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Seipin-linked congenital generalized lipodystrophy type 2: a rare case with multiple lytic and pseudo-osteopoikilosis lesions

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Abstract

Congenital generalized lipodystrophy (CGL), or Berardinelli–Seip syndrome (BSCL), is a part of lipodystrophic syndromes that constitute a heterogeneous group of genetic or acquired generalized or partial body fat loss disorders. It is a rare autosomal recessive disease characterized by a near-absence of adipose tissue from birth or early infancy and severe insulin resistance. CGL is classified as type 1–4, depending on the gene involved, and bone lytic lesion is found frequently in type 1 especially in long bones, but reported to be rare in type 2. Here we report an active lifestyle 25-year-old woman with type 2 CGL showing multiple bone lytic and pseudo-osteopoikilosis lesions in hands and feet. Radiograph bone survey showed no apparent abnormality in pelvic bone or axial skeletons. Bone marrow was completely absent and extra-skeletal general fat loss was also evident in whole-body magnetic resonance imaging sparing the orbital, axial, sole, and palmar regions. Radiographic bone survey is important even for type 2 CGL to find the change of bones to provide direction of preventing excessive overload or activity.

Keywords

Congenital generalized lipodystrophy, Berardinelli–Seip syndrome, magnetic resonance imaging, leptin

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Introduction

Lipodystrophic syndromes comprise various heterogeneous genetic or acquired disorders with generalized, partial, or localized body fat loss. Although patients with localized lipodystrophy mainly have only cosmetic issues, generalized and partial lipodystrophy occurs associated with severe insulin resistance and its associated complications (1). Congenital generalized lipodystrophy (CGL) is a rare but widely distributed autosomal recessive disease characterized by the absence of body fat from birth (2). CGL is clinically characterized by insulin-resistant diabetes mellitus, hypertriglyceridemia, and fatty liver, caused by a profound deficiency of adipose tissue due to a low plasma concentration level of leptin (3). Effective control of fatty liver, hyperglycemia, diabetes, and other complications has been achieved with leptin replacement therapy (4,5). However, while the diagnosis of CGL is based on clinical examination and genetic analysis, understanding the striking imaging features and importance of bone survey can also contribute to an accurate and timely diagnosis of CGL. CGL is classified as type 1, 2, 3, or 4, depending on the gene mutation point. The two main forms of CGL are acylglycerol-3-phosphate-O-acyltransferase 2 (AGPAT-2)-linked CGL type 1,

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mutation localized to chromosome 9q34, and seipin-linked CGL type 2, mutation localized to chromosome 11q13 (4,6). Seipin-linked CGL type 2 was identified subsequently to AGPAT-linked CGL type 1 and few studies have documented the range of musculoskeletal imaging findings (4,7). Here we report the imaging findings in a 25-year-old woman with a 10-year history of leptin replacement therapy as seipin-linked CGL type 2, who demonstrated multiple osteolytic and patchy sclerotic lesions in the left radius and bones of the bilateral feet and hands. Osteosclerosis, osteolytic lesions, and patchy sclerotic lesions (osteo-poikilosis) have been reported as the imaging features of CGL (7). Osteolytic lesions in small tubular bones or patchy sclerotic lesions have not been previously described in seipin-linked CGL2, though they are a common finding in patients with AGPAT-2-linked CGL type 1 (7). This report describes a case of sepin-linked CGL type 2 showing multiple bone lytic and pseudo-osteopoikilosis lesions limited to the hands and feet with typical clinical and laboratory features. Informed consent was obtained from the patient included in this case report.

