An Autosomal Recessive Syndrome of Joint Contractures, Muscular Atrophy, Microcytic Anemia, and Panniculitis-Associated Lipodystrophy

Abhimanyu Garg, Maria Dolores Hernandez, Ana Berta Sousa, Lalitha Subramanyam, Laura Martínez de Villarreal, Heloísa G. dos Santos, and Oralia Barboza

Division of Nutrition and Metabolic Diseases (A.G., L.S.), Department of Internal Medicine and the Center for Human Nutrition, University of Texas Southwestern Medical Center, Dallas, Texas 75390; Departamento de Genética (M.D.H., L.M.d.V.) and Departamento de patología (O.B.), Facultad de Medicina, Universidad Autónoma de Nuevo León, 66451 Monterrey, Nuevo León, México 66603; and Servicio de Genética Médica (A.B.S., H.G.d.S.), Hospital de Santa María, 1649-035 Lisbon, Portugal

Context: Genetic lipodystrophies are rare disorders characterized by partial or complete loss of adipose tissue and predisposition to insulin resistance and its complications such as diabetes mellitus, hypertriglyceridemia, hepatic steatosis, acanthosis nigricans, and polycystic ovarian syndrome.

Objective: The objective of the study was to report a novel autosomal recessive lipodystrophy syndrome.

Results: We report the detailed phenotype of two males and one female patient, 26–34 yr old, belonging to two pedigrees with an autosomal recessive syndrome presenting with childhood-onset lipodystrophy, muscle atrophy, severe joint contractures, erythematous skin lesions, and microcytic anemia. Other variable clinical features include hypergammaglobulinemia, hepatosplenomegaly, generalized seizures, and basal ganglia calcification. None of the patients had diabetes mellitus or acanthosis nigricans. Two had mild hypertriglyceridemia and all had low levels of high-density lipoprotein cholesterol. Skin biopsy of an erythematous nodular skin lesion from one of the patients revealed evidence of panniculitis. The lipodystrophy initially affected the upper body but later became generalized involving abdomen and lower extremities as well.

Conclusions: We conclude that these patients represent a novel autoimmune syndrome resulting in joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy. The molecular genetic basis of this disorder remains to be elucidated. (J Clin Endocrinol Metab 95: E58–E63, 2010)

In the last decade, great progress has been made in elucidation of molecular genetic basis and phenotypic characterization of the major types of genetic lipodystrophies such as congenital generalized lipodystrophy, familial partial lipodystrophy, and mandibuloacral dysplasia-associated lipodystrophy (1, 2). The molecular basis of extremely rare types such as the SHORT (short stature, hyperextensibility of joints and/or inguinal hernias, ocular depression, Rieger anomaly and teething delay) syndrome and neonatal progeroid (Wiedemann-Rautenstrauch) syndrome, however, remains to be determined (1). We now report a distinct autosomal recessive syndrome presenting with joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced childhood-onset lipodystrophy (JMP) in three patients from two pedigrees.

Patients and Methods

All patients, their family members, and the normal healthy volunteer gave written informed consent. The study protocol was

Abbreviations: HDL, High-density lipoprotein; JMP, joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced childhood-onset lipodystrophy; LMNA, lamin A/C; MRI, magnetic resonance imaging.
FIG. 1. Pedigrees and clinical features of our patients with JMP syndrome. A, Pedigrees of the patients. Circles denote females and squares denote males. Arrows indicate probands. Filled symbols indicate affected and unfilled symbols indicate unaffected subjects. A diagonal line across a symbol indicates a deceased subject. A small filled circle indicates a miscarriage. B, Anterior view of patient JMP 100.3 showing marked loss of sc fat from the face, neck, chest, and upper extremities. The loss of sc fat is less evident from the abdomen and lower extremities. There is also loss of muscle mass from the upper extremities. Contractures of the upper extremities with flexion contractures at the elbows and wrists and contractures of the hands are seen. The patient has mild gynecomastia. He has no loss of scalp hair. C, JMP 200.3 showing similar features as seen in JMP100.3. In addition, there is marked loss of sc fat from the abdomen and lower extremities. The lower extremities also show marked loss of muscle mass. D, JMP 200.4 shows more marked loss of sc fat from the face, neck, chest, and upper extremities than from the abdomen, hips, and lower extremities, which were spared. The breasts are atrophic and the neck and chest showed many discrete, small, erythematous nodular skin lesions. She had mild contractures of the hand joints. E, View of the hand from patient JMP 200.3 showing flexion contractures at the elbow and wrist. The metacarpophalangeal joints were hyperextended, and the proximal and distal interphalangeal joints showed flexion contractures. F, The foot of patient JMP 200.3 showing hallux valgus deformity and flexion contractures of the rest of the toes. He also had severe inversion at the ankle joint. G, Lateral radiograph of the right hand and the forearm of patient JMP 100.3 showing flexion deformity of the wrist with poor visualization of the carpal bones. Extension deformity of the metacarpophalangeal joints and flexion deformity of proximal interphalangeal joints is seen. H, Antero posterior radiograph of the foot of patient JMP 100.3 showing juxtaarticular osteopenia. Heads of metatarsals were unusually large with thin shafts. There was hallux valgus deformity. No acroosteolysis was seen. I, Hematoxylin and eosin stain of the skin and sc tissue biopsy specimen from JMP 200.4 showing lymphocytic infiltrate permeating deep dermal collagen and sc adipose tissue, with a perivascular component (lower left part of field) consistent with panniculitis. No vasculitis or fat necrosis is seen (×200).

