INTRODUCTION

Lipodystrophy syndromes (LD) are a heterogeneous group of congenital or acquired disorders characterized by generalized or partial loss of adipose tissue, depending on the types of LD. Generalized LD (GLD) affects the entire body, whereas partial LD (PLD) occurs only in selective parts of the body, such as arms and legs. To facilitate diagnosis and management, LD has been further divided into four categories including congenital generalized LD (CGL), acquired generalized LD (AGL), familial partial LD (FPLD), and acquired partial LD (APL).

LD syndromes are extremely rare diseases with an estimated prevalence of 1.3–4.7 cases/million population for all LD types (excluding those of HIV-associated), 0.2–1.0 cases/million for GLD, and 1.7–2.8 cases/million for PLD worldwide. Another study reported that the estimated prevalence of GLD was 0.96 cases/million and PLD was 1.67 cases/million. Similarly, the estimated prevalence of FPLD is as low as 1 case/million, while that of CGL was approximately around 1 case/10 million population.

LD often causes hormonal and metabolic derangements, leading to the emergence of severe comorbidities and complications, or even death. Adipose gland deficiency causes insulin resistance, which is responsible for serious complications such as hypertriglyceridemia (HTG), diabetes mellitus (DM), hepatic steatosis, and non-alcoholic liver disease (NAFLD). Mortality among patients with LD syndromes is usually related to cardiovascular diseases (which are mostly associated with hyperlipidemia), liver disease, kidney disease, acute pancreatitis, and sepsis. Nevertheless, diagnosis and management of LD are still challenging due to its rarity and limited diagnostic criteria. Meanwhile, appropriate management is critical to correct metabolic abnormalities and lower the presence of severe comorbidities among patients. In this article, we reported a case of a patient with LD syndromes, as well as its diagnosis and possible management. This case report follows the CARE guidelines as presented in other case-reports.

CASE PRESENTATION

A 27-year-old female patient came to Dr. Soetomo General Academic Hospital, Surabaya, Indonesia on July 18th, 2019 with a chief complaint of abdominal pain for the past two weeks, particularly at the epigastrium region. The pain increased...
after eating and drinking. The patient also complained of diarrhea during the same period with a frequency of 3–4 times/day. No blood or mucus was observed during diarrhea. Additional complaints included recurrent nausea and vomiting (4–5 times/day) since a month ago and blurred vision since 3 months ago. The patient also reported weight loss and decrease in appetite.

The patient had a history of unidentified dermatologic conditions when she was 8 years old and started to get ill quite frequently since then. At the age of 10 years, she had a history of pneumonia with complete medical treatment. The patient was diagnosed with T2DM at the age of 15 years (HbA1C: 10.3%), when she presented with unintentional weight loss. Four years later, the patient started insulin therapy until it was replaced with acarbose and glimepiride a year earlier. However, the patient stopped glycemic control and medication several months prior to the hospital admission. The patient also had a history of dyslipidemia and severe HTG, with triglyceride levels of 2.030 mg/dL (tested in 2011). Three months before hospitalization, the patient had been diagnosed with diabetic retinopathy and glaucoma. A history of hypertension was not identified. The menstrual cycle was

Figure 1. The patient showed subcutaneous fat loss from the limbs, particularly in the extremities, and excessive fat accumulation in the face and slightly on the neck.

