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A woman with multifocal lipodystrophy in unilateral trunk and extremities

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Abstract

Adipose dystrophy, also known as lipodystrophy, is a heterogeneous disease characterized by the complete or partial loss of adipose tissue. In some cases, patients with lipodystrophy may exhibit fat accumulation in other areas of the body, as well as metabolic abnormalities such as insulin resistance, hyperlipidemia, liver disease, and increased metabolic rate. The condition may also be associated with gene mutations, including those in acylglycerol-3-phosphate O-acyltransferase 2 (AGPAT2), Berardinelli–Seip Congenital Lipodystrophy 2 (BSCL2), caveolin-1 (CAV1), polymerase I and transcript release factor (PTRF), lamins A (LMNA), zinc metalloproteinase (ZMPSTE24), peroxisome proliferator-activated receptor gamma (PPARG), v-AKT murine thymoma oncogene homolog 2 (AKT2), perilipin 1 (PLIN1), and proteasome subunit, β-type, 8 (PSMB8). Lipodystrophy can be either congenital or acquired, and it may present as a systemic or localized condition. In this report, we describe a rare case of localized lipodystrophy characterized normal development and partial multifocal fat atrophy. This case aims to enhance clinicians' understanding of the clinical manifestation of this uncommon disease.

Abbreviations:

HIV	- Human immunodeficiency virus
CT	- Computed tomography
ECG	- Electrocardiogram
EEG	- Electroencephalogram
EMG	- Electromyogram
MRI	- Magnetic resonance imaging
MRA	- Magnetic resonance arteriography
CGL	- Congenital generalized lipodystrophy
AGPAT2	- 1-acylglycerol-3-phosphate O-acyltransferase 2
BSCL2	- Berardinelli-Seip congenital lipodystrophy 2
CAV1	- Caveolin 1, 22kDa (caveolae protein, 22kDa)
PTRF	- Polymerase I and transcript release factor
FPLD	- Familial partial lipodystrophy
LMNA	- Lamins A
PPARG	- Peroxisome proliferative activated receptor gamma
AKT2	- v-AKT murine thymoma viral oncogene homolog 2
PLIN1	- Perilipin 1
MAD	- Mandibuloacral dysplasia
ZMPSTE24	- Zinc metalloproteinase STE24
PSMB8	- Proteasome subunit β-type 8
DXA	- Dual-energy X-ray absorptiometry

CASE REPORT

CASE

A 23-year-old female was admitted to the hospital with a history of "atrophy of the left trunk and limbs for 8 years, worsening over the past 2 years". The patient reported experiencing atrophy of soft tissue on her left trunk and limbs without an obvious cause since the age of 15. Initially, she noticed a depression on her left thigh, which gradually progressed to include sunken atrophy of the left hip, left chest, left abdomen, left axilla, and ultimately, the left upper and lower extremities. She frequently experienced itching, burning sensations, and muscle throbbing in the affected parts. As the atrophy progressed, the skin overlying the affected became thin, hard and dark. Over the past two years, she felt that her symptoms gradually worsened, and occasionally experienced numbness in her left little finger and the fifth toe of her left foot. She also reported a slight loss of memory and a history of "hypotension" without fatigue, blurred vision, syncope, convulsions, balance disturbances, choking, or dysphagia. Her nutrition, diet, growth and development after birth have been normal, and she has been able to study and work normally. She has no history of abnormal blood glucose or blood lipids, liver or renal disease, digestive tract disorders, heart disease, thyroid disease, anemia, trauma, liposuction or cosmetic surgery. In addition, she has no history of long-term medication use or HIV infection. She also denied any hereditary issues or consanguineous marriage within her family.

Physical examination: blood pressure was 75/54 mmHg. There was localized subcutaneous soft tissue reduction in the left axilla, left chest, left abdomen, left hip, left upper and lower extremities. The left upper and lower extremities were significantly thinner compared to the opposite side. The affected skin was tough, thin, dark and sensitive, with visible subcutaneous vascular patterns, and elicited stinging pain upon touch (Figure 1). No obvious mandibular deformity was observed. Muscle strength and muscle tone in the affected limbs were normal. Physiological reflexes were present, and pathological reflexes were not elicited. No significant abnormalities were found in the comprehensive neurological examination.

