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Familial partial lipodystrophy as differential diagnosis of polycystic ovary syndrome

Rodzinna częściowa lipodystrofia w diagnostyce różnicowej zespołu policystycznych jajników

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Abstract

According to current diagnostic criteria, polycystic ovary syndrome (PCOS) is effective as a diagnosis of exclusion. Here, we present a case of a 31-year-old woman with a history of oligomenorrhoea and hirsutism, who, despite a "muscular" appearance and a normal body mass index (22.27 kg/m^2), was found to have an extreme insulin resistance and diabetes accompanied by hyperandrogenism and polycystic ovaries. An autoimmune screen for possible latent autoimmune diabetes in adults was negative. She was subsequently found to have familial partial lipodystrophy (FPLD2, OMIM #151660) caused by an R482Q mutation in the *LMNA* gene encoding lamin A/C. This mutation results in arginine to glutamine substitution at the protein level, while phenotypically this condition presents with a loss of body fat, insulin resistance, dyslipidaemia, and other features mimicking PCOS. Interestingly her mother, with a history of myocardial infarction and diabetes at the age of 46 but no oligomenorrhoea, was also found to harbour the same mutation (*LMNA* R482Q).
Conclusions: Our case highlights the importance of assessment of adipose tissue distribution, as well as a significance of assessment of glucose tolerance and insulin resistance in the differential diagnosis of PCOS. Furthermore, patients with atypical adipose tissue distribution should be referred for formal genetic testing. **(Endokrynol Pol 2015; 66 (6): 550–554)**

Key words: *insulin resistance; lipodystrophy; polycystic ovary syndrome*

Streszczenie

Według aktualnych kryteriów diagnostycznych, zespół policystycznych jajników (PCOS) jest rozpoznaniem z wykluczenia. W pracy przedstawiono przypadek 31-letniej kobiety z wywiadem zaburzeń miesiączkowania o typie rzadkich miesiączek oraz hirsutyzmu, u której mimo „muskularnego" wyglądu i prawidłowego wskaźnika masy ciała (22,27 kg/m^2) stwierdzono bardzo wysoką insulinooporność, cukrzycę i hiperandrogenizm ze współistniejącą morfologią policystycystyczną jajników. Badania autoimmunologiczne w kierunku możliwej autoimmunologicznej cukrzycy u dorosłych (tzw. LADA) były ujemne. Przeprowadzono diagnostykę genetyczną, rozpoznając rodzinną lipodystrofię częściową spowodowaną przez mutację laminy A/C genu *R842Q* (FPLD2, OMIM # 151660). Powyższa mutacja prowadzi do podstawienia argininy glutaminą (R482Q) na poziomie białka, natomiast fenotypowo objawia się utratą tkanki tłuszczowej, insulinoopornością, dyslipidemią, jak również cechami naśladującymi PCOS. Co ciekawe u matki pacjentki również rozpoznano tę samą mutację (lamina A/C genu *R842Q*). U matki wystąpił również zawał serca i cukrzyca w wieku 46 lat, jednak nie było u niej zaburzeń miesiączkowania o typie oligomenorrhoea.
Wnioski: Opisany przypadek podkreśla znaczenie oceny dystrybucji tkanki tłuszczowej, jak również znaczenie oceny tolerancji glukozy i insulinooporności w diagnostyce różnicowej PCOS. Autorzy pracy zalecają również, aby pacjentki z nietypowym rozkładem tkanki tłuszczowej były kierowane do dalszej diagnostyki genetycznej. **(Endokrynol Pol 2015; 66 (6): 550–554)**

Słowa kluczowe: *insulinooporność; lipodystrofia; zespół policystycznych jajników*

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Presentation

A 31-year-old female (IZ-821203) presented with a history of oligomenorrhoea and excessive hair growth. Her menstrual cycles were irregular since menarche (age 12). She finally decided to investigate her irregular periods as she was planning to get married. She was a non-smoker, did not take any regular medication, and was working as a clerk in a regional court. She had a healthy sister (married with one healthy son) aged 34. Their mother suffered an anteroseptal myocardial infarction at the age of 46, as well as dyslipidaemia and diabetes mellitus, diagnosed at the time of myocardial infarction, and treated with insulin as an initial treatment (Mixtard 30 Penfill® 38 units in the morning 18 units in the afternoon). At the time of her myocardial infarction she had a normal body weight (BMI 24 kg/m^2). Two years later the mother was also found to have toxic multinodular goitre and was treated with