JMP 100.3
This 35-yr-old Portuguese male was a normal infant born to nonconsanguineous parents, both of whom came from a small village (Fig. 1 and Table 1). His younger sister had similar features and died suddenly at age 8 yr. Throughout childhood, he could never run well. At age 12 yr, he started developing erythematous skin lesions. He was a computer programmer and had no mental retardation.

He had a short stature (144 cm), severe generalized lipodystrophy, and atrophic skin with patchy areas of erythema. The face appeared progeroid with prominent eyes and a beaked nose, with no mandibular hypoplasia. He had a high arched palate. There was no alopecia, but some graying of the hair in the frontal region. He had bilateral gynecomastia, female distribution of pubic hair, and a single, soft, 8-ml right testicle. The liver and spleen were palpable 10 and 4 cm below the costal margin, respectively. He had stiff joints and contractures of the knee, elbow, wrist, and metacarpophalangeal and interphalangeal joints. The feet showed hallux valgus deformity and flexion contractures of the other toes.

Laboratory investigations revealed microcytic anemia and elevated erythrocyte sedimentation rate (110 mm/h). Fasting serum glucose (76 mg/dl) and creatinine (0.3 mg/dl) were normal. Serum aspartate aminotransferase level was 29 U/liter (normal 7–27) and alanine aminotransferase, 14 U/liter (normal 8–30). Total cholesterol was 115 mg/dl, triglycerides 166 mg/dl, and high-density lipoprotein (HDL) cholesterol 23 mg/dl. Urinalysis showed mild proteinuria (30 mg/dl) and with 12 red and two white blood cells per high-power field. Serum protein electrophoresis showed total protein 8.1 g/dl with increased α1-globulins (2.7 g/dl). Echocardiography revealed a holosystolic prolapse of the mitral valve with no transvalvular regurgitation. Abdominal ultrasound and computed tomography confirmed moderate hepatomegaly with multiple solid isoechogenic nodules and homogenous 12-cm spleen.

Hand radiographs revealed juxtaarticular rarefaction of bones with reduced joint space (Fig. 1). He had a short fourth right metacarpal. The proximal phalanges were dumbbell shaped. He had flexion deformity of the wrists with poor visualization of the carpal bones. Extension deformity of the
There was cephalad bowing of the clavicles, the humeri were deformed, and the metacarpophalangeal joints were wide. Pelvic radiographs showed wide sacroiliac joints and pubic symphysis and valgus deformity of the femur (Supplemental Fig. 1, published on The Endocrine Society’s Journals Online web site at http://jcem.endojournals.org). The skull was peaked with loss of many teeth. This 30-yr-old man was born to nonconsanguineous parents (8). He had severe constipation, dryness of mouth, cranial nerve palsies, generalized seizures since age 13 yr, requiring carbamazepine. He also had severe anemia, necessitating blood transfusion at age 28 yr. He had severe constipation, dryness of mouth, nasal twang, and dysphagia for 2 yr. He did not go to school but had no mental retardation.

He was 153 cm tall and weighed 34.6 kg. He had generalized lipodystrophy; however, the fat loss was more pronounced over the face, neck, and upper extremities than over the trunk and lower extremities. The eyes showed some scleral injection and multiple red punctate lesions on the upper eyelids. He had a pinched nose. His skin was dry, hard, and shiny and was thick on the face, neck, and upper extremities than over the trunk and lower extremities. There was cephalad bowing of the clavicles, the humeri were gracile with large heads, the scalpula was small, and no clavicular resorption or acroosteolysis was seen.

