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Acquired Partial Lipodystrophy Associated With Hypocomplementemia

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- Acquired partial lipodystrophy is a rare condition with onset in childhood or adolescence. It is characterized by progressive loss of subcutaneous fat of the face, neck, trunk, and upper extremities in a cephalocaudal fashion and usually is coupled with C_3 hypocomplementemia.
- Insulin resistance and its accompanying complications appear to be infrequent. Women are affected approximately 3 times more often than are men.
- Owing to its rarity in male patients, we are presenting the case of acquired partial lipodystrophy in a 12-year-old boy with a granular accumulation of C_3 in the basement membrane on skin biopsy.

The lipodystrophy syndromes are a heterogeneous group of syndromes characterized by selective loss of fat from various parts of the body.[1] They are classified into 2 major types: familial and acquired. The main subtypes of familial lipodystrophies are congenital generalized lipodystrophy, an autosomal recessive disorder characterized by near complete lack of metabolically active adipose tissue from birth, and familial partial lipodystrophy, Dunnigan type, an autosomal dominant disorder characterized by loss of subcutaneous fat from the extremities at puberty and excess fat accumulation in the face and neck. Patients with acquired generalized lipodystrophy have generalized loss of subcutaneous fat, but those with acquired partial lipodystrophy have fat loss limited to the face, trunk, and upper extremities.[2] (**Table 1**)

Acquired partial lipodystrophy is a rare condition with approximately 250 described patients of various ethnic origins.[3] This variety (like acquired generalized lipodystrophy) occurs approximately 3 times more often in women, begins during childhood, and has underlying autoimmunity.[2]

Table 1_Classification of Lipodystrophy Syndromes

Familial or Genetic Types	Acquired Types
1. Congenital generalized lipodystrophy (Berardinelli-Seip Syndrome)	1. Acquired generalized lipodystrophy (Lawrence syndrome)
2. Familial partial lipodystrophy a. Dunnigan variety b. Köbberling variety c. Mandibuloacral dysplasia variety	2. Acquired partial lipodystrophy (Barraquer–Simons syndrome) 3. Lipodistrophy in human immunodeficiency virus-patient
3. Other types	4. Localized lipodystrophies a. Drug-induced b. Pressure-induced c. Panniculitis variety d. Centrifugal variety e. Idiopathic

Case Report

A 12-year-old boy presented with a history of progressive loss of fat for the last 2 years. He was a product of a non-consanguineous marriage, born at term with a birth weight of 3 kg. His development was normal and the child was asymptomatic until 10 years of age when progressive thinning of face was first noted. There was no history of fever, loss of appetite, polyuria, polydypsia, or chronic diarrhea. He had been evaluated for tuberculosis and malabsorption syndromes. There was no history of similar cases in the family. Clinical examination was unremarkable except for a marked symmetrical atrophy of fat over buccal region and temples (**Images 1 and 2**). His weight, height, triceps skinfold, and subscapular skinfold thickness were 35 kg, 141cm, 3.37 mm, 4.37 mm, respectively. There was no hepatomegaly. Laboratory evaluation revealed normal levels of hemoglobin, serum electrolytes, blood urea, fasting and postprandial blood sugar, liver, and the thyroid function tests (**Table 2**). First phase insulin response (FPIR) in intravenous glucose tolerance test: (1'+3') was 109 mU/mL with 6.93 value for K; fasting glucose/insulin ration (Go/Io) was 13.70; homeostatic model assessment (HOMA) was 1.80. The lipid profile was also normal with serum total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and total triglyceride levels of 149 mg/dL, 41mg/dL, 18 mg/dL, and 90 mg/dL, respectively. The Mantoux test was negative, and urinalysis revealed no abnormality. Autoantibodies were negative. Plasma leptin level was 5 mg/mL for BMI: 20.29 kg/m². Plasma complement 3 (C_3) level was reduced to 21 mg/dL. On skin biopsy, there was a granular accumulation of C_3 in the basement membrane (**Image 3**). A diagnosis of partial lipodystrophy was considered because of gradual onset loss of subcutaneous fat from the face, neck, trunk, and upper extremities occurring during childhood (essential criterion), low serum C_3 associated with accumulation of C_3 in the basement membrane, and absence of insulin resistance and metabolic complications.[2] Since the patient's main concern was the facial appearance, he was referred

