal androgen levels with no hirsuitism. This possibly indicates that hyperinsulinemia is the primary factor involved in polycystic ovaries in patients with lipodystrophy, hyperandrogenism, and its peripheral manifestations ensue secondarily.

In conclusion, these were two rare cases of polycystic ovarian syndrome in patients with lipodystrophy.

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