Case report

A 25-year-old woman complained of continuous pain in the right fifth finger, which had started a few months previously without preceding trauma. She was a caregiver and had belonged to a rowing club in her college days. The patient's history was not obtained at the first consultation in our hospital. Physical examination revealed a Japanese woman of normal intelligence who looked androgynous and muscular. Her height was 166 cm and weight 53 kg. Movement of her fifth finger was associated with mild pain. Swelling or numbness was not observed. Her hands and feet were large as observed in acromegaly. Her facial features were exaggerated due to prominence of the mandibular bone. Hyperpigmentation was also observed. On radiographs, a lytic bone lesion without calcification was observed in the fifth middle phalanx accompanied by mild adjacent joint space narrowing and subchondral bone sclerosis (Fig. 1). Enchondroma was suspected first and magnetic resonance imaging (MRI) was performed. On MRI of the right hand, bone marrow showed diffuse intermediate signal intensity (iso-signal intensity to muscles) on T1-weighted (T1W) images and very high signal intensity on T2-weighted (T2W) and STIR images (Fig. 2). On fat image with the DIXON method, an almost total lack of subcutaneous and bone marrow fat was evident. The lytic lesion detected on radiograph showed a similar signal to that of the surrounding bone marrow in all sequences. Conditions showing serous bone marrow were suspected from the imaging findings, and the patient's history and medication history were taken.

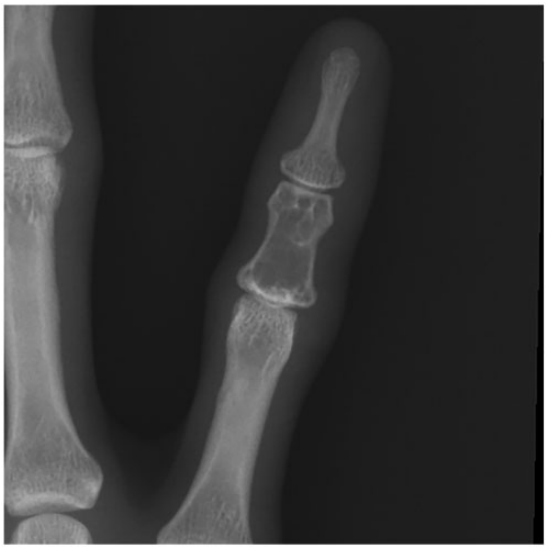

Fig. 1. Frontal radiograph of the right fifth finger. An osteolytic lesion without calcification was observed in the fifth middle phalanx accompanying adjacent joint space narrowing and subchondral bone sclerosis.

The patient had been diagnosed with CGL since birth and genetically diagnosed as having seipin-linked CGL2 when she was 15 years, when she started leptin replacement therapy. One of her two younger brothers was also diagnosed with CGL. Laboratory tests showed mild elevation of AST/ALT and HbA1c of 7.8%, with other parameters within the respective normal ranges.

Bone survey was performed. Background bone mineral density was increased. Multiple osteolytic lesions were noted in the bilateral phalanxes and metacarpal bones in hands (Fig. 3), and bilateral first to fifth metatarsal bones, phalanges, and navicular bones in the feet (Fig. 4). Most of the lytic lesions were located adjacent to subchondral bone. The lesions in the right second, fifth, and left fifth intermediate phalanxes were accompanied by adjacent joint space narrowing and subchondral bone sclerosis with or without geode formation. Multiple epiphyseal osteolytic changes with coarsening of trabeculae were also observed. There was a tendency in the feet to show honeycomb-like osteolytic lesions. Multiple osteopoikilosis-like patchy sclerotic lesions were also observed in the bilateral first metacarpal bones, third middle phalanxes, and left distal radius. Enlargement of maxillary sinuses and prognathism with gaps between the teeth was observed on the skull. Sella tunica was not enlarged. Coxa profunda was observed in the bilateral hip joint. Other long tubular bones, spine, and pelvic bones showed no obvious lytic or sclerotic lesion. Computed tomography (CT) of the right hand also showed multiple lytic and sclerotic lesions without