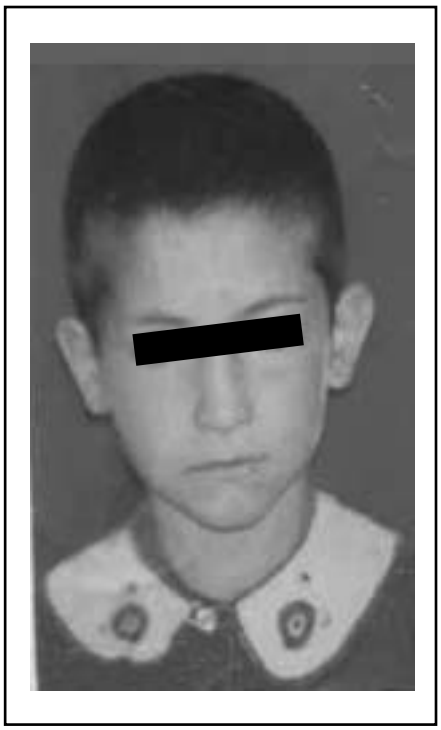

Image 1_Facial appearance of patient at 6 years of age.

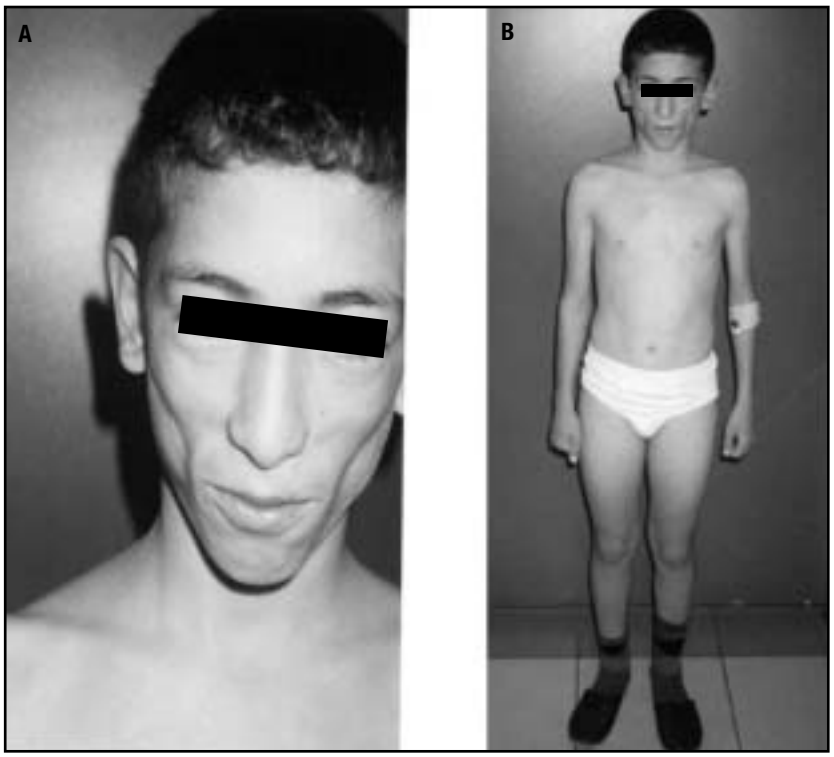

Image 2 A-B_Facial appearance of patient at 12 years of age showing loss of buccal fat, neck, trunk, and upper extremities' subcutaneous fat.

to a plastic surgeon. A graft surgery was advised, which was, however, refused by the child's parents.

Discussion

Initially reported by Mitchell and later by Barraquer and Simons, acquired partial lipodystrophy occurs before the age of 16 years, with a median age of 8 years.[2] The onset of symptoms is usually preceded by an episode of an acute viral infection. Afterwards there is a symmetrical disappearance of facial fat, extending to involve the neck, shoulders, arms, forearms, thoracic region and upper abdomen, while occasionally extending to the groin or thighs. Usually legs and hips are spared. The face is affected first, and in advanced cases, takes on a characteristic cadaverous look. Ten percent of cases may have hemilipodystrophy involving half of the face or body.[4] Whereas, the Dunnigan variety of the familial type of partial lipodystrophy, commencing at puberty is characterized by loss of subcutaneous fat only from the limbs, with maintenance of fat on face and trunk.[5]