**TABLE 1.** Clinical features in our patients and previously reported patients from Japan: comparison with other progeroid syndromes due to laminopathies

<table>
<thead>
<tr>
<th></th>
<th>JMP 200.3</th>
<th>JMP 200.4</th>
<th>Japan 1 (3)</th>
<th>Japan 2 (3)</th>
<th>Japan 3 (6)</th>
<th>MAD (8, 12)</th>
<th>HGPS (13, 14)</th>
<th>APS (15)</th>
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<td>14</td>
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<td>6</td>
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Hypertiglyceridemia was defined as fasting serum triglycerides greater than 200 mg/dl. M, Male; F, female; −, absent; +, present; +/-, present in some and absent in others; NA, not available; NR, not relevant; IGT, impaired glucose tolerance; MAD, mandibuloacral dysplasia due to LMNA or ZMPSTE24 mutations; HGPS, Hutchinson-Gilford Progeria syndrome; APS, atypical progeroid syndrome; ESR, erythrocyte sedimentation rate.

\a Died at age 47 yr due to congestive heart failure.

\b Mean corpuscular volume was reported to be low.

JMP 200.3

This 30-yr-old man was born to nonconsanguineous parents who belonged to a small ranch in Mexico with normal phenotype (Fig. 1 and Table 1). At age 3 yr, asymmetrical, nodular, erythematous skin lesions appeared over the face and trunk, which spread to the arms and legs over a period of months. Upon healing, the lesions resulted in loss of sc fat and a hyperpigmented macule. At age 5–7 yr, he noticed difficulty in running and handling small objects. He then developed swelling of both hands and feet with diffuse bone pain and later joint deformities. He had generalized seizures since age 13 yr, requiring carbamazepine. He also had severe anemia, necessitating blood transfusion at age 28 yr. He had severe constipation, dryness of mouth, nasal twang, and dysphagia for 2 yr. He did not go to school but had no mental retardation.
Radiographs of the upper and lower extremities showed severe joint contractures. Both humeri appeared gracile. There was joint space narrowing and mild acroosteolysis of some of the distal phalanges. Periarticular osteopenia was noted in most of the joints of the hands (Supplemental Fig. 1). There was no evidence of clavicular resorption. The skull radiograph revealed thickening of the occipital bone with loss of some teeth and small right basal ganglion calcification.

**JMP 200.4**

This 26-yr-old woman (Fig. 1 and Table 1) was normal at birth but had generalized seizures at age 2 yr requiring carbamazepine. At age 14 yr, she developed progressive weight loss and erythematous skin lesions, diffuse bone pain, and contractures of the hands and feet. She reported swelling and pain in the knees and ankles. She had redness in her right eye. Menarche was at 17 yr and she was having irregular menstrual periods. She also reported constipation. She went to primary school but had no mental retardation.

She was 146 cm tall and weighed 32.5 kg. She had partial lipodystrophy with fat loss predominantly from the face, upper chest, and upper extremities with sparing of sc fat in the abdomen and lower extremities. The skin was dry and hard, and several erythematous nodular lesions were present on the trunk. She had no axillary hair and the breasts were Tanner 1. The liver and spleen were palpable 6 and 2 cm below the costal margin, respectively. She had mild flexion contractures at the elbow and wrist, hyperextension of the metacarpophalangeal and distal interphalangeal joints, and flexion of the proximal interphalangeal joints. Hallux valgus deformity was noted. Her motor strength was normal in the lower extremities but slightly reduced in the upper extremities. Sensory examination was normal. The deep tendon reflexes were diminished. Genital examination showed hypoplasia of the labia minora with normal introitus.

Laboratory investigations showed severe microcytic hypochromic anemia with anisocytosis, hypochromasia, and micromegakaryocytes. Hemoglobin electrophoresis did not reveal any abnormal hemoglobin. Fasting blood glucose was 81 mg/dl, triglycerides were 154 mg/dl, and HDL cholesterol was 30 mg/dl. Serum aspartate aminotransferase level was 33 U/liter (normal 10–30) and alanine aminotransferase, 15 U/liter (normal 6–40). Serum total protein was 8.9 g/dl with increased globulin of 4.8 g/dl (normal 2.2–3.9). TSH was elevated (9.1 mIU/liter) with low normal free T4 (0.98 ng/dl). She was currently taking 50 µg levothyroxine daily.