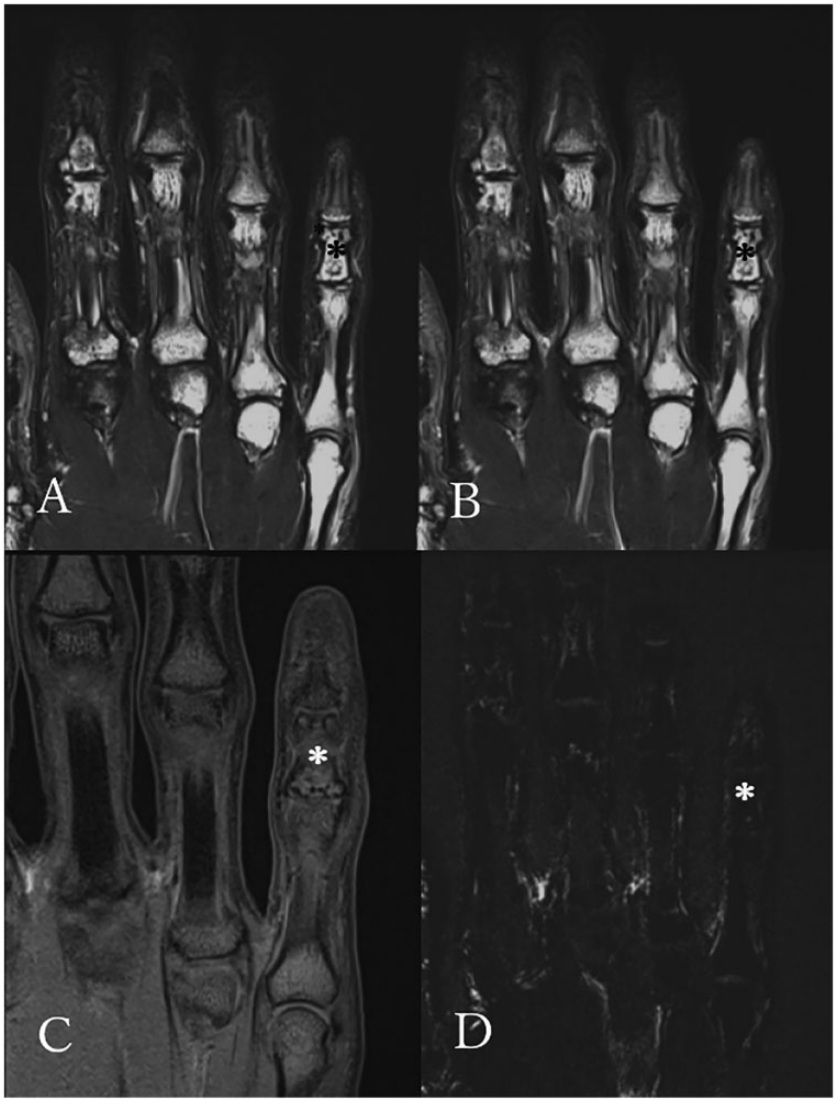

Fig. 2. MRI of the right hand. (a) Coronal T2-weighted and (b) STIR image show very high signal in bone marrow and soft tissue, whereas (c) T1-weighted image shows iso-signal intensity to muscles. (d) DIXON fat image shows total lack of fat. *The osteolytic lesion detected on radiograph. MRI, magnetic resonance imaging.

evident fracture or periosteal reaction. The whole-body MRI performed 10 years ago when she was diagnosed with seipin-linked CGL type 2 was reviewed. The study showed almost a total lack of fat tissue, with only a small amount of fat preserved in the retro-orbital, axillar, sole, and palmar regions (Fig. 5). Observation was selected due to the patient's poorly controlled diabetes, although curettage would normally be undertaken for management of painful lytic lesions in a young active woman because of concern about impending fracture.

Discussion

CGL, or Berardinelli-Seip syndrome (BSCL), is a part of the spectrum of lipodystrophic syndromes constituting a heterogeneous group of disorders categorized based on etiology (genetic or acquired) and distribution of lost adipose tissue, affecting the entire body (generalized) or only regionally (partially) (8). Recent progress in the characterization of the phenotypes of various types of genetic lipodystrophies and elucidation of the molecular defect in many of them has led to increased recognition of these syndromes. However, today, the most prevalent type of lipodystrophy is an acquired form occurring in individuals with HIV infection treated with highly active antiretroviral therapy (HAART) including HIV-protease inhibitors (PI) and HIV-associated lipodystrophy syndrome (HALS) (1).