It is well documented that the patients with familial lipodystrophy (partial or generalized) develop insulin-resistant diabetes mellitus, and have high triglycerides and free fatty acids levels. Their plasma leptin concentrations are generally low, consistent with absence of body fat.[6] However, patients with acquired partial lipodystrophy seldom have metabolic abnormalities associated with insulin resistance such as elevated lipid levels, acanthosis nigricans, hirsutism, or menstrual abnormalities.[7] Abnormal glucose tolerance tests and hypertriglyceridemia are inconsistently reported findings.[8] Experiments using lipoatrophic mice, developed by disruption of adipogenesis or inducing adipocyte death, have demonstrated that the metabolic disorder correlates with the amount of fat loss, suggesting that insulin resistance results from the lack of adipose tissue.[9] The lack of white adipose tissue also causes leptin deficiency, which

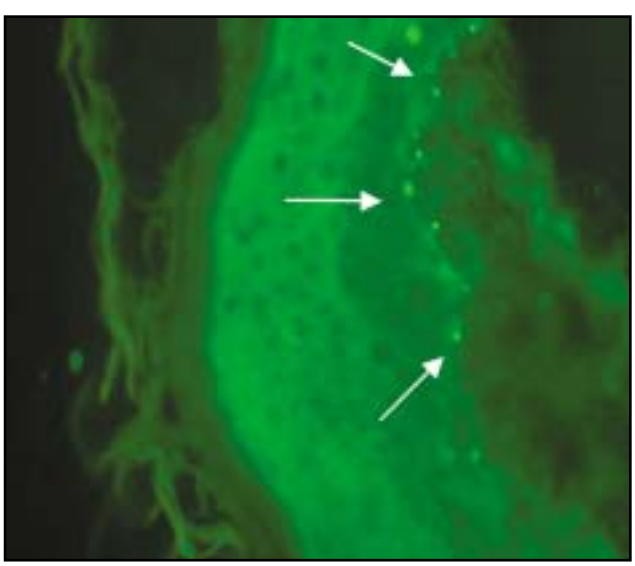

Image 3_Immunofluorescence micrograph from skin biopsy demonstrating granular accumulation of C_3 along the basement membrane.

contributes to the insulin resistance. On the other hand, the new classification of human white adipose tissue into metabolically active adipose tissue, which is located in the most subcutaneous areas, intraabdominal and intrathoracic regions, bone marrow, and parathyroid glands, and mechanical adipose tissue, presented in the orbits, crista galli, buccal region, tongue, palms and soles, scalp, perineum, vulva, periarticular regions, epidural area, and pericalyceal regions of the kidney might contribute to the explanation of metabolic derangements in different types of lipodystrophy syndromes. Owing to it, patients with acquired partial lipodystrophy who have well preserved metabolically

Table 2_Laboratory Data of the Presented Patient

Laboratory Data	Value	Reference Range
Hemoglobin	12.0 mg/dL	11.5-15.5 mg/dL
Urea Nitrogen	10 mg/dL	7-18 mg/dL
Aspartate aminotransferase (AST)	30 U/L	5-45 U/L
Alanine aminotransferase (ALT)	22 U/L	50-45 U/L
Thyroid Stimulating Hormone (TSH)	2.9 µIU/mL	0.34-5.6 uIU/mL
Free Triiodothyronine (FT3)	3.6 pg/mL	2.39-6.79 pg/mL
Free Thyroxine (FT4)	0.98 ng/dL	0.58-1.64 ng/dL
Total Triiodothyronine(TT3)	1.2 ng/mL	0.87-1.78 ng/mL
Total Thyroxine (TT4)	10.2 mg/dL	6.09-12.23 mg/dL
Fasting Glucose	86 mg/dL	60-100 mg/dL
Postprandial Glucose	102 mg/dL	<120 mg/dL

Oral glucose tolerance test (OGTT)	Minute	Glucose mg/dL	Minute	Glucose mg/dL
	0	99	0	70-105
	60	146	60	120-170
	90	104	90	100-140
	120	105	120	70-120

Intravenous glucose tolerance test (IVGTT)	Minute	Insulin mU/mL	Glucose mg/dL	Minute	Insulin mU/mL	Glucose mg/dL
	0	7.3	100	0	7-24	70-105
	1	59	282	1	25-231	200-280
	3	50	275	3	18-276	200-280
	5	34	170	5	16-166	150-200
	10	22.6	126	10	4-38	100-150