Auxiliary examination: Urinary red blood cell count was 10 p/μL, and urinary leukocyte count 27 p/μL. Serum albumin was 38.4 g/L, aspartate aminotransferase was 12.40 IU/L, potassium was 3.23 mmol/L, and chlorine was 111.00 mmol/L. Uric acid was 487.7 μmol/L. The blood antinuclear antibody spectrum showed that the antinuclear antibody was positive (+, 1:100) without any specific positive antibody. Blood thyroid microsomal antibody was 71.91%, and thyroglobulin antibody 258.70%. Other tests, including blood routine, erythrocyte sedimentation rate, liver and kidney function, muscle enzyme, lipid, glucose, rheumatoid antibody, antiphospholipid antibody, and coagulation, showed no significant abnormalities. Tests for hepatitis B, syphilis, and HIV were negative. Ultrasound revealed a congenital "bilobar" malformation of aortic valve with mild regurgitation and a patent foramen ovale. No significant abnormality was observed in the liver, biliary ducts, pancreas, spleen, and kidney on ultrasound. CT scans of the heart and

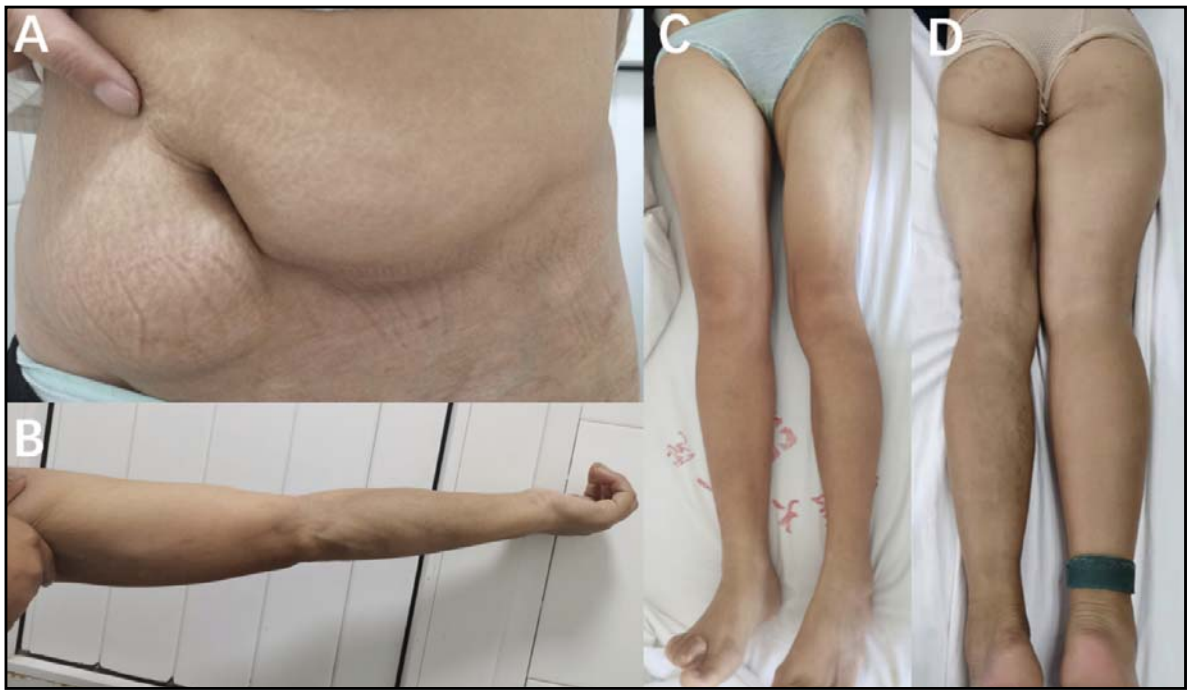

Fig. 1. Subcutaneous soft tissue loss can be seen in left lower abdomen (A), left forearm (B), front of left lower limb (C) and back of left lower limb (D). Thin and dark skin and subcutaneous vascular shadow can be seen in the affected site, and the left limb is thinner than that the opposite side.