Radiographs showed the contractures and mild joint space narrowing (Supplemental Fig. 1). A skin biopsy revealed evidence of panniculitis with superficial and deep perivascular and periadnexal lymphocytic infiltrate. Lymphocytic infiltrate also permeated deep dermal collagen and subcutaneous tissue with a perivascular component (Fig. 1 and Supplemental Fig. 2). There was no evidence of vasculitis or fat necrosis.

**Methods**

Hierarchical cluster analysis for clinical features of our cases and previously reported three patients from Japan (3–6) was performed with an agglomerative clustering algorithm using between-group linkage and Euclidean distance measure (PASW 17.0; SPSS Inc., Chicago, IL) (7). Phenomic analysis for heat map generation was performed with Hierarchical Clustering Explorer 3.5 (Human-Computer Interaction Lab, University of Maryland, College Park, MD; http://www.cs.umd.edu/hcil/).

Anthropometric measurements, whole-body magnetic resonance imaging (MRI), and dual-energy x-ray absorptiometry (Hologic Delphi W densitometer; Hologic, Inc., Waltham, MA) were performed to determine total body fat and its distribution as described previously (8). Fasting serum glucose and lipoproteins were analyzed as part of a systematic multichannel analysis (Synchroon CX9 ALX clinical system; Beckman, Fullerton, CA). The exons and splice-site junctions of lamin A/C (LMNA) and zinc metalloproteinase (ZMPSTE24) genes were sequenced using genomic DNA (9, 10).

**Results**

The hierarchical cluster analysis showed that our patients did cluster separately from those reported previously from Japan. However, they also had many common clinical features (Supplemental Fig. 3).

All skinfold thicknesses were below the 10th percentile in JMP 200.3, but in his sister, the chin, chest, subscapular, axillary, biceps, triceps, and forearm all showed loss of sc fat, but the abdomen, suprailliac, hips, thigh, and calf were all normal (Supplemental Fig. 4).

The dual-energy x-ray absorptiometry scan revealed only 17.2% total body fat in JMP 200.3 (normal mean ± SD for age and ethnicity matched males: 27.2 ± 5.3%) (11). The truncal and upper and lower extremity fats were 15.9, 17.5, and 20.7%, respectively. Whole-body MRI in JMP 200.3 revealed marked loss of sc fat from the head, neck, thorax, and upper extremities but preservation in the lower extremities (Fig. 2).

Genotyping of the LMNA and ZMPSTE24 genes in the probands, JMP 100.3, and JMP 200.3 did not reveal any mutations.

**Discussion**

All three patients showed many common clinical features, suggesting that they all have the same syndrome (Table 1 and Supplemental Fig. 3). These features include severe panniculitis-induced lipodystrophy, affecting the face, arms, and thorax initially and more severely than the abdomen and lower extremities. There was no acanthosis nigricans, diabetes, or hyperinsulinemia. Only mild hypertriglyceridemia, markedly low HDL cholesterol, and mild elevations of liver enzymes were noted. Thus, overall, these mild metabolic disturbances could be due to partial lipodystrophy, sparing the lower limbs. All the patients had limb muscle atrophy and varying degree of joint contractures, initially and predominantly affecting the hands and feet and later other joints. Other common features were microcytic hypochromic anemia and hypergammaglobulinemia.
We reviewed the literature extensively and found three cases previously reported from Japan that shared at least some features with our patients (3–6) (Table 1). Two of them were siblings with generalized lipodystrophy in the male and partial, upper-body lipodystrophy in the female (3, 4). Both of them had muscle atrophy, joint contractures, and recurrent skin eruptions, which were reported to be steroid responsive. Other features included hypergammaglobulinemia, elevated erythrocyte sedimentation rate, macroglossia, hepatosplenomegaly, calcification of basal ganglia, and mental retardation. Skin biopsy from the female patient showed infiltration of lymphocytes and histiocytes in the region of sweat glands and proliferation of vessels. An autopsy of the male patient revealed severe discrete, multifocal atrophy, and fibrosis of skeletal muscles (5). The im nerves and neuromuscular junctions were well preserved. Calcium deposition was seen in the small vessels of the globus pallidus and centrum semiovale. The patient also had myocardial hypertrophy, chronic pancreatitis, central fatty degeneration of the liver with acute cell necrosis, and a lack of spermatogenesis.

