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Asymmetric Hypertrophic Cardiomyopathy in Generalized Lipodystrophy Characterized by Cardiovascular Magnetic Resonance

Alessandra Scatteia, MD;[1] Carmen Pagano, MD;[2] Pasquale Guarini, MD;[3] Carmine Pascale, RT;[3] Gennaro Marotta, MD;[2] Pasquale Perrone-Filardi, MD, PhD;[1] Chiara Bucciarelli-Ducci, MD[4], PhD; Santo Dellegrottaglie, MD, PhD.[3,5]

[1]Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy; [2]Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy; [3]Division of Cardiology, Ospedale Medico-Chirurgico Accreditato Villa dei Fiori, Acerra (Naples), Italy; [4]NIHR Cardiovascular Biomedical Research Unit, Bristol Heart Institute, University of Bristol, UK, [5]Z. and M.A. Wiener Cardiovascular Institute and M.-J. and H.R. Kravis Center for Cardiovascular Health, Mount Sinai Medical Center, New York, NY, USA.

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Correspondence to:

Dr. Santo Dellegrottaglie
Division of Cardiology
Ospedale Medico-Chirurgico Accreditato Villa dei Fiori
C.so Italia, 157
80011, Acerra (Naples), Italy

Tel: +39-081-3190403
Email: santo.dellegrottaglie@mssm.edu

Abstract

Lipodystrophy is a rare syndrome characterized by loss of adipose tissue, insulin resistance, hypertriglyceridemia, steatohepatitis, splenomegaly, acanthosis nigricans and cardiomyopathy. It can be congenital or acquired with partial or generalized involvement. The most frequent cardiac finding is that of an hypertrophic symmetric cardiomyopathy which progresses with age. We describe here a case of a young man with generalized lipodystrophy who came to our cardiovascular magnetic resonance (CMR) laboratory to assess cardiac involvement. CMR showed a focal area of hypertrophy involving the basal anterior septum and basal anterior free wall, with normal wall thickness of remaining left ventricle segments. There was also an intramyocardial area of late gadolinium enhancement with the same distribution, with no evidence for myocardial edema and/or fatty infiltration at the same level. No left ventricular outflow tract obstruction was found. To our knowledge this is the first reported case of asymmetric hypertrophic cardiomyopathy in generalized lipodystrophy fully characterized by CMR. The mechanisms underlying the cardiomyopathy in this disease are still unclear.

Key-words: Hypertrophy; cardiomyopathy; magnetic resonance imaging.

Introduction

Lipodystrophy is a rare syndrome characterized by loss of adipose tissue, with typical persistence of fat in certain anatomical regions such as buccal region, tongue, palm of the hand and sole of the foot.[1] The etiology may be congenital (with an autosomal recessive pattern) or acquired and the involvement can be partial or generalized.[2] Other clinical features may include insulin resistance, hypertriglyceridemia, steatohepatitis, acanthosis nigricans, splenomegaly, acromegaloid features and cardiomyopathy.

Cardiac abnormalities associated with lipodystrophy may range from incidental evidence of asymptomatic cardiomyopathy, with hypertrophic phenotype (more often with a diffuse left ventricular involvement) or with dilated phenotype, up to severe heart failure symptoms.[3,4] In this condition, the underlying mechanisms of cardiomyopathy are still unclear, but the cardiac involvement seems to be associated with a poor prognosis.[4] We report here a case of generalized lipodystrophy with evidence of asymmetric hypertrophic cardiomyopathy.

Case Report

The patient is a male subject diagnosed with generalized lipodystrophy at birth because of severe lipoatrophy and acanthosis nigricans involving the skin of axillae and groin. He was then referred to pediatric outpatient clinic for periodic follow-up and the diagnosis was confirmed during the growth. Since the age of 10 months abdominal ultrasound showed hepatic steatosis with hepatosplenomegaly and a 3/6 systolic murmur was noted. During puberty, echocardiography showed asymmetric hypertrophic cardiomyopathy involving the interventricular septum with no left ventricular outflow tract

obstruction and mild mitral regurgitation. His blood pressure values have consistently been within normal ranges. ECG showed Q waves in the precordial leads. At the age of 17, esophagogastroduodenoscopy evidenced the presence of esophagus varices and treatment with propranolol was established. Laboratory results showed impaired fasting glucose, thrombocytopenia and mild hypertriglyceridemia. At the age of 30, ECG showed inverted T waves in precordial leads and echocardiography confirmed left ventricular hypertrophy confined to the interventricular septum. He was then referred to our CMR laboratory at a time when the phenotype of a generalized lipodystrophy was evident (**Figure 1**).