Table 1. The results of the patient’s laboratory test

<table>
<thead>
<tr>
<th>Lab Parameters (unit)</th>
<th>Initial test</th>
<th>Day 2</th>
<th>Day 5</th>
<th>Day 7</th>
<th>Day 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>8.0</td>
<td>8.3</td>
<td>8.0</td>
<td>6.6</td>
<td>9.1</td>
</tr>
<tr>
<td>Erythrocytes (/µL)</td>
<td>2.94 x 10⁶</td>
<td>3.04 x 10⁶</td>
<td>2.49 x 10⁶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrits (%)</td>
<td>22.2</td>
<td>23.3</td>
<td>22.3</td>
<td>18.9</td>
<td></td>
</tr>
<tr>
<td>Mean corpuscular volume (fL)</td>
<td>75.5</td>
<td>76.4</td>
<td>74.6</td>
<td>75.6</td>
<td></td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin (pg)</td>
<td>27.2</td>
<td>27.0</td>
<td>26.4</td>
<td>26.4</td>
<td></td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin Concentration (g/dL)</td>
<td>36.0</td>
<td>35.0</td>
<td>35.4</td>
<td>34.4</td>
<td></td>
</tr>
<tr>
<td>Leukocytes (/µL)</td>
<td>4,380</td>
<td>4,190</td>
<td>4,400</td>
<td>3,600</td>
<td>4,600</td>
</tr>
<tr>
<td>Platelets (/µL)</td>
<td>76,000</td>
<td>82,000</td>
<td>86,000</td>
<td>84,000</td>
<td>87,000</td>
</tr>
<tr>
<td>Basophils (%)</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>78.1</td>
<td>77.0</td>
<td>64.0</td>
<td>70.8</td>
<td>74.2</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>17.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Eosinophils (%)</td>
<td>1.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td>2.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum glutamic oxaloacetic Transaminase (U/L)</td>
<td>26.0</td>
<td>15.0</td>
<td>21.0</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>Serum glutamic pyruvic Transaminase (U/L)</td>
<td>33.0</td>
<td>25.0</td>
<td>25.0</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
<td>31.0</td>
<td>22.0</td>
<td>34.0</td>
<td>34.0</td>
<td>28.0</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>2.11</td>
<td>2.87</td>
<td>2.62</td>
<td>2.50</td>
<td>2.48</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.6</td>
<td>3.2</td>
<td>2.9</td>
<td>2.7</td>
<td>2.72</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>138.0</td>
<td>135</td>
<td>138</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.9</td>
<td>3.8</td>
<td>3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>101.0</td>
<td>99</td>
<td>106</td>
<td></td>
<td></td>
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<tr>
<td>Random blood glucose (mg/dL)</td>
<td>175</td>
<td>177</td>
<td>225</td>
<td>89</td>
<td>109</td>
</tr>
<tr>
<td>Amylase (U/L)</td>
<td>24</td>
<td></td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipase (U/L)</td>
<td>124</td>
<td></td>
<td>88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>627</td>
<td>545</td>
<td>567</td>
<td>547</td>
<td>547</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>924</td>
<td>1,033</td>
<td>878</td>
<td>812</td>
<td></td>
</tr>
<tr>
<td>High-density lipoprotein (mg/dL)</td>
<td>61</td>
<td>57</td>
<td>50</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Low-density lipoprotein (mg/dL)</td>
<td>183</td>
<td>214</td>
<td>180</td>
<td>172</td>
<td></td>
</tr>
<tr>
<td>Thyroid-stimulating hormone (uIU/mL)</td>
<td>1,302</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
normal until 3 months earlier. A family history of DM (all siblings) was reported.

Physical examination revealed a fair general condition, with a Glasgow Coma Scale (GCS) of E4M6V5. Vital signs showed blood pressure of 180/110 mmHg, heart rate of 107 x/minute, respiratory rate of 20x/minute, temperature of 36.7°C, and oxygen saturation of 99% (without oxygen supplementation). Body mass index (BMI) was 17.4 kg/m² (weight: 38 kg and height: 142 cm). The head and neck examinations within normal limits. The jugular venous pressure (JVP) and lymph nodes were normal. Chest examination indicated within normal limits. The lung-hepatic border was found in the 6th intercostal space in the right midclavicular line. A regular single S1 and S2 were detected. The results of the lung examination showed within normal limits. Abdominal examination indicated increased bowel sounds, distended abdomen, abdominal pain at epigastrium (pain scale: 4), hepatomegaly 3 fingers below arcus costae, splenomegaly as big as Schuffner 2 Hocket 2 (S2H2), minimal ascites, epigastric tenderness, and non-palpable liver and spleen. Examination of the extremities revealed cold, wet, and pale acral. There are hypopigmented macules in the cruris dextra et sinistra. Capillary refill time was less than 2 seconds. No edema was observed. Subcutaneous adipose tissue was absent in some parts of the body, especially in the extremities, and excessive fat accumulation on the face and slightly on the neck (Figure 1).

Initial laboratory examination indicated low hemoglobin (8.0 g/dL) and platelet (76,000/µL) levels. Peripheral blood smear suggested normochromic normocytic anisocytosis anemia and thrombocytopenia. A high level of serum creatinine (2.2 mg/dL) was recorded, considered to indicate kidney damage. Random blood glucose (RBG) levels revealed hyperglycemia (175 mg/dL). Urine test showed proteinuria (4+), but negative for glucose, bilirubin, ketone, erythrocyte, leucocytes, and nitrite (Table 1). The result of the chest x-ray was within normal limits.