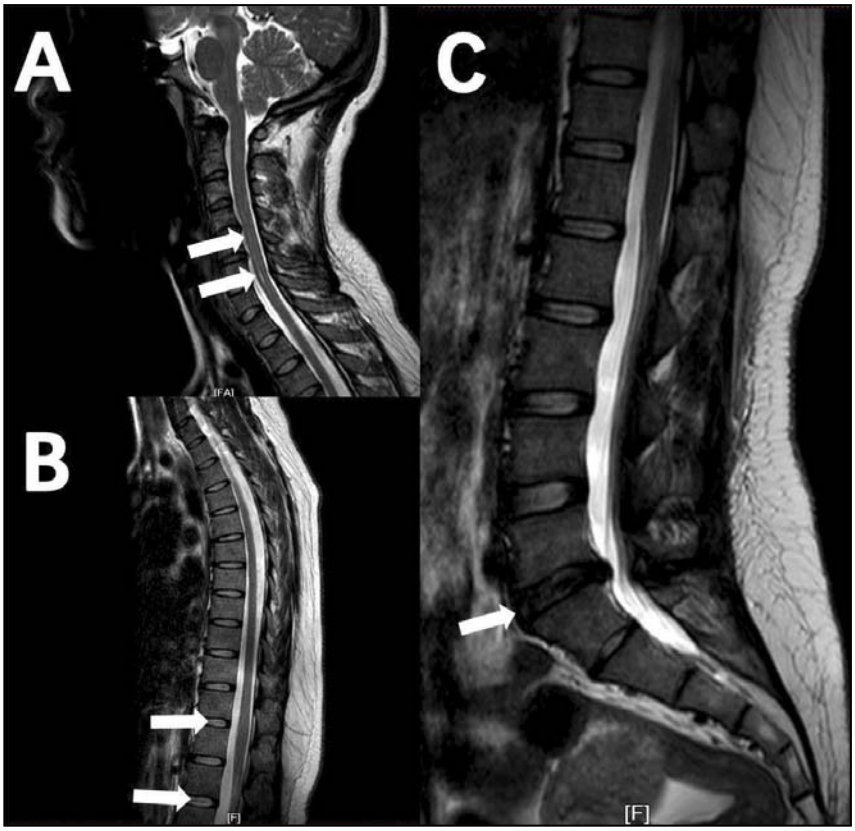

Fig. 2. It showed high signal on T2 of C5-7 segment (A) and degeneration of thoracic intervertebral disc (B), degeneration of lumbar intervertebral disc (C).

lungs showed no abnormalities. Ambulatory blood pressure monitoring showed an average blood pressure of 95/55 mmHg, with the highest being 117/64 mmHg, and the lowest blood being 83/44 mmHg. ECG revealed sinus arrhythmia with no abnormal rhythm detected. EEG and EMG were normal. MRI and MRA of the head, neck, and spine showed lacunar changes in the left basal ganglia, cervical intervertebral disc degeneration, posterior protrusion of the C4-6 intervertebral discs, central canal dilation at the C5-7 level, nerve root cuff cysts in the C4-6 bilateral intervertebral foramina, thoracic intervertebral disc degeneration, lumbar intervertebral disc degeneration, posterior protrusion of the L5-S1 intervertebral disc, and narrowing of the adjacent spinal canal (Figure 2). MRI of both thighs showed atrophy in the left thigh, thinning of the subcutaneous fat layer, and slight thickening of the local skin (Figure 3). The patient and her families declined genetic testing.