CMR images were acquired with a 1,5 Tesla scanner equipped with a multi-element phased-array cardiac coil. Scout images confirmed the general lack of subcutaneous and visceral adipose tissue (**Figure 2**). The cardiac imaging protocol included the acquisition of a series of cine SSFP images, dark-blood FSE T1-weighted and STIR T2-weighted images, and late post-contrast T1-weighted images (acquired 10-15 min after the injection of a bolus of gadobenate dimeglumine; 0.10 mmol/kg) in standard cardiac views. At the left ventricular level, CMR showed normal regional and global systolic function (ejection fraction = 71%), an increased global indexed mass (130 gr/m^2) and myocardial hypertrophy limited to the basal anterior septum and the contiguous anterior free wall (maximum end-diastolic wall thickness = 22 mm; **Figure 3**). The remaining left ventricular segments showed normal values of wall thickness. In the same anterior/antero-septal region, the demonstration of an hypointense signal on pre-contrast dark-blood images was not compatible with the presence of myocardial edema and/or fatty infiltration (**Figure 4**). Instead, post-contrast images revealed a distinct focal

area of late gadolinium enhancement in the hypertrophied region of the left ventricle as a possible marker of myocardial fibrosis/necrosis (**Figure 5**). Left atrium was dilated, no significant mitral valve regurgitation was detected and no left ventricular outflow tract obstruction was found.

Discussion

Lipodystrophies are a rare group of diseases characterized by generalized or partial lipoatrophy, the former affecting all fat deposits, with the latter sparing visceral fat and adipose tissue in the upper part of the body.[2] They can be due to genetic or acquired causes, and the loss of adipose tissue leads to severe metabolic alterations such as insulin resistance, low leptin levels with increased appetite, hypertriglyceridemia, and fat deposits in lymphoreticular tissues. Cardiac abnormalities have been described since 1959 in the context of congenital generalized lipodystrophy, but they have not been noted in partial lipodystrophies such as the Dunnigan-type.[1] The most frequent cardiac abnormality is symmetric hypertrophic cardiomyopathy, typically seen in patients with mutations involving the gene encoding for seipin which is important for fat biosynthesis.[3] Additional cardiac abnormalities described in the literature are marked autonomic disfunction and dilated cardiomyopathy with severe heart failure.[3-5] The pathophysiology of the cardiomyopathies remains unclear, but it does not appear to be linked to the development of hypertension, as this is a rather unusual finding in patients with lipodystrophy.

From a theoretical standpoint, the insulin resistance typically observed in these patients may prompt cardiomyocyte hypertrophy by activating insulin-like growth factor (IGF)-1

receptors, which are largely expressed in the myocardial tissue and stimulate cell growth.[6] A magnetic resonance spectroscopy and imaging study found that myocardial triglyceride content was elevated in hypertrophied cardiomyocytes of patients affected by generalized lipodystrophy.[7] These findings suggest that triglyceride deposit might cause a “lipotoxic cardiomyopathy”, as exceeding lipids are shunted into non-oxidative pathways with the accumulation of toxic lipid species.[8] This may alter, in turn, cellular signaling, promoting mithocondrial dysfunction and cell apoptosis.

Asymmetric left ventricular hypertrophy has been reported only in few cases, involving young patients with lipodystrophy.[9] It may possibly be consequence of the hyperinsulinaemia-induced overgrowth of an otherwise healthy heart, finally resulting in disproportionate thickening of the interventricular septum.[10] To our knowledge this is the first case with complete CMR tissue characterization of an asymmetric left ventricular hypertrophy observed in an adult affected by generalized lipodystrophy. The patient had evidence of a focal area of cardiac hypertrophy involving the basal anterior septum and anterior free wall, with normal wall thickness of the remaining left ventricular segments. There was also a limited area of late gadolinium enhancement with the same regional distribution, indicating myocardial tissue damage (potentially myocardial fibrosis/necrosis). This is a highly intriguing finding, as asymmetric hypertrophy with late gadolinium enhancement involving the hypertrophied segment has been repeatedly described in patients with sarcomeric hypertrophic cardiomyopathies and, recently, has been linked to an adverse prognosis.[11,12] In this specific case, pre-contrast dark blood images helped to rule out the presence of edema or fatty infiltration in the hypertrophic

segments, while the observed area of signal hypointensity on both T1- and T2-weighted images could be indicative of reduced cellularity or tissue colliquation.