Based on all those data the patient was diagnosed with abdominal pain, T2DM, acute gastroenteritis, diabetic nephropathy, diabetic retinopathy with Osmotic Demyelination Syndrome (ODS), glaucoma oculus sinister (OD), bicytopenia (anemia and thrombocytopenia), and stage II hypertension JNC VII (The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure). The patient was then treated with a high protein B1 diet 1500 kcal daily, NaCl 0.9% infusion 1000cc within 24 hour intravenous, omeprazole 40 mg every 24 hour intravenous, metoclopramide 10 mg every 8 hour intravenous, paracetamol 500 mg per oral every 8 hour, amlodipine 10 mg per oral every 24 (evening), losinopril 5 mg per oral every 24 hour (morning), and timolol 2 drops every 12 hour in the left eye. The patient was then planned for an abdominal USG and thyroid stimulating hormone (TSH) level examination.

On the second day of treatment, the patient still complained of abdominal pain (pain scale: 3), nausea, and bloating sensation, causing poor appetite. The frequency of diarrhea was 3-4 times/day, unaccompanied by either blood or mucus. Urine volume was 1500 mL within 24 hours. Vomiting and fever were denied. The vital signs showed hemodynamic stability: blood pressure of 160/90 mmHg, heart rate of 105 x/minute, respiratory rate of 22x/minute, and temperature of 36.2°C. Laboratory examination indicated anemia, thrombocytopenia, kidney disease, and an additional diagnosis of hyperlipidemia (total cholesterol: 627 mg/dL; triglyceride: 924 mg/dL; LDL: 183 mg/dL) (Table 1). Simvastatin 20 mg per oral every 24 hours (evening) was added for therapy.

Abdominal pain and nausea were slightly reduced on the fifth day of treatment (pain scale: 3). The patient was able to eat despite the bloating sensation being persistent. Vomiting was denied and diarrhea had been cured. Physical examination exhibited general weakness but the patient was completely conscious (compos mentis). The vital signs were as follows: blood pressure of 160/80 mmHg, heart rate of 102 x/minute, respiratory rate of 22 x/minute, and temperature of 37.2°C. Urine volume was under control (1800 mL within 24 hours). Laboratory findings revealed anemia, thrombocytopenia, kidney disease, T2DM (RBG: 225 mg/dL), decreased serum albumin level (<3 g/dL), and hyperlipidemia (Table 1). Abdominal USG indicated bilateral parenchymal kidney disease, splenomegaly, gallbladder polyps, and ascites, whereas liver/pancreas/bladder/uterus/the right and left adnexa were observably normal. These data led to the diagnosis of LD syndromes. In fact, as informed by the patient's family, LD syndrome had been diagnosed previously when the patient presented with high levels of cholesterol and blood sugar. Additional treatments were given to the patient, including pioglitazone 15 mg per oral every 24 hours, fenofibrate 300 mg per oral every 24 hours, and insulin glargine 6 IU/24 hours injected subcutaneously.

On the 7th day of therapy, the patient admitted less abdominal pain (pain scale: 2). Nausea appeared while eating but no vomiting. Diarrhea had completely stopped and fever was denied. The patient complained of weakness and fatigue. Physical examination showed general weakness, compos mentis with GCS of 456, blood pressure of 150/80, heart rate of 105 x/minute, respiratory rate of 22 x/minute, and temperature of 36.7°C. The head and neck examination exhibited anemic conjunctiva. Urine volume was within the normal limit (1800 mL/24 hour). Laboratory evaluation revealed declined Hb levels (6.6 g/dL), thus 1 bag/day of pack red cells (PRC) transfusion was performed to achieve a Hb target of ≥ 8 g/dL. There was also a reduction in RBG level, thus subcutaneous insulin glargine therapy was lowered to 4 IU/24 hours, whereas other previous medications were continued.