Based on the patient's history and examination, systemic lipodystrophy was ruled out. So the diagnosis is considered to be localized lipodystrophy. The presentation of partial and multifocal fat loss in this patient is rare in clinical practice. Since no significant metabolic abnormalities, organ dysfunction, or infections were detected, the patient was discharged with instructions for ongoing follow-up. During the most recent follow-up on June 15, 2024, the patient reported persistent tightness in the affected areas, along with a tingling sensation upon touch.

DISCUSSION

Lipodystrophy is a heterogeneous condition that can be classified into congenital and acquired forms (Fiorenza *et al.* 2011; Garg 2011). According to the extent of fat atrophy, clinical manifestations can be categorized into systemic (generalized) and localized forms (Fiorenza *et al.* 2011). It is often accompanied by a variety of abnormal growth and development, metabolic function abnormalities, organ dysfunction, infection and so on (Fiorenza *et al.* 2011; Garg & Agarwal 2009a).

Congenital generalized lipodystrophy (CGL) is inherited as an autosomal recessive trait, with frequent parental consanguinity. At present, there may be four types (Garg & Agarwal 2009b; Garg 2004; Garg & Agarwal 2009a): Type 1 CGL (CGL1) is due to AGPAT2 gene mutations. This gene has been mapped to chromosomes 9q34. It encodes the enzyme 1-acylglycerol-3-phosphate O-acyltransferase 2 (AGPAT2). Affected individuals typically have normal intelligence, and their mechanical fat is preserved. However, they lack metabolically active adipose tissue in most subcutaneous areas, intraabdominal and intrathoracic regions, and bone marrow, whereas mechanical adipose tissue, which fulfills a protective and cushioning function, appears to be spared. Type 2 CGL (CGL2) results from mutations in the Berardinelli–Seip Congenital Lipodystrophy 2 (BSCL2) gene. This gene is located in chromosome 11q13 and encodes a 398-amino-acid protein called seipin. Type 2 CGL is often associated

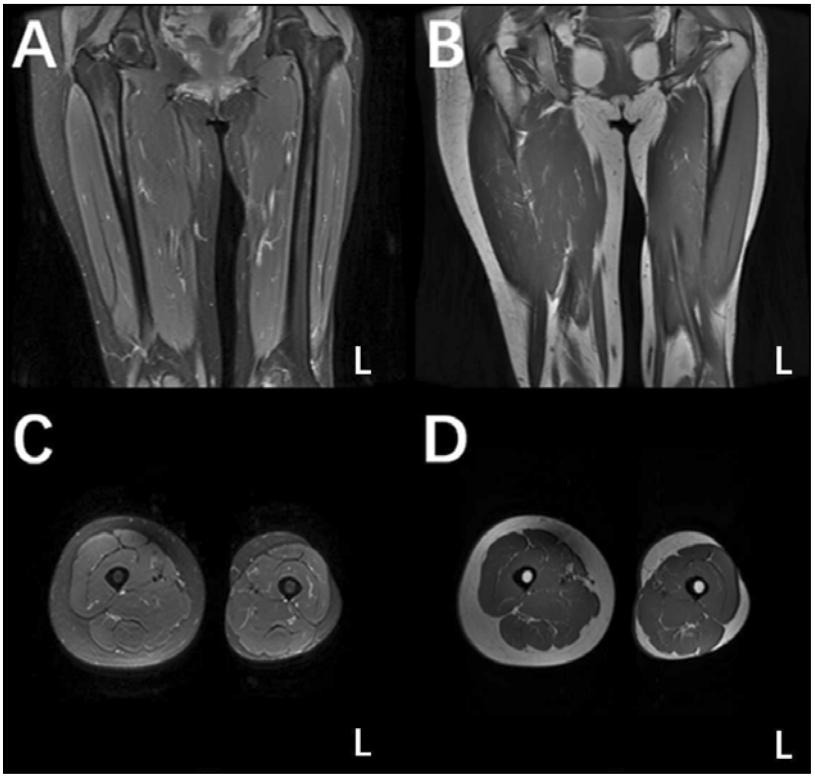

Fig. 3. The left thigh is thinner than the right thigh. The subcutaneous fat layer of the left thigh shrinks, and the local skin thickens slightly in the anterior posterior position (A, B) and cross section (C, D) of both lower extremities.