In conclusion, in this case describing a patient with generalized lipodystrophy, CMR imaging was used to assess cardiac involvement with tissue characterization and documented asymmetric non-obstructive left ventricular hypertrophy with a distinct area of late gadolinium enhancement. Our findings might help shedding new light on the yet mysterious pathophysiology of the cardiac involvement that, when detected in a patient with lipodystrophy, is considered to be associated with poor prognosis. However, more studies are needed to better characterize the big range of cardiac abnormalities that can occur in these rare diseases.

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Figure legend

Figure 1: Patient's phenotype showing the features of a thin young man with an acromegaloid appearance and lack of subcutaneous fat.

Figure 2: Coronal scout image confirming the absence of subcutaneous and visceral adipose tissue; severe spine scoliosis is also noted.

Figure 3: Focal hypertrophy (arrow) of the basal anterior septum and the contiguous anterior free wall as seen on short-axis view (**A.**) and 3-chamber view (**B.**) on SSFP imaging.

Figure 4: Pre contrast dark blood images with FSE T1-weighted technique (**A.**) and STIR T2-weighted technique (**B.**), both showing a hypointense area (arrow) in the hypertrophic anterior/antero-septal region excluding, respectively, the presence of fatty infiltration and edema.

Figure 5: Late post-contrast images in short-axis view (**A.**) and modified 2-chamber view (**B.**) showing a focal area of late gadolinium enhancement (arrow) involving the hypertrophic anterior/antero-septal region and suggestive of myocardial fibrosis/necrosis.

Figure 1.

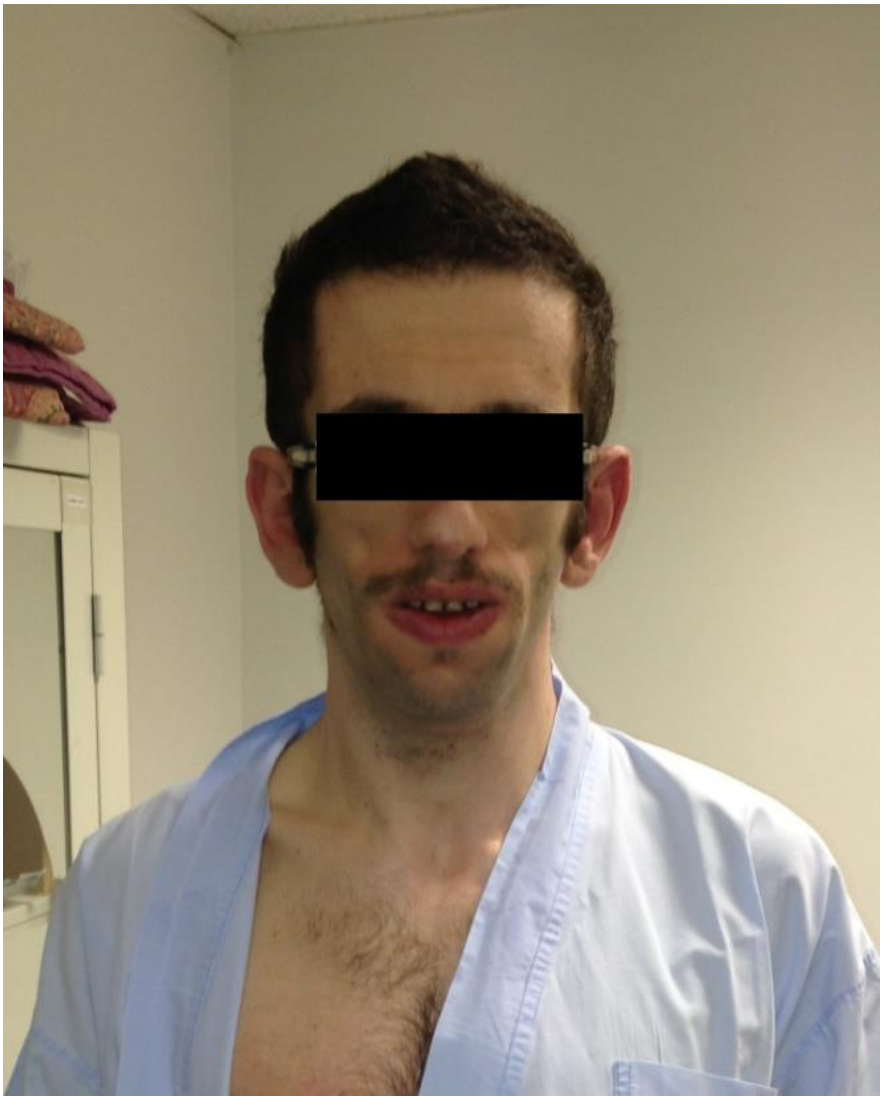


Figure 2.