CGL is a rare autosomal recessive disorder first reported by Bernardinelli and Seip, with a prevalence

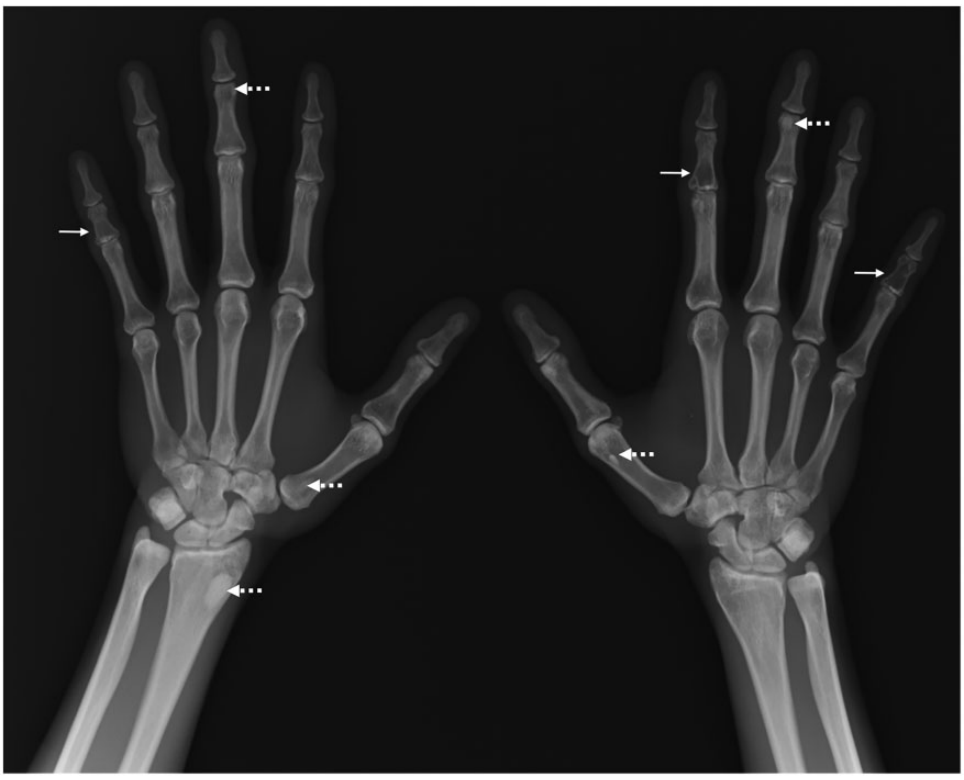

Fig. 3. Anteroposterior radiograph of bilateral hands. Multiple osteolytic lesions (arrows) and osteopoikilosis-like lesions (broken line arrows) in bilateral appendicular bones and left distal radius. Adjacent joint space narrowing and subchondral bone sclerosis are evident in the right second and fifth and left fifth intermediate phalanges.