with cardiomyopathy and mild intellectual disability. Compared to CGL1, CGL2 patients exhibit a more pronounced absence of body fat, including metabolically active fat in subcutaneous, intermuscular, bone marrow, intra-abdominal and intrathoracic regions, as well as mechanical fat in the orbital regions, palms, soles, and joints. Type 3 CGL (CGL3) is caused by a homozygous nonsense mutation in the caveolin-1 (CAV1) gene, likely resulting from a consanguineous union. The CAV1 gene is located on chromosome 7q31. Patients with CGL3 typically have normal intelligence, and their mechanical fat is preserved. Type 4 CGL (CGL4) is caused by mutations in the PTRF gene. PTRF, also known as cavin, is a polymerase I and transcript release factor involved in the biogenesis of caveolae and regulates the expression of caveolin 1 and 3. Clinical features of CGL4 include moderate lipodystrophy, congenital myopathy, esophageal dysfunction, pyloric stenosis, atlantoaxial instability, QT interval prolongation with exercise-induced ventricular tachycardia, and sudden death (Hayashi *et al.* 2009).

Familial partial lipodystrophy (FPLD) encompasses several types: FPLD Type 1 (Köbberling lipodystrophy) is characterized by the loss of adipose tissue in the extremities while maintaining normal adipose tissue in other areas. Affected individuals may have excessive amounts of subcutaneous truncal fat (Herbst *et al.* 2003). The genetic defect associated with Köbberling-type lipodystrophy is currently unknown, and no mutations in lamins A (LMNA) or peroxisome proliferator-activated receptor gamma (PPARG) have been identified. FPLD Type 2 (Dunnigan lipodystrophy) is an autosomal dominant genetic disorder caused by mutations in the LMNA gene. LMNA encodes lamin A/C, a protein located at the inner nuclear envelope. This type is characterized by the gradual loss of subcutaneous fat in the extremities starting from puberty, with excessive fat deposition potentially occurring in the face and neck. Patients may also develop excess supraclavicular fat and a round face later in life, and may exhibit acanthosis nigricans, hirsutism, and menstrual abnormalities due to ovarian hyperandrogenism (Garg *et al.* 1999; Spuler *et al.* 2007).FPLD Type 3 is associated with heterozygous mutations in the PPARG gene. The phenotype is similar to Dunnigan lipodystrophy, but fat accumulation in the head and neck may be spared. Patients with FPLD Type 3 generally exhibit more severe metabolic abnormalities compared to those with FPLD Type 2 (Agarwal & Garg 2002; Garg 2004). FPLD Type 4 can result from mutation in the v-AKT murine thymoma oncogene homolog 2 (AKT2) gene. AKT2 is a serine/threonine-protein kinase involved in cell signaling, growth, glycogen synthesis, and insulin-stimulated glucose transport. Mutations in AKT2 may lead to lipodystrophy due to defective adipocyte differentiation. A single family has been reported with loss of subcutaneous fat from the extremities (Garg 2011). FPLD Type 5 is associated with mutation in the PLIN1 gene, which encodes perilipin 1, a protein essential for lipid droplet membranes, lipolysis, and lipid storage. This type is characterized phenotypically by the loss of subcutaneous fat from the extremities (Gandotra *et al.* 2011; Garg 2011). Besides, partial lipodystrophy due to CAV1 mutation is a rare condition. CAV1 mutations are an infrequent cause

of both lipodystrophy and hypertriglyceridemia (Cao *et al.* 2008). Mandibuloacral dysplasia (MAD) is an extremely rare autosomal recessive disorder with two distinct phenotypes. Type A is associated with mutations in the LMNA gene and involves loss of subcutaneous fat from the arms and legs, while fat deposition remains normal or excessive in the face and neck. Type B is linked to mutations in the zinc metalloproteinase (ZMPSTE24) gene, and is characterized by a more generalized loss of subcutaneous fat (Garg 2004; Simha *et al.* 2003; Garg 2011). Autoinflammatory syndromes include the JMP (joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy) syndrome of childhood, which is a rare, autosomal recessive autoinflammatory disorder. Clinical features include hepatosplenomegaly, intermittent fever, calcification of the basal ganglia, and hypergammaglobulinemia. Sequencing of candidate genes revealed a loss-of-function mutation in the proteasome subunit β-type 8 (PSMB8) gene on chromosome 6 (Garg 2011).