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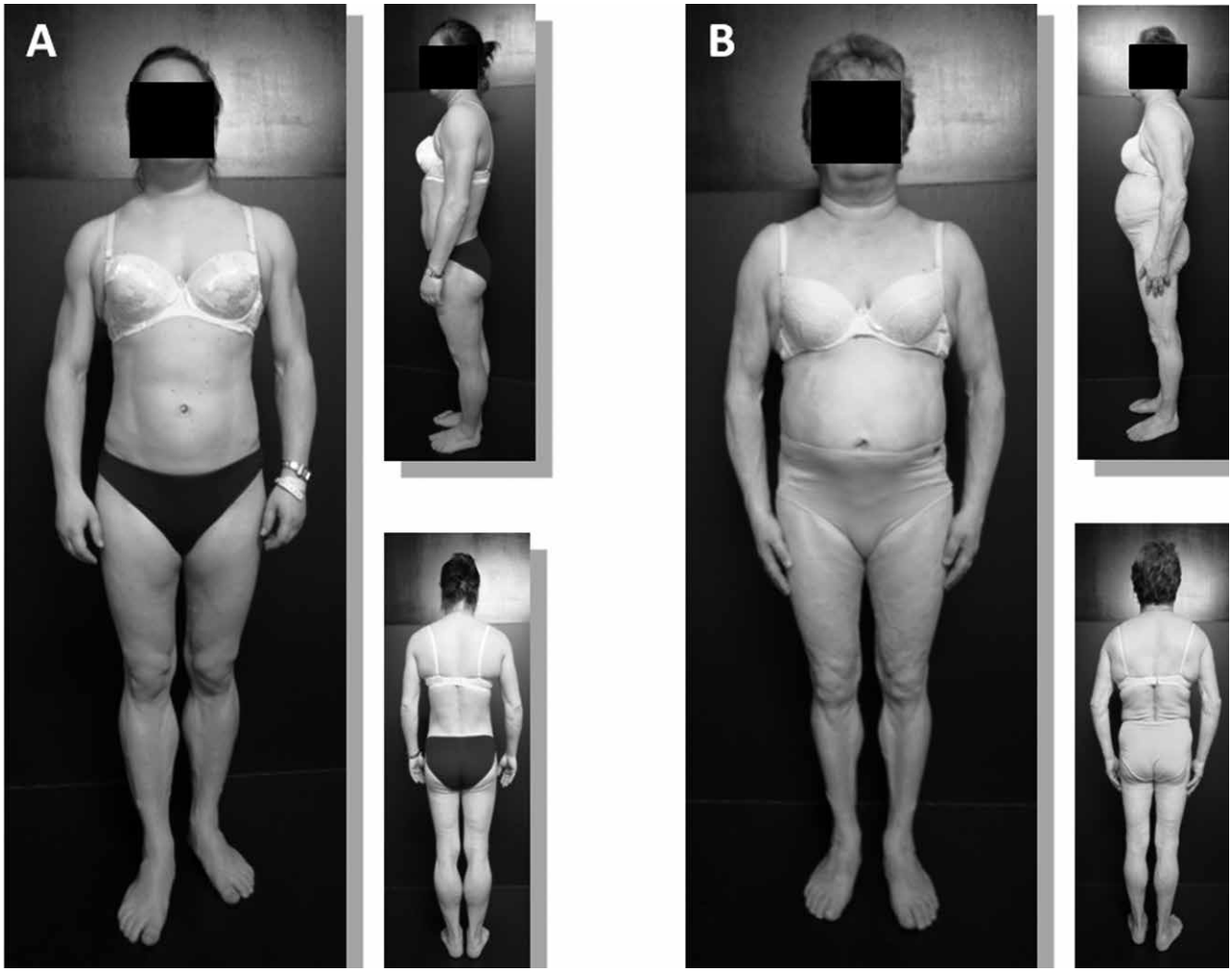