First phase insulin response		
FPIR(1'+3') IVGTT	109 mU/mL	>100 mU/mL
K (Glucose Assimilation Coefficient) = 69/t	6.9	>1.3
Fasting Glucose/Insulin Ration (Go/Io)	13.7	>6
Homeostatic Model Assessment (HOMA)	1.8	<2.5
Total Cholesterol	149 mg/dL	130-204 mg/dL
High-Density Lipoprotein (HDL-Cholesterol)	41mg/dL	35-84 mg/dL
Low Density Lipoprotein (LDL- Cholesterol)	18 mg/dL	10-170 mg/dL
Triglyceride (TG)	90 mg/dL	36-138 mg/dL
Antinuclear Antibodies (ANAs)	Negative	<1/40
Anti–Double-Stranded DNA Antibodies (Anti-DNA)	Negative	480-800 U (Upper limit of normal)
Plasma Leptin	5 mg/mL (BMI: 20.29 kg/m²)	3-5 mg/mL (BMI: 20-25 kg/m²)
Plasma C_3	21 mg/dL	83-177 mg/dL
Plasma C_4	32 mg/dL	15-45 mg/dL

active adipose tissue seldom have metabolic abnormalities; however, patients with congenital generalized lipodystrophy in whom metabolically active adipose tissue is almost absent develop diabetes, hypertriglyceridemia, low levels of high-density lipoprotein cholesterol, and atherosclerotic vascular disease.[2]

Molecular basis of lipodystrophy syndromes has not been elucidated. Two molecularly distinct forms of congenital generalized lipodystrophy have been defined as type 1 and type 2. Some patients have neither type, so additional genes are most likely involved.[10] The identification of a locus for the Dunnigan variety of familial partial lipodystrophy, on chromosome 1q21-22 led to the identification of a missense mutation in the gene encoding lamins A and C (LMNA). Subsequently, many more missense LMNA mutations have been reported. Recently, a heterozygous missense mutation - Arg397Cys - in the PPAR [gamma] gene was described[3] (**Table 3**). In contrast, the pathogenesis of an acquired form of lipodystrophy has not been elucidated at the molecular level. Nevertheless, it has been well documented that acquired partial lipodystrophy is associated with autoimmune disorders. Systemic lupus erythematosus has developed in 6 patients, 2 to 28 years after the onset of lipodystrophy. Other autoimmune diseases, such as dermatomyositis, hypothyroidism, pernicious anemia, celiac disease, dermatitis herpetiformis, rheumatoid arthritis, temporal arteritis, and leukocytoclastic vasculitis have also been reported. Several patients had antinuclear and anti-double-stranded DNA antibodies in their serum.[2,6]

Consequently, Reitman and colleagues suggested that adipocyte deficiency can be caused by autoimmune destruction.[1] Moreover, C_3 hypocomplementemia, seen in 70% of patients, supports the hypothesis for autoimmunity based on complement activation.[11] Recent studies showed that complement components and proteins identical to factors D and B could be expressed both by the adipose and renal cells. Therefore, the existence of these factors and in particular factor D is the reason for more serious destruction in adipose and renal tissue. In a large number of cases, there may be an associated presence of C_3 nephritic factor.[12] A significant number of cases (25% to 90%) may have renal involvement with biopsy showing membranoproliferative glomerulonephritis. Onset of acquired partial lipodystrophy and complement abnormalities antedates the renal disease, sometimes by long periods. Many of these patients may have histologically detectable glomerulonephritis before overt clinical manifestations. The proportion of patients who eventually develop significant renal disease is not known.

Table 3_Molecular Basis of Hereditary Lipodystrophy Syndromes

Familial or Genetic Types				
1. Congenital Generalized Lipodystrophy (Berardinelli-Seip Syndrome)			2. Familial Partial Lipodystrophy	
Type 1	Type 2	Other	Dunnigan variety	Mandibuloacral dysplasia variety
Chromosome 9q34	Chromosome 11q13	?	Chromosome 1q21-22	Chromosome 1q21-22
CGL1gene[2]			LMNA gene[3,9]	LMNA gene[3,9]
AGPAT2gene[3]			PPAR[gamma] gene[3]	ZMPSTE24 gene[3]

However, in a reported series of 12 patients with acquired partial lipodystrophy, 4 died of renal failure after onset of lypodystrophic changes.[13]

Presenting this patient, we want to emphasize once again that each lipodystrophy has not only a unique clinical picture but also an unique underlying pathogenic mechanism. Therefore, enlightening of autoimmune base in the etiopathogenesis of acquired partial lipodystrophy may also lead to the discovery of therapeutic approaches to prevent the loss of adipocytes, induce adipogenesis in lipodystrophic regions, and prevent or delay the onset of metabolic complications in patients with lipodystrophy.[14] LM

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