Acquired partial lipodystrophy includes: (1) Lipodystrophy in patients with HIV infection: This form of lipodystrophy occurs in individuals infected with human immunodeficiency virus (Garg 2011; Viskovic *et al.* 2009). (2) Barraquer-Simons syndrome: The syndrome is characterized by the loss of adipose tissue in the upper part of the face and trunk, while fat in the rest of the body remains normal or even increased. Almost all patients have low levels of serum C3 and the presence of the C3 nephrotic factor autoantibody (Garg 2004; Misra *et al.* 2004). (3) Acquired generalized lipodystrophy: Fat loss typically begins during childhood and adolescence, affecting large areas of the body, particularly the face, arms, and legs. In about 25% of patients, the onset of this condition is preceded by an episode of subcutaneous inflammatory nodules, termed panniculitis (Garg 2004). (4) Localized lipodystrophies: Most people with localized lipodystrophies lose subcutaneous fat from small areas, leaving indentations. In some, large regions of the trunk or limbs may be involved. The cause of such localized fat loss varies and may be related to injected drugs such as insulin and corticosteroids, recurrent pressure, panniculitis, or unknown mechanisms (Garg 2000; Garg 2011).

Clinically, measurements of skin folds, hip circumference, waist circumference, and limb circumference can assist in diagnosis. Additionally, Dual-energy X-ray absorptiometry (DXA), MRI and CT provide superior objectivity and precision. Ultrasonography is also emerging as an alternate quantitative tool, offering accuracy along with being comparatively affordable and accessible (Fiorenza *et al.* 2011).

The onset of symptoms in this female patient began at puberty, primarily manifesting as fat loss in the trunk and limbs below the neck, predominantly on the left side with multiple discontinuous areas. This presentation is relatively rare. The clinical features are consistent with partial lipodystrophy. There was no significant medical and family history, and relevant examinations did not reveal any obvious abnormalities. However, several congenital or growth-related issues were noted, including a patent foramen ovale, cardiac valvular malformation, and central canal dilatation of the spinal cord. While these findings may suggest a potential genetic basis, they do not conclusively establish a genetic etiology for the lipodystrophy. The patient declined genetic testing. Therefore, the diagnosis is considered to be localized lipodystrophy.

Current management strategies for lipodystrophy include cosmetic surgery and the early identification and treatment of metabolic and other complications. This can involve dietary adjustments, exercise, hypoglycemic medications, and lipid-lowering agents (Garg 2011). However, metabolic disorders associated with acquired partial lipodystrophy are rare. Patients with aesthetic concerns related to localized fat loss may benefit from fat filling procedures. In this case, the presence of multiple lesions renders surgical intervention challenging. Future research is needed to explore more effective treatments and strategies to prevent further localized fat loss.

LIMITATIONS

The patient was not given special treatment. And The patient's condition did not improve significantly.

DECLARATIONS

Ethics approval and consent to participate

We have obtained the patient's written consent

Consent for publication

Written informed consent was obtained from the patient for publication of the case report and the images

Statement

I am Haiyan Zi, as the first author of this manuscript, I guarantee that I have obtained the informed consent of the patient. As the patient is not local, the informed consent form is signed on Wechat. I hereby declare that I am willing to take full responsibility for any false act.

Availability of data and material

Not applicable.

Competing interests

The authors declares that we have no competing interests.

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Author contributions statement

Haiyan Zi collates and writes manuscripts, Xiaoguang Lei modifies and guides manuscripts, Ailan Pang provides ideas, and Ting Pu provides pictures. All authors reviewed the manuscript.

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