Figure 1. *Photographs depicting an anterior, side, and posterior view of a FPLD2-affected patient at the age of 31 years* **(A)** *and her affected mother at the age of 56 years* **(B)** *(reproduced with informed consent obtained from both patients)*

Rycina 1. *Fotografie przedstawiające pacjentki z FPLD2 od przodu, z boku i tyłu; pacjentka 31-letnia* **(A)** *i jej matka w wieku 56 lat* **(B)** *(zamieszczone po uzyskaniu świadomej zgody obu pacjentek)*

radioactive iodine. As her periods were regular during her reproductive years, she had never been investigated for potential hyperandrogenaemia or the presence of polycystic ovaries.

On examination the patient had a normal body weight (57 kg, height 160 cm, BMI 22.27 kg/m^2) and appeared strongly "muscular", though she denied doing any body-building exercises or taking dietary/muscle-building supplements (Fig. 1A). There was a moderate hirsutism (15 points on the Ferrimann-Galwey scale) but no clitoromegaly. An overnight 1.0 mg dexamethasone suppression test was performed before her admission and revealed satisfactory suppression of cortisol release (0.65 μg/dL/18 nmol/L), thus excluding hypercortisolaemia according to current guidelines [1]. Pelvic ultrasound examination revealed polycystic ovarian morphology.

Initial hormonal tests and lipids are presented in Table I.

Oral glucose tolerance test (OGTT) with insulin measurements was performed and revealed striking insulin resistance, i.e. out of proportion to her normal BMI, with glucose excursions into a diabetic range (Table II). She had a high insulin resistance index, calculated according to the Belfiore method [2], as well as high HOMA, calculated according to the formula HOMA = [glucose (mmo/L)] × [insulin (μIU/mL)]/22.5 [3].

Further tests revealed normal 17-hydroxy-progesterone responses during 250-μg short-Synacthen test, thus excluding congenital adrenal hyperplasia (Table III). Given the diagnosis of diabetes mellitus and her young age she was screened for antibodies typical for type 1 diabetes (in case of coexistent LADA — latent autoimmune diabetes in adults). The above-mentioned autoimmune screen was negative (Table IV).

Late onset (non-classical) congenital adrenal hyperplasia is suspected when 17-hydroxy-progesterone response to 250 μg Synacthen exceeds 10 ng/mL (30 nmol/L) [4]. In view of the above findings a suspicion of lipodystrophy was made, and she was referred

Table I. *Initial hormonal and metabolic parameters of a 31-year-old patient with a history of oligomenorrhoea and hirsutism (BMI 22.27 kg/m²)*

Tabela I. *Wstępne parametry metaboliczne i hormonalne 31-letniej pacjentki z wywiadem oligomenorrhoea i hirsutyzmu (BMI 22,27 kg/m²)*

Parameter	Concentration/Titre	Reference range
HbA_{1c} (%)	6.89	< 6
TSH [μIU/mL]	2.12	0.27–4.2
fT_3 [pg/mL]	3.61	2.6–4.4
fT_4 [ng/mL]	0.87	0.98–1.63
Anti-TPO antibodies [IU/mL]	< 10	< 34
Anti-Thyroglobulin antibodies [IU/mL]	< 10	< 115
LH [IU/L]	3.88	2.4–12.6
FSH [IU/L]	2.54	3.5–12.5
Estradiol [pg/mL]	198	12.5–166
Testosterone [ng/mL]	0.47	0.084–0.481
Androstenedione [ng/mL]	4.1	0.3–3.3
DHEA-S [μg/dL]	395.7	98.8–340
Prolactin [ng/mL]	6.53	3.9–25.4
Triglycerides [mg/dL]	443	< 150
Total cholesterol [mg/dL]	198	< 200
HDL-cholesterol [mg/dL]	32	> 40
LDL-cholesterol [mg/dL]	98	< 100

Table II. *Glucose and insulin during oral glucose tolerance test (75 g) in a 31-year-old patient investigated for oligomenorrhoea and hirsutism*

Tabela II. *Stężenie glukozy i insuliny w doustnym teście tolerancji glukozy (75 g) u 31-letniej pacjentki z wywiadem oligomenorrhoea i hirsutyzmu*