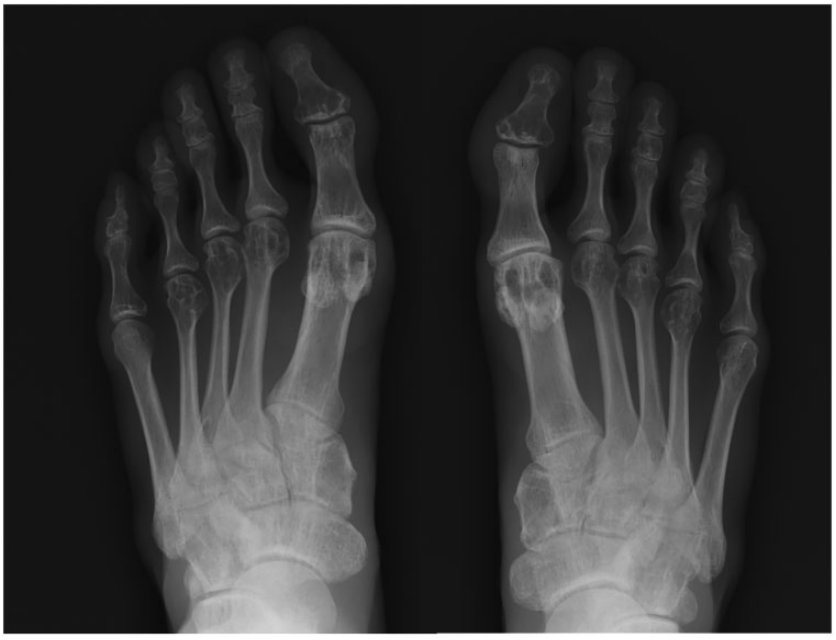

Fig. 4. Anteroposterior radiograph of bilateral feet. Bilateral first to fifth metatarsal bones and phalanges show multiple honeycomb-like osteolytic lesions.

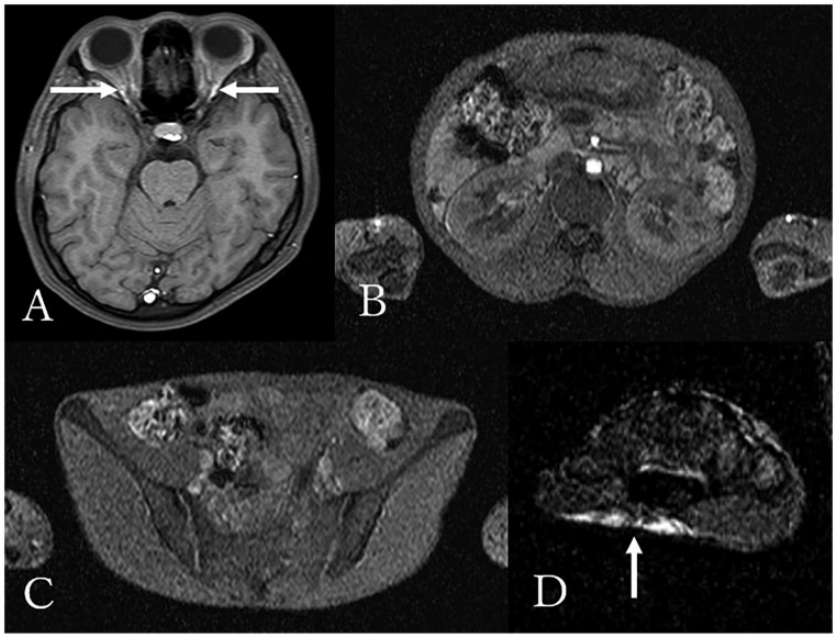

Fig. 5. Whole-body MRI performed 10 years ago. (a) Orbital, (b) renal hilar, (c) pelvic level, and (d) left hand on axial T1-weighted image shows an almost total lack of fat tissue, while a small amount of fat was preserved in the palm and retro-orbital space (arrows).

of less than one in a million in the general population. Since then, >300 patients have been reported in the English literature. Although the two main forms of CGL are acylglycerol-3-phosphate-O-acyltransferase 2 (AGPAT-2)-linked CGL type 1, mutation localized to chromosome 9q34, and seipin-linked CGL type 2, mutation localized to chromosome 11q13, genome-wide linkage analysis has facilitated the identification of two other genes, caveolin 1 (CAV1; type 3) and polymerase I and transcript release factor (PTRF; type 4) (4). Patients with CGL are recognized at birth or soon thereafter due to a near total lack of body fat and prominent muscularity (9). Seipin-linked CGL type 2 was identified subsequently to AGPAT-linked CGL type 1, and only a limited number of reports are available on the musculoskeletal imaging findings in seipin-linked CGL type 2 (7). Patients with CGL type 1 lose all metabolically active adipose tissue present in subcutaneous, intra-abdominal, and intrathoracic regions and bone marrow, but have well-preserved mechanical adipose tissue located in the palms, soles, retro orbita, and periarticular regions (10). On the other hand, patients with CGL type 2 lose both types of adipose tissues earlier in life. The seipin-encoded protein appears to play a role in lipid droplet formation and may also be involved in adipocyte differentiation (11,12). In our patient, scanty fat tissue was preserved in the palm in the most recent MR study, but the almost total lack of fat disappeared as reported previously.