FIG. 2. MRI scans of patient JMP 200.3 in the right panels compared with a control subject (32 yr old healthy Mexican-American male with a body mass index of 21.7 kg/m²) in the left panels. A, Axial MRI of the head through the orbits shows reduction of sc fat but preservation of retroorbital fat. B, Axial MRI of the head through the nose shows reduction of sc fat from the posterior occipital region and from the malar region. C, Axial MRI of the neck just below the chin shows near total loss of sc fat from the neck. D, Sagittal MRI of the head, neck, and thorax through the orbits shows marked reduction in sc fat from the head, neck, and thorax. E, Coronal MRI of the shoulder and arm shows reduced sc fat and muscle mass. F, Coronal MRI through the abdomen and pelvis at the level of the kidneys shows marked loss sc fat from the abdomen and thighs with preservation of retroperitoneal fat. G, Axial MRI through the thorax shows marked loss of sc fat. H, Axial MRI through the abdomen at the level of the kidneys reveals marked loss of sc fat with preservation of perirenal and ip fat. I, Axial MRI through the pelvis at the level of the femoral head shows marked loss of sc fat, especially from the posterior region. Bone marrow fat and the mechanical fat around the hip joint are well preserved. Axial MRIs through the arm (J) and forearm (K) show marked loss of sc fat and reduced muscle mass. Axial MRI of the thigh (L) shows marked loss of sc fat from the posterior and lateral regions but preservation of sc fat from the anterior-medial region and of the calf (M) shows loss of sc fat from the lateral region extending to the anterior and posterior regions with preservation of sc fat in the anterior and medial region. The muscle mass in the thigh appears well preserved, but in the calf it is slightly reduced.
The third patient was a 38-yr-old female with lipodystrophy of the face and upper body, skin rash, deformity of the fingers and toes, basal ganglia calcification, low intelligence quotient, and hepatosplenomegaly (6). Her skin biopsy revealed lymphocytic infiltration in appendages and vessels.

None of the patients from Japan had generalized seizures or anemia, and the pattern of lipodystrophy was not systematically assessed. In contrast, none of our patients had any mental retardation. Nonetheless, some overlapping clinical features and cluster analysis suggest that the Japanese patients may have had the same syndrome seen in our patients. Comparison of the features of these six patients with JMP syndrome with mandibuloacral dysplasia (8, 12), Hutchinson-Gilford progeria syndrome (13, 14), and atypical progeroid syndrome (15) (Table 1) revealed it to be quite distinct from the laminopathies-associated syndromes.

It is likely that the JMP syndrome belongs to the class of inherited autoinflammatory diseases such as familial Mediterranean fever; TNF receptor-associated periodic syndrome; hyperimmunoglobulinemia D with periodic fever syndrome; pyogenic arthritis, pyoderma gangrenosum, and acne syndrome; and the cryopyrinopathies, which are due to mutations in the family of PYRIN domain-containing proteins, proteins interacting with pyrin, and others, resulting in activation of the IL-1β pathway (16, 17). The molecular basis of the JMP syndrome remains to be elucidated.

Acknowledgments

We thank Frank Vuitch, M.D. (Pathology Associates of Texas, Fort Worth, TX) for help in reviewing the histopathology of skin biopsy samples; Geral Dietz, M.D. (University of Texas Southwestern Medical Center, Dallas, TX) for reviewing radiographs of the patients; and Beverley Adams-Huet (University of Texas Southwestern Medical Center, Dallas, TX) for reviewing radiographs. We thank Frank Vuitch, M.D. (Pathology Associates of Texas, Dallas, TX) for help in reviewing the histopathology of skin biopsy samples; and Beverley Adams-Huet (University of Texas Southwestern Medical Center, Dallas, TX) for reviewing radiographs of the patients. We also thank the Dr. Minerva Gómez (Dermatology Service, University of Texas Southwestern Medical Center) for conducting hierarchical cluster analysis and Beverley Adams-Huet (University of Texas Southwestern Medical Center, Dallas, TX) for reviewing radiographs of the patients. None of the patients from Japan had generalized seizures or anemia, and the pattern of lipodystrophy was not systematically assessed. In contrast, none of our patients had any mental retardation. Nonetheless, some overlapping clinical features and cluster analysis suggest that the Japanese patients may have had the same syndrome seen in our patients.

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Address all correspondence and requests for reprints to: Abhimanyu Garg, M.D., Chief, Division of Nutrition and Metabolic Diseases, Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, K5.214, Dallas, Texas 75390. E-mail: abhimanyu.garg@utsouthwestern.edu.

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References