		0 minute	60 minutes	120 minutes
Glucose	[mmol/L]	5.83	15.61	12.61
Insulin	[μIU/mL]	19.59	255.2	231.0
	[pmol/L]	(117.5)	(1531)	(1386)

Conversion factor for insulin concentrations: 1 μU/mL = 6.00 pmol/L.
IRI — Insulin Resistance Index $_{(gly\text{-}area)}$: 1.81 (reference range: up to 1.25),
HOMA 5.076 (where HOMA = [glucose (mmo/L)] × [insulin (μIU/mL)]/22.5) [3]

Table III. *250-μg Synacthen test for cortisol and 17-hydroxy-progesterone secretion in a patient investigated for oligomenorrhoea and hirsutism*

Tabela III. *Test z 250 μg Synacthenu z oceną wydzielania kortyzolu oraz 17-hydroksy-progesteronu u badanej pacjentki z oligomenorrhoea i hirsutyzmem*

		0 minutes	30 minutes	60 minutes
Cortisol	[μg/dL]	9.66	35.17	40.16
17-hydroxy-progesterone	[ng/mL]	0.61	3.94	3.94

Table IV. *Results of the screen for antibodies typical for type 1 diabetes in a 31-year-old patient investigated for hirsutism and oligomenorrhoea*

Tabela IV. *Wyniki miana przeciwciał typowych dla cukrzycy typu 1 u 31-letniej pacjentki diagnozowanej z powodu hirsutyzmu i oligomenorrhoea*

Diabetes-related antibodies	Titre	Reference range
IAA [IU/mL]	0.4	0–2.4
IA-2Ab [IU/mL]	< 10.0	0–10
Anti-GAD [IU/mL]	< 10	0–10

IAA — insulin autoantibodies, IA-2Ab — protein tyrosine phosphatase-like protein antibodies, anti-GAD — anti-glutamic acid decarboxylase antibodies

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for genetic evaluation in the Department of Genetics, Polish Mother's Memorial Hospital — Research Institute, Lodz, Poland. Based on direct DNA sequencing of the *LMNA* gene the patient was diagnosed with familial partial lipodystrophy (FPLD2, OMIM #151660) caused by lamin A/C gene R482Q mutation (*LMNA* — NM_005572.3) (Fig. 2). Molecular diagnostic testing was performed in the Department of Clinical and Laboratory Genetics, Medical University in Lodz, Poland. Once a diagnosis of partial lipodystrophy was established in our patient, her mother, with a history of early myocardial infarction and diabetes mellitus, was also investigated. On examination she was found to have a similar body habitus, suggestive for partial lipodystrophy (Fig. 1B). She was eventually found to harbour the same mutation in the lamin A/C gene, thus confirming the presence of familial partial lipodystrophy. Family tree depicting both cases is presented in Figure 3.

In view of her marriage plans and possible future pregnancy slow release metformin therapy was started (Glucophage XR 750® up to 1500 mg/day and Dydrogesterone (Duphaston®) between the 16th and 25th day of menstrual cycle). A clinical review after about six months revealed her stable condition with an excellent glycaemic control with an HbA_{1c} of 5.2%. No change in her medication was undertaken at this point.

Discussion

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies affecting 4–8% of women in reproductive age [5]. PCOS is characterised by ovarian dysfunction (oligo- or anovulation), hyperandrogenaemia and/or hyperandrogenism, and/or polycystic ovaries, where according to current diagnostic criteria [6] other causes of menstrual irregularities and hyperandrogenism have been ruled out. We describe the case of

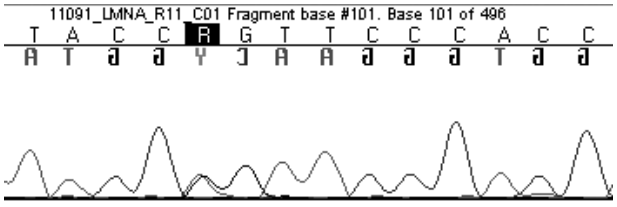

Figure 2. *Fluorescent peak trace chromatogram showing LMNA sequence with a base substitution from G to A in one allele. Mutation results in arginine to glutamine substitution (R482Q) at the protein level*

