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Musculoskeletal

Denervation pseudohypertrophy of calf muscles associated with diabetic neuropathy

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ABSTRACT

Denervation of muscle usually leads to muscle atrophy with fatty replacement but, uncommonly, also results in muscle hypertrophy or pseudohypertrophy with fatty replacement. We report the ultrasonographic and magnetic resonance imaging (MRI) findings of a patient with diffuse fatty infiltration of calf muscles as a result of denervation pseudohypertrophy. The elevated fasting glucose, neurogenic electromyographic changes, and muscle atrophy with adipose tissue infiltration are consistent with diabetic neuropathy as the cause of denervation pseudohypertrophy. Lumbosacral radiculopathy and plexopathy were excluded by MRI. The imaging features reported in the literature are reviewed. The important differential diagnosis of infiltrating lipoma and denervation hypertrophy, as well as other causes of monomelic hypertrophy or swelling, is discussed. This case report demonstrates the importance of MRI, with clinical, biochemical, electrophysiological, and histologic correlation in the diagnosis of denervation pseudohypertrophy. Correct diagnosis of denervation pseudohypertrophy has an important role in guiding further investigations and treatment of the disease and the underlying cause.

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Introduction

Denervation of muscle could be a result of trauma, neoplasia, neuropathy, infection, autoimmune process, and vasculitis

[1]. Findings from magnetic resonance imaging of denervated muscles are well documented in the literature [1,2]. Characteristic signal abnormalities of the muscles involved depend on the stage of denervation. Acute and subacute denervation show high signal intensity in fluid-sensitive

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sequences [1]. Although these denervation changes have been reported as early as 4 days after a nerve insult, the hyperintense signal is usually not detectable at 2 to 3 weeks [2]. Chronic denervation shows increased T1-weighted signal intensity that is related to fatty infiltration [1]. Denervation often leads to muscle fiber atrophy and results in the loss of muscle volume. Uncommonly, the muscle may respond to denervation by enlargement, such as the muscles in pseudohypertrophy [3]. We described a patient with denervation pseudohypertrophy of unilateral calf muscles related to diabetic neuropathy, with a review of the literature.

Case report

A 53-year-old man with good health in the past presented at our institution with painful swelling on the right calf of 3 days' duration. He had no history of overt recent trauma; however, he had an injury 2 months before the swelling was noted. The patient was hit by a vehicle as a pedestrian and complained of pain in the left ankle and foot, which, during presentation, had already subsided after conservative management. On examination, the patient's right calf was swollen and tense with increased warmth; however, there was no excessive pain on passive ankle dorsiflexion. The vital signs, including blood pressure, pulse rate, and oxygen saturation, were normal. Blood test results were normal, except that random blood glucose was elevated at 12.1 mmol/l. Diabetes was subsequently confirmed by a fasting glucose level of 10.8 mmol/l and HbA1c of 9.0%.

Urgent ultrasound scan of the right lower limb showed diffusely increased reflectivity of the calf muscles including the gastrocnemius and soleus muscles. An elongated complex hypoechoic area was present along the myotendinous junction of the lower gastrocnemius muscle (Fig. 1). There was no



Fig. 1 – Ultrasound image of the right leg, extended longitudinal view. Fatty infiltration of gastrocnemius (arrow) and soleus (arrowhead), as evidenced by diffusely increased echogenicity of the muscles, was present. Muscle tear of gastrocnemius, as evidenced by an elongated hypoechoic structure at myotendinous junction (in between calipers), was present.

evidence of deep vein thrombosis in the right lower limb. No popliteal cyst was detected. No subcutaneous edema or gaseous shadow was evident to suggest cellulitis or necrotizing fasciitis. In view of the suspected muscle pathology such as myositis and muscle tear, MRI of the right leg was performed (Fig. 2). It showed diffuse fatty infiltration of the posterior superficial compartment of right calf muscles, including the gastrocnemius and soleus muscles. There was no evidence of muscle atrophy, but the right calf muscles showed a larger volume compared with the left calf. The features are consistent with either denervation pseudohypertrophy or an infiltrative lipomatous lesion. A lentiform area of intermediate signal intensity on T1-weighted images, and slightly high signal intensity on T2-weighted images was present at the myotendinous junction of the right gastrocnemius muscle, representing muscle tear. There were muscle edema and mild contrast enhancement, especially immediately adjacent to the site of the muscle tear.

Follow-up MRI of the right calf at 3 months from presentation (Fig. 3) showed persistent diffuse intramuscular fatty infiltration and mild hypertrophy of superficial posterior compartment of the right leg. The muscle tear became hypointense on both T1- and T2-weighted images, consistent with healing. There was interval resolution of muscle edema and contrast enhancement.