Multiple osteolytic lesions were found in the bilateral phalanxes and metacarpal bones in the hand and in the bilateral first to fifth metatarsal bones, phalanges, and navicular bones in the feet of the patient. Most of the lytic lesions were located adjacent to subchondral bone, with some of them associated with joint space narrowing, subchondral bone sclerosis, or geode in the hands. Focal lytic lesions in the long bones have been reported to be more prevalent in CGL type 1, especially in the appendicular bones and epiphysis of the long bones, and rare in type 2 (7). Although the pathogenesis of lytic lesions in CGL is poorly understood, they are known to grow in size and increase in number during puberty (2,7). Pathologically, cysts, occupied by tissue rich in blood capillaries and thin-walled veins, were reported in patients with CGL (13). Teboul-Core et al. (7) found maldevelopment of the normal adult fatty bone marrow to induce diffuse serous transformation of the bone marrow and cystic change, with all cases showing lytic lesions without sclerotic margin. The radiographic findings in our patient indicated that mechanical stress also underlies the formation of epiphyseal cystic lesion. Lytic bone lesions in patients with CGL are not usually at increased risk of fracture, but pathologic fracture has been also reported (7). Our patient presented with right fifth pain at the point of osteolytic lesion and possible impending fracture. Imaging follow-up and patient education along with modification of patient lifestyle are critical to preventing excessive overload or activity

resulting in fracture. Once fracture occurs, surgical management is surmised to be more difficult in patients with CGL because of insulin resistance and possible cardiac, hepatic, and/or renal dysfunctions. Osteopoikilosis-like patchy sclerotic lesions were also observed in the bilateral first metacarpal bones, third middle phalanxes, and left distal radius in our patient. In contrast to the previous reports, they also showed a tendency to distribution in the appendicular bones in her (2,7).

The differential diagnosis of congenital lipodystrophy includes anorexia nervosa, cachexia, starvation, diencephalic syndrome, progeria, progeroid syndromes, and disorders affecting growth and development. The diagnosis of lipodystrophy itself and typing rely mainly on clinical and genetic testing; laboratory tests can provide additional supportive evidence. Imaging findings of dual-energy X-ray absorptiometry, CT, or whole-body T1W MRI have also been applied to evaluate the pattern of fat loss.

Many complications of lipodystrophy are secondary to the deficient adipose mass, resulting in ectopic storage in the liver, muscle, and other organs, causing insulin resistance. Insulin resistance may lead to diabetes mellitus, hypertriglyceridemia, polycystic ovary syndrome, and non-alcoholic fatty liver disease, which may in turn promote mortality from causes such as heart diseases (cardiomyopathy, heart failure, or myocardial infarction), liver failure, hepatocellular carcinoma, renal failure and acute pancreatitis, and sepsis (8,14). Leptin, a hormone produced by fat cells, is considered to play a major role in the regulation of energy homeostasis (15). The metabolic abnormalities noted in lipoatrophic patients are caused mainly by a shortage of leptin. Currently meterleptin (recombinant human methionyl leptin) replacement therapy is approved for generalized lipodystrophy (8). Meterleptin replacement therapy has been reported to decrease fasting glucose levels and HbA1c, triglycerides, proteinuria, hepatic steatosis, serum transaminase, and normalize gonadotropin secretion in women (4,16). The prognosis of CGL with meterleptin replacement therapy has become more favorable, and bony or rather minor complications will likely have a greater impact on patient quality of life in the near future.

In conclusion, we report a case of sepin-linked CGL type 2 showing multiple bone lytic and pseudo-osteopoikilosis lesions limited to the hands and feet with typical clinical and laboratory features. Understanding the characteristic imaging features and importance of bone survey could contribute to the accurate and timely diagnosis of CGL.

Declaration of conflicting interests

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