Rycina 2. *Chromatogram fluorescencyjny pokazujący sekwencję LMNA z zamianą pary zasad (G do A) w jednym allelu. Mutacja powoduje zamianę argininy na glutaminę (R482Q) w strukturze białka*

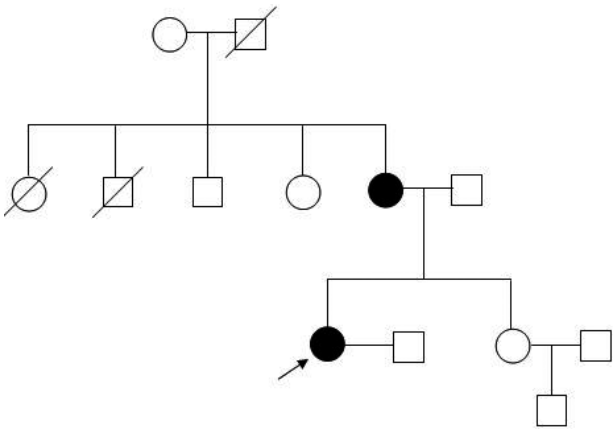

Figure 3. *Family tree depicting both a 31-year-old patient and her mother. The described FPLD2 affected patient marked by an arrow (→)*

Rycina 3. *Drzewo genealogiczne 31-letniej pacjentki i jej matki. Opisana pacjentka z FPLD2 zaznaczona strzałką (→)*

a normal-weight 31-year-old woman with typical features of PCOS (clinical, hormonal, as well as a polycystic ovarian morphology) accompanied, however, by profound insulin resistance and diabetes. Additionally, clinical examination revealed a "muscular" appearance with visible paucity of adipose tissue. In a standard situation patients who appear muscular typically have very good insulin sensitivity. In this case, however, the patient was found to be profoundly insulin resistant during OGTT, with peak insulin concentrations during OGTT exceeding 1500 pmol/L, which, according to Semple et al. [7], is suggestive of possible genetic syndromes associated with severe insulin resistance. Furthermore glucose levels at 120 minutes were already within diabetic range. Her mother had a similar body habitus, with early onset of cardiovascular complications (myocardial infarction at the age of 46) that coincided with a diagnosis of diabetes mellitus, treated with insulin since the time of diagnosis. It should be noted that her mother was originally considered to have type 1 diabetes because of relatively high glucose levels (about 300 mg/dL) in the setting of normal body mass index (24 kg/m^2) and relatively high insulin requirement (50 units/per day with body weight of 60 kg, i.e. 0.83 unit/kg). Final diagnosis was, however, only confirmed once partial lipodystrophy was diagnosed in her daughter. The phenotype with muscular hypertrophy and marked insulin resistance led us to screen for genes involved in familial partial lipodystrophy. The patient proved to be heterozygous for the mutation in the *LMNA* gene. We recognised familial partial lipodystrophy of Dunnigan variety [8] (FPLD2, OMIM #151660), complicated by severe insulin resistance and diabetes with secondary PCOS.

To the best of our knowledge this is the first case familial partial lipodystrophy described in Poland in the context of differential diagnosis of PCOS.

PCOS is thought to be a familial polygenic condition that is attributed to both genetic and environmental factors. There has been much debate about the aetiopathogenesis of PCOS in the past decade. Recently, several studies have indicated that a defect in insulin action may be the primary cause of PCOS. Thus, it should be kept in mind that Mendelian forms of insulin resistance, for which the genetic basis is known, have been described. Mutations in the insulin receptor (*INSR*) gene may result in a broad range of phenotypes such as severe autosomal recessive Donohue syndrome (Leprechaunism), which combines somatic anomalies and dysmorphic features with hyperinsulinaemia, hypertrichosis, acanthosis nigricans, and hypoglycaemia [9]. *INSR* mutations may also result in diabetes, insulin resistance, and acanthosis nigricans without other associated anomalies. Another group of disorders to be considered include lipodystrophies, which consist of a loss of body fat and insulin resistance. At least 11 genes with mutations have been reported so far. Two of the more common disorders include congenital generalised lipodystrophy, an autosomal recessive disorder with at least four genes (*AGPAT2*, *BSCL2, CAV1, PTRF*) identified, and familial partial lipodystrophy, an autosomal dominant disorder where at least four genes (*LMNA, PPARG, AKT3, PLIN1*) have been identified [10].