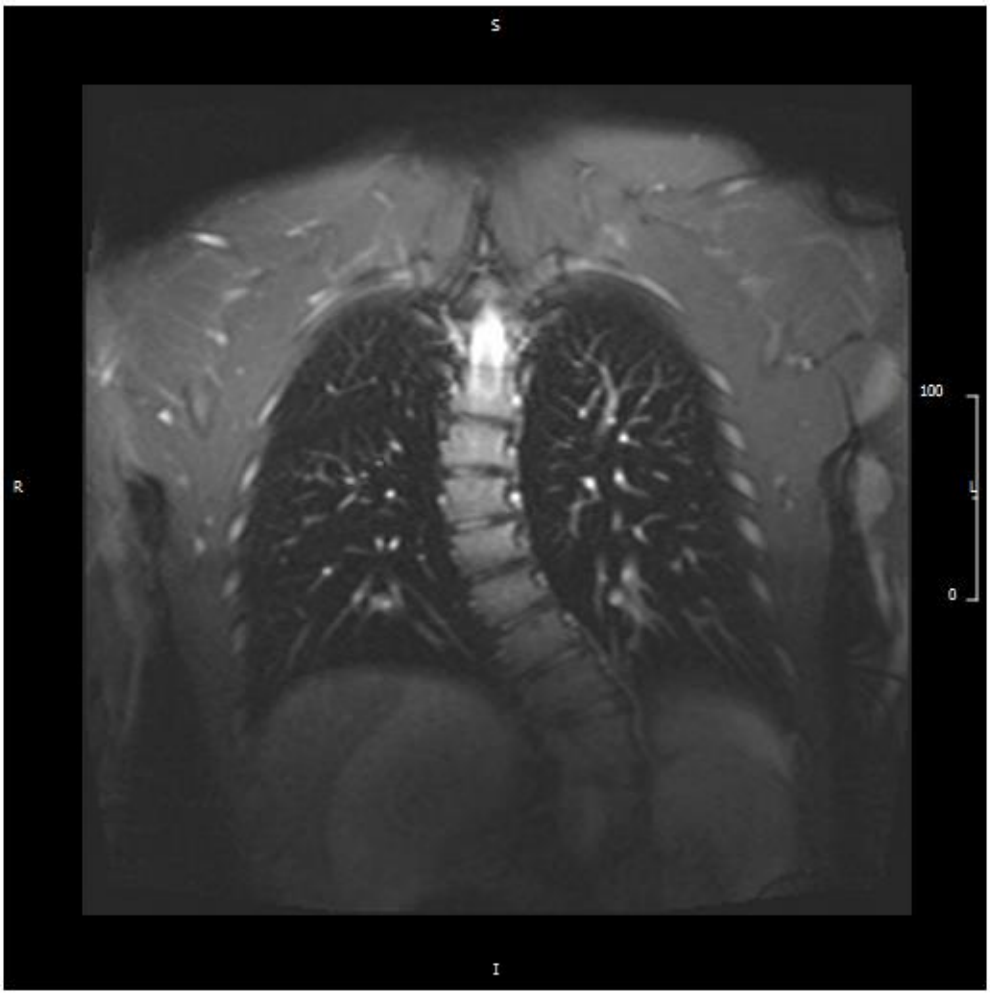
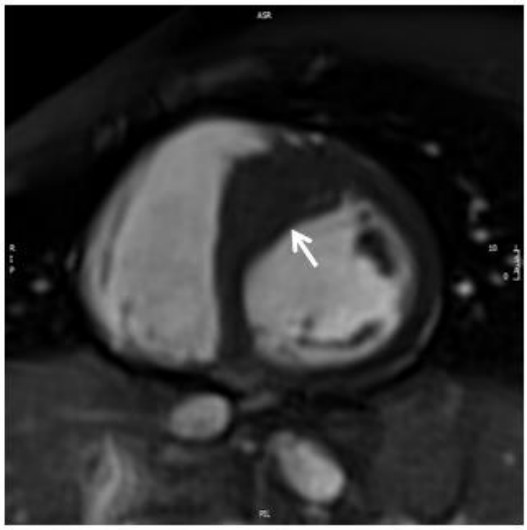


Figure 3.