Two days later, the patient's condition had improved. Abdominal pain (pain scale: 1) no longer interfered with the patient's activities. The patient was able to eat properly although in the presence of nausea. No vomiting, diarrhea, or fever was reported. Physical examination suggested general weakness, compos mentis, and blood pressure of 140/80, urine volume remained the same (1800 mL/24 hour). The patient was discharged and underwent outpatient treatment with pioglitazone 15 mg, fenofibrate 300 mg, simvastatin 20 mg, omeprazole 20 mg, metoclopramide 10 mg, and...
amlo migraine 10 mg per oral every 24 hour; metoclopramide 10 mg per oral every 8 hour; timolol 2 drops in the left eye every 12 hour; and insulin glargine injection 4 IU every 24 hour subcutaneously.

**DISCUSSION**

LD is a group of various congenital and acquired disorders characterized by a total or partial reduction of adipose tissue, depending on LD types. CGL is characterized by a complete absence of body fat starting at birth or shortly after, accompanied by generalized muscularity and metabolic derangements. AGD presents similar phenotypes as CGL, except fat loss develops during childhood or adolescence, unaccompanied by generalized muscularity. FPLD exhibits a partial loss of subcutaneous fat, particularly from limbs, and manifests with several metabolic disturbances. In its subtype of FPLD2, increased muscularity and excess accumulation of fat in the face and neck are observed. APL presents with subcutaneous adipose tissue loss from the face, neck, upper extremities and continues to the trunk. Excess fat over the gluteal region, thighs, and calves are also observed in some patients.

The degree of fat loss is correlated with the severity of the metabolic abnormality. Patients with severe LD show severe insulin resistance which often manifests as DM, accompanied by severe hyperlipidemia, severe HTG, progressive liver disease, and increased metabolic rate. The absence of adipose glands in LD patients decreases the ability of the body to store long-term energy, which results in impaired insulin sensitivity and fat metabolism.

Lack of adipose tissue lowers the release of adipokines, leading to increased levels of triglyceride and lipid intermediates in the circulation, triggering ectopic fat accumulation in other organs including the liver and muscle. Reduction in adipose tissue also impedes leptin production which plays important roles in glucose and fat homeostasis. Leptin itself is responsible for appetite regulation, in which low leptin levels in patients with LD trigger uncontrolled hunger/hyperphagia.

In addition, both congenital and acquired LD are associated with kidney disease with proteinuria, glomerulosclerosis, or membranoproliferative. Other metabolic abnormalities accompanying LD include, acute pancreatitis, hepatic cirrhosis, and premature cardiovascular disease.

Diagnosis of LD is often clinically established based on the patient’s medical history, distribution of adipose glands in the body, physical examination, and metabolic abnormalities. This syndrome should be suspected in any patient with generalized or partial lack of adipose tissue, failure to thrive, early onset of insulin resistance and DM, severe HTG that is nonresponsive to conventional therapy (triglyceride levels stay persistently ≥500 despite receiving optimized therapy), hepatic steatosis, hepatosplenomegaly, significant hyperphagia, and a history of pancreatitis due to HTG. Decreased adiponectin levels are among other considerably important signs for the diagnosis of this syndrome.

Family medical record evaluation helps distinguish the diagnosis of congenital and acquired LD, and analysis of C3 and C4 concentrations can support the diagnosis of the later LD syndrome (which often decreases). Furthermore, patients with LD often come with complaints of decreased quality of life, increased quality and intensity of pain throughout the body, sleep disturbances, gastrointestinal dysmotility, and mood disturbances (depression and anxiety).

The patient in the current case had a history of getting ill frequently and losing body fat at the age of 8 years. By then, the patient reported an increase in appetite, yet on the contrary, started to experience unintentional weight loss. At the age of 15 years, the patient was diagnosed with T2DM (HbA1C: 10.3%; C-peptide: 4.2 ng/mL, tested in 2008) and had a history of severe HTG (triglyceride level: 2.030 mg/dL) recorded in 2011. Complement analysis in 2017 showed normal C3 (98.2 mg/dL) and slightly increased C4 (54.3 mg/dL) levels. During the present hospital admission, absence of subcutaneous adipose tissue in some parts of the body, especially in the extremities, and excessive fat accumulation on the cheeks and slightly on the neck were observed on physical examination.

There was also enlargement of the liver and spleen, as well as the presence of ascites. Diabetic retinopathy was also evidenced. Blood screening revealed hyperglycemia, dyslipidemia, and severe HTG (average triglyceride: 912 mg/dL). The urine analysis results were considered indicative of renal dysfunction (creatinine level: 2.11 mg/dL and proteinuria: 4+) (Table 1). The patient was diagnosed with familial partial lipodystrophy 2 (FPLD2) (Dunnigan syndromes) based on all these medical history, physical examination, and laboratory investigations.