Familial partial lipodystrophy of Dunnigan variety (FPLD) is a rare autosomal dominant disorder, first described by Dunnigan et al. in 1974 [8], with over 300 subsequent patients being reported. It is caused by heterozygous mutations in the lamin A/C (*LMNA*) gene with a hot spot in C-terminal Ig-like domain. About 85% of FPLD2 patients present mutation at *LMNA* codon 482, substituting a basic amino acid (arginine) for a neutral one (glutamine, tryptophan). Knowledge on molecular mechanisms of *LMNA*-linked lipodys-

trophy remains scarce. Lamins encoded by the *LMNA* gene are intermediate filaments and are located at the filamentous network underlying the inner nuclear membrane. They interact with a variety of proteins in the nucleus and are important for nucleus assembly, structure, shape, and stability.

Patients with FPLD2 have normal fat distribution during childhood, but, following puberty, typically develop progressive loss of subcutaneous fat in the arms and legs with variable loss of fat in the body corpus, and often excess fat deposition in the face, neck, and intra-abdominal regions. Interestingly, prominent lipoatrophy is accompanied by an extensive musculature in patients with FPLD2. The phenomenon was recently explained with the discovery of interplay of *FXRP1* and *LMNA* proteins in preadipocytes. R482 substitution abrogates lamin A interaction with *FXRP1* protein leading to delocalisation and accumulation of the latter. The process, in turn, elicits switching an adipogenic differentiation into a myogenic program [11]. Other notable features include acanthosis nigricans and hepatomegaly (not present in our patient). Metabolic abnormalities related to insulin resistance such as diabetes mellitus, hypertriglyceridaemia, and hepatic steatosis are commonly noted. Metabolic abnormalities associated with FPLD typically manifest in early adulthood. Hypertriglyceridaemia is a common finding in FPLD and can be severe, potentially leading to acute pancreatitis. Finally, some patients with FPLD may develop myopathy, cardiomyopathy, and/or conduction system abnormalities.

A significant proportion of patients with FPLD develop hirsutism, menstrual abnormalities, polycystic ovaries, and other gynaecological complications necessitating, in some cases, early oophorectomy or hysterectomy [12]. These signs of androgen excess probably result from both the decrease in sex-hormone binding globulin (SHBG) production from the liver caused by hyperinsulinaemia, and the direct effect of insulin on theca cells leading to androgen production. Interestingly, there is evidence that insulin *per se* stimulates ovarian growth, even in the setting of low, e.g. prepubertal, gonadotropin concentrations [13], while treatment with leptin therapy improves insulin sensitivity leading to a fall in androgen concentrations and an increase in SHBG [14]. There is also evidence that thiazolidinediones are superior to metformin in the treatment of FPLD [15]. However, in view of the procreative plans of our patient, her good glycaemic control on a diet and metformin, as well as a lack of any reimbursement of the costs of thiazolidinediones in the Polish health insurance system, we decided to continue treatment with metformin with plans to instigate insulin treatment, once her final plans for pregnancy are established. However, we keep in mind the possibility of pioglitazone treatment after possible pregnancy and breastfeeding in case of significant deterioration of her glycaemic control.

In summary, although the association of PCOS with obesity and insulin resistance is well known, not all women with PCOS are clinically obese. The reported case underlines the importance of physical examination, which can suggest important hints to diagnoses that extend beyond the standard range of conditions associated with oligomenorrhoea and/or hirsutism/ /hyperandrogenaemia. Recognition of lipodystrophy is, however, very important for the later diagnosis of more serious metabolic abnormalities in patients and their families. Hence, the awareness of a possibility of familial partial lipodystrophy is important for both endocrinologists and gynaecologists, as well as for physicians involved in the treatment of diabetes mellitus. Our case is thus an important reminder that the assessment of insulin sensitivity and adipose tissue topography is a key part of the initial evaluation of patients with PCOS. It is important to consider the diagnosis of FPLD in lean, muscular women who have polycystic ovarian syndrome.

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