Electrophysiological tests including nerve conduction study and electromyography were performed at 5 months from presentation. There was evidence of mild polyneuropathy of bilateral tibial and sural nerves with prolonged distal latency and decreased motor velocity. Neurogenic changes in the right gastrocnemius muscle with positive sharp waves and fasciculations, and giant amplitude of motor unit action potential with reduced recruitment pattern were present. The absence of muscle activity in the right soleus muscle was evident. Giant amplitude of motor unit action potential consistent with neurogenic change was also present in bilateral vastus lateralis and right lumbar paraspinal muscles.

Follow-up MRI at 7 months (Fig. 4) showed persistent fatty infiltration of calf muscles and scarring of the old muscle tear. There was further resolution of muscle edema. MRI of the lumbosacral spine and plexus was performed at 9 months, and there was no evidence of lumbosacral radiculopathy or plexopathy. In view of the possibility of a lipomatous lesion as shown on MRI, muscle biopsy was performed. Intraoperatively, marked fatty infiltration of the right gastrocnemius and soleus muscle was found.

Histopathologic examination showed prominent multifocal scattered atrophic skeletal muscle fibers in the midst of mature adipose and fibrous connective tissue (Fig. 5). Nuclear bags appearing as clumps of nuclei encircled by the remaining sarcolemmal membrane were also seen (Fig. 6). The features are those of prominent atrophy of skeletal muscle fibers associated with infiltration by mature adipose tissue and focal nuclear bag formation, consistent with neurogenic myopathy with fatty infiltration. The findings are not those of an intramuscular lipoma, which is a well-circumscribed adipocytic lesion characterized histologically by lobules of mature fat cells bordered by skeletal muscle fibers at the periphery. Multifocal scattered atrophic skeletal muscle fibers and nuclear bags are inconspicuous in this lesion.

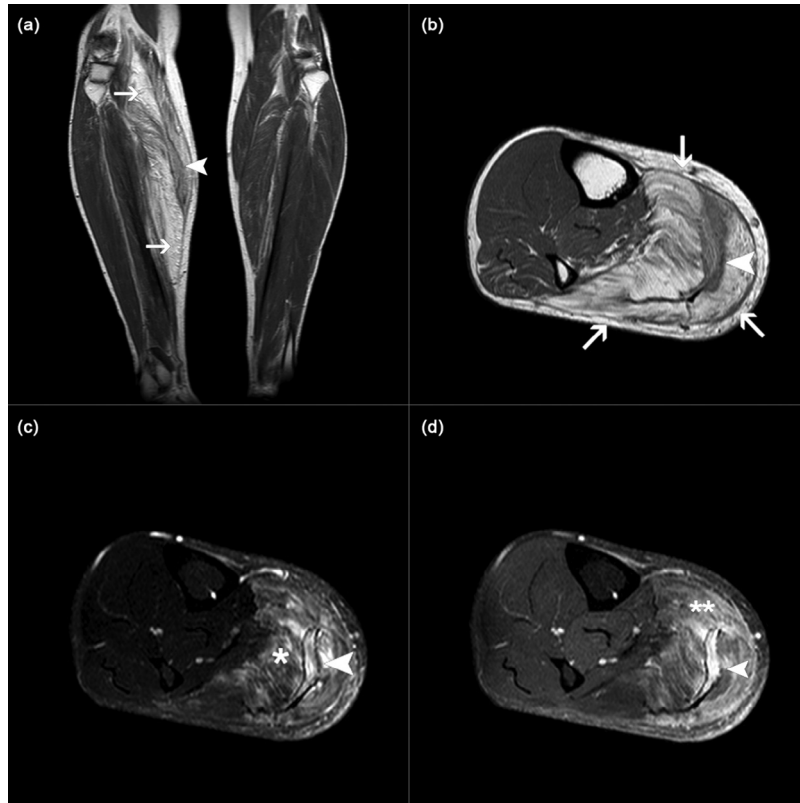


Fig. 2 – MRI of right leg. (a) Coronal proton density (PD)-weighted image of both leg (TR = 3000 ms, TE = 30 ms). (b) Axial T1-weighted image (TR = 668 ms, TE = 7 ms), (c) Axial T2-weighted fat-saturated image (TR = 3821 ms, TE = 70 ms), (d) Post-gadolinium axial T1-weighted fat-suppressed image (TR = 598 ms, TE = 20 ms) of middle level of right leg. Diffuse fatty infiltration and mild enlargement of right gastrocnemius and soleus muscles (arrows), as evidenced by intramuscular high signal intensity in T1- and PD-weighted images, and low signal intensity in fat-suppressed images, were present. Feather-like muscle architecture was preserved. Myotendinous tear of right gastrocnemius muscle (arrowhead) with surrounding edema (asterisk) and contrast enhancement (double asterisk) was present.

On follow-up after 1 year, the calf hypertrophy persisted but was less tense. The patient had calf tension discomfort on prolonged walking.

Discussion

The differential diagnosis of the unilateral calf enlargement includes inflammatory, infective, vascular (lymphedema, venous thrombosis, and hemorrhage), and neoplastic conditions [4]. Congenital causes of unilateral calf enlargement include hemihypertrophy syndromes, including as Klippel-Trenaunay syndrome, Proteus syndrome, macrodystrophia lipomatosa, and dystrophic muscle conditions such as Duchenne muscular dystrophy [4]. These conditions should start at a young age. Denervation pseudohypertrophy of the calf muscles is a rare cause of unilateral calf enlargement and is usually overlooked.

Denervation pseudohypertrophy is characterized by muscle enlargement due to prominent accumulation and interspersation of fat in between muscle fibers, instead of hypertrophy of muscle fibers. It is the result of partial denervation of muscle and may be associated with various causes of muscle denervation. These include intraspinal neurinoma, anterior horn cell

diseases (such as poliomyelitis and spinal muscular atrophy), spina bifida, radiculopathy (especially those at S1 level related to disc herniation), or peripheral nerve disease or injury [3,5,6]. In a series of 5 cases by Pantazis et al. [6], 2 patients had remote trauma, 2 had chronic radiculopathy, and 1 had a history of poliomyelitis. Pseudohypertrophy is also a well-recognized phenomenon in patients with Duchenne and other muscular dystrophies [3]. Lee et al. [7] described the association of denervation pseudohypertrophy of calf muscles with diabetic neuropathy. The pathophysiology of the fatty infiltration of denervation pseudohypertrophy has been reported [4]. The denervation led to a reduction in muscle fiber size, resulting in the reduction of muscular tension and relative inactivity. The pluripotent mesodermal cells are stimulated to form lipocytes, leading to fatty infiltration.

Clinically, denervation pseudohypertrophy may present as a painless palpable swelling or mass of the muscle involved. There may be a clinical history of neurologic disease. Previous case reports [3,5,6,8] described the involvement of calf muscles, such as the gastrocnemius, soleus, flexor hallucis longus, and peroneal muscles, in denervation pseudohypertrophy. Involvement of the gluteal muscles, namely the tensor fasciae latae and gluteus medius [3], infraspinatus muscle [9], masticatory muscles [10], and tongue muscles [11], has also been reported.

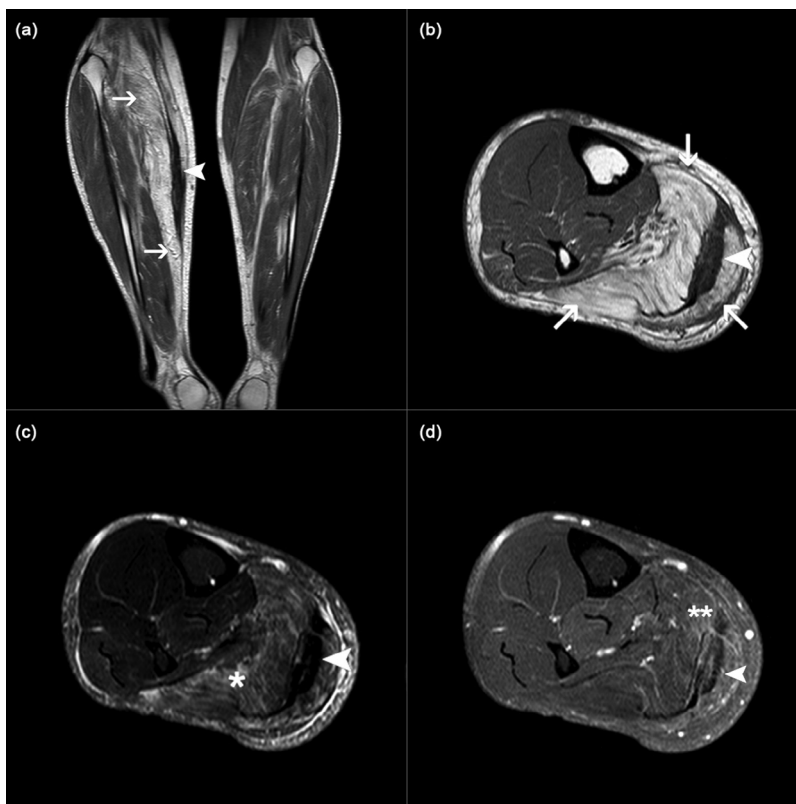


Fig. 3 – Follow-up MRI of right leg, 3 months after images in [Figure 2](#) were taken. (a) Coronal proton density-weighted image of both legs (TR = 3000 ms, TE = 30 ms). (b) Axial T1-weighted image (TR = 612 ms, TE = 7 ms), (c) Axial T2-weighted fat-saturated image (TR = 4840 ms, TE = 70 ms), (d) Post-gadolinium axial T1-weighted fat-saturated image (TR = 548 ms, TE = 20 ms) of middle level of right leg. Persistent diffuse intramuscular fatty infiltration and mild hypertrophy of superficial posterior compartment of right leg (arrows). Scarring at the site of muscle tear was evidenced by hypointensity on T1- and T2-weighted images (arrowhead). There was partial resolution of muscle edema (asterisk) and contrast enhancement (double asterisk).

On ultrasound scan, pseudohypertrophy of muscle is evident by reflective linear strands within the muscle belly [4]. Computed tomography shows an enlarged circumference of the involved limb. There is reduced attenuation of the muscle,

showing low-attenuation feather-like strands within the muscle involved. MRI also shows linear and feather-like T1-weighted high signal intensity areas within the muscle, which is suppressed in fat-saturated sequences. The computed tomography

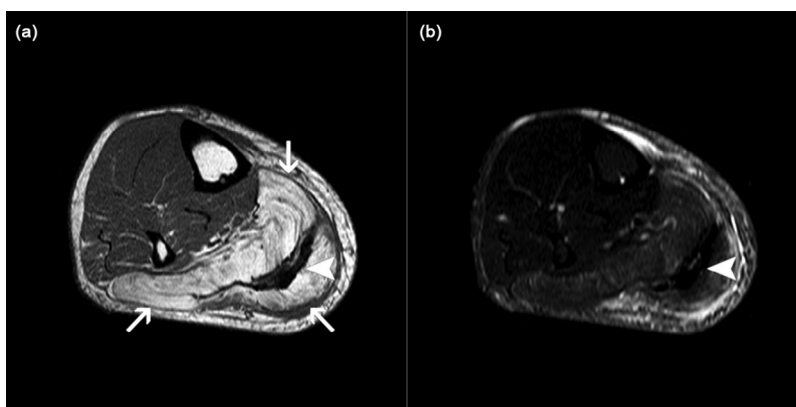


Fig. 4 – Follow up MRI of right leg, 7 months after images in [Figure 2](#) were taken. (a) Axial T1-weighted image (TR = 556 ms, TE = 7 ms), (b) Axial T2-weighted fat-saturated image (TR = 5725 ms, TE = 70 ms) at middle level of right leg. Persistent intramuscular fatty infiltration (arrows) and scarring related to old muscle tear (arrowheads). There was further resolution of muscle edema.

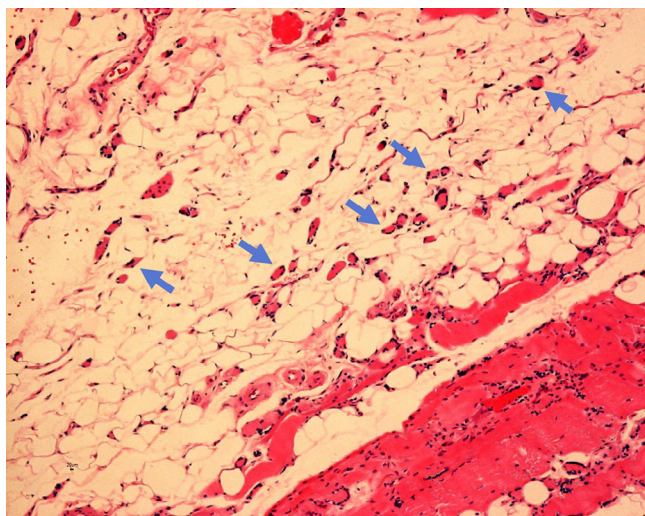


Fig. 5 – The muscle biopsy showed prominent multifocal scattered atrophic skeletal muscle fibers (arrows) in the midst of mature adipose and fibrous connective tissue.

and MRI findings correspond to the interspersion of fats in between muscle fibers [4,6,12]. There is generalized enlargement of the affected muscle, with diffuse distribution of fat and preservation of normal architecture. Associated muscle edema, as demonstrated by T2-weighted hyperintensity, and mild contrast enhancement may occur [6].

An important differential diagnosis of the MRI features of denervation pseudohypertrophy is deep infiltrating intramuscular lipoma, which cannot be distinguished from denervation pseudohypertrophy by imaging of the affected muscle alone. Deep infiltrating intramuscular lipoma was classified as a deep soft-tissue lipoma in the review by Murphey et al. [13]. It was reported as a mass isointense to subcutaneous fat that infiltrated and extensively interdigitated the muscle, creating a striated appearance. This type of lipoma could extend across

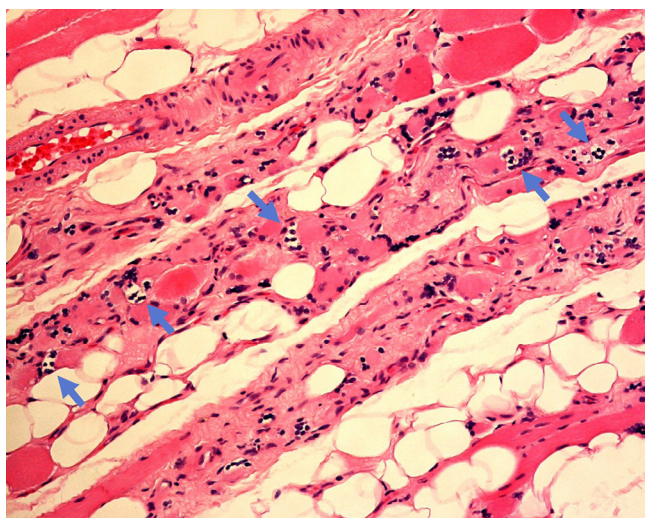


Fig. 6 – Scattered nuclear bags (arrows) appearing as clumps of nuclei encircled by the remaining sarcolemmal membrane were present.

intermuscular planes and may involve multiple muscles. The characteristic striated appearance was reported to allow a confident diagnosis of intramuscular lipoma [13]. In general, deep soft-tissue lipomas were reported [13] to affect large muscle groups of the lower extremity, trunk, shoulder, and the upper extremity. Infiltrating intramuscular lipomas in the lower extremity were also reported as infiltrating lipomas [14], diffuse intramuscular lipomas [15], or diffuse intramuscular lipomatosis [16]. Histologic examination showed mature lipocytes interspersed or intervened between normal skeletal muscle fibers [14] or skeletal muscle fibers with atrophy in some areas [16]. Results of a nerve conduction test and electromyography were normal [14]. There were no degenerative changes to suggest primary muscular diseases in the histologic examination [16]. Primary muscular disease and neurologic disorders may be evident on clinical history [16]. Therefore, based on the clinical features, electrophysiological and pathologic investigations are helpful in distinguishing such intramuscular lipomatous lesions from denervation pseudohypertrophy.

Focal intramuscular mass lesions with hyperintense T1-weighted signal interspersed including hemangiomas, lipomatous masses, hemorrhagic processes, and abscesses show mass effect with distortion of the muscle contour [3]. This is different from pseudohypertrophy or infiltrating lipoma, which shows generalized muscle enlargement with mottled fatty infiltration and preservation of normal smooth contour.

True hypertrophy related to muscle denervation, which is characterized by enlargement of the remaining innervated muscle fibers, has been reported in the literature [3,4]. Such cases are characterized by the absence of signal changes on MRI, with signal intensities identical to normal muscles [3]. These features enable the differentiation of hypertrophy from pseudohypertrophy. Coexisting denervation hypertrophy [3] or atrophy [7] with denervation pseudohypertrophy has been reported. Other causes of muscle hypertrophy include overuse of the muscle and compensatory hypertrophy of the muscle as a response to functional loss of other muscles [12].

Myonecrosis should be considered in a diabetic patient who presents with acute painful swelling in the lower extremity. On ultrasound, it is shown as diffuse muscle swelling and edema evident by increased echogenicity [17], which could be indistinguishable from myositis or pseudohypertrophy. On MRI, there is diffuse muscle edema on fat-suppressed T2-weighted images. The involved area is hypointense on T1-weighted images with loss of clear definition of muscle fiber pattern [18]. Foci of hyperintensity on T1-weighted images due to hemorrhage may be present [19]. A mass with peripheral gadolinium enhancement and central necrosis may be found [18]. Therefore, MRI, with