The patient in this case also complained of intermittent abdominal pain in the solar plexus for the past 2 weeks before the hospital admission, especially during eating or drinking. The pain reportedly worsened over time, sometimes radiating through to the back. Pain accompanied by nausea, and sometimes vomiting, had started a month earlier. At the hospital admission, abdominal distension and tenderness in the epigastric region were detected during physical assessment. The results of abdominal USG indicated bilateral parenchymal kidney disease, splenomegaly, gallbladder polyps, and ascites, whereas liver/pancreas, bladder/uterus/the right and left adnexa were found normal. Lipase levels were within normal limits (Table 1). In this case, abdominal pain was seemingly associated with severe HTG and chronic pancreatitis.

As previously reported, triglycerides levels of >1000 mg/dL may present the symptoms of failure to thrive in children, eruptive xanthoma, lipemia retinal, hepatosplenomegaly, abdominal pain, recurrent nausea and vomiting, and the risk of acute pancreatitis. Chronic pancreatitis also presents the symptom of constant dull abdominal pain extended to the back, along with complaints of nausea, vomiting, and rapid weight loss as a result of decreased calorie intake. Underweight (BMI of <18.5 kg/m²), in turn, increases the risk of comorbidities among patients, including those with LD.

There is currently no cure for LD. Treatments restricted only to limiting or preventing comorbidities and complications of the syndromes. Lifestyle modification including diet and exercise are essential for metabolic disorders. There is no specific diet basically available to correct adipose gland deficiency; however,
a low-fat diet to reduce HTG in patients is recommended. A low-carbohydrate diet, along with insulin or other antidiabetics such as metformin or thiazolidinediones, may also be given to LD patients with DM. Administration of metformin and/or thiazolidinediones is expected to correct HTG and hyperglycemia. Thiazolidinediones in particular, which are PPARG modulators, are also expected to increase adiponectin levels. High-dose insulin is usually required to control insulin resistance and blood sugar levels. A combination of fibrates and statins can be prescribed for HTG control to reduce the risk of acute pancreatitis. Another drug, metreleptin (a leptin analogue), is suggested as adjuvant treatment as a replacement therapy for the treatment of complications owing to leptin deficiency. In partial LD, metreleptin is designated if leptin levels are below 4 ng/mL, together with the presence of severe metabolic abnormalities (HbA1C > 8% and triglyceride > 500 mg/dL). Metreleptin is currently the only drug approved for the treatment of LD of all ages.

Patients in this case received insulin injections and pioglitazone for the treatment of hyperglycemia. Pioglitazone was also expected to reduce HTG in addition to simvastatin and fenofibrate. Several symptomatic drugs such as paracetamol, omeprazole, metoclopramide were given to reduce symptoms of the disease. Timolol drops to treat glaucoma, as well as lisinopril and amlodipine to treat hypertension were also prescribed. Metreleptin therapy could not be performed since it was not available in the current hospital.

CONCLUSION

We report a case of a 27-year-old woman with a chief complaint of abdominal pain, accompanied by nausea and vomiting for the past 2 weeks before being admitted to the hospital. The patient was diagnosed with lipodystrophy (LD) syndromes based on all the medical history, physical examination, and laboratory findings. The complaints were assumingly associated with severe metabolic disturbances, which included severe HTG and uncontrolled T2DM as result of adipose gland deficiency. Therapeutic management was mainly in the form of symptomatic treatments to prevent progression to severe comorbidities and complications associated with metabolic derangements. There is no cure currently for LD syndrome. Thereby, increasing knowledge and awareness of the symptoms indicative of LD is prominent to prevent and ameliorate comorbidities.

PATIENT CONSENT

The patient had agreed and signed informed consent regarding publishing this clinical case in an academic journal without exposing the patient's identity.

ACKNOWLEDGMENTS

The authors would like to thank the patient and all the hospital staff in the department of internal medicine involved in the patient's care.

DISCLOSURE OF CONFLICTS OF INTEREST

The authors declare no conflict of interest regarding the manuscript.

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None.

AUTHOR CONTRIBUTION

Both authors contributed equally to the study.

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