A.



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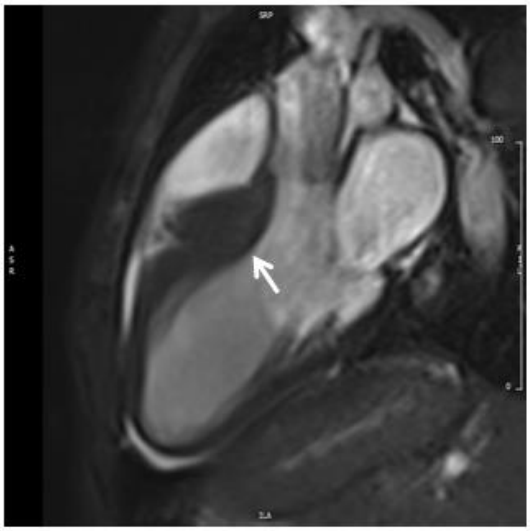
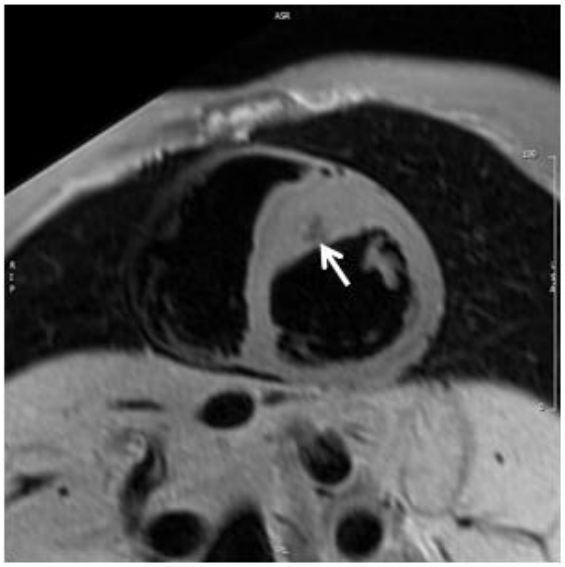


Figure 4.

A.



B.

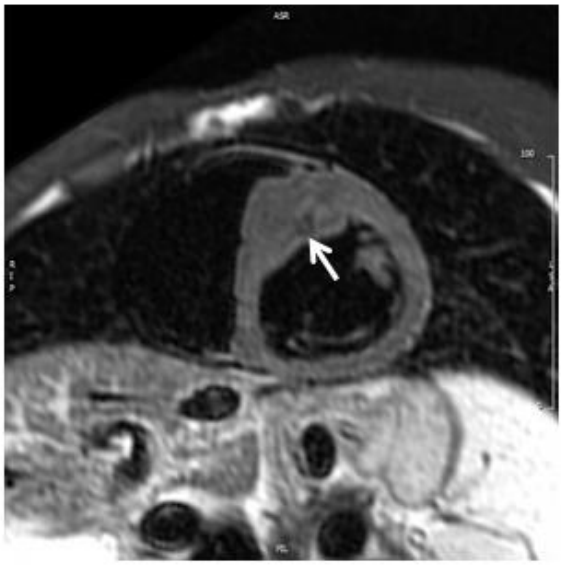
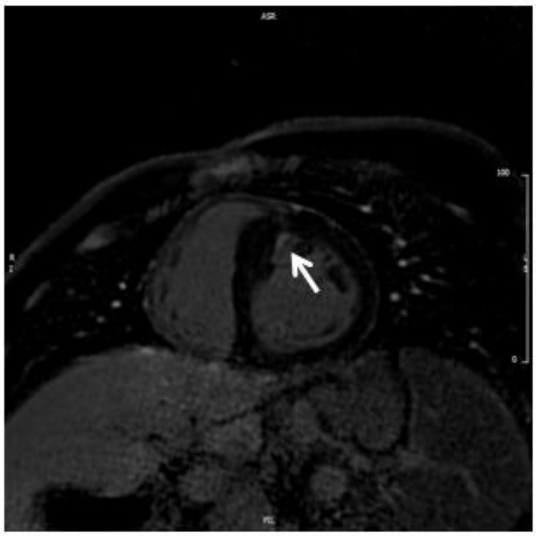


Figure 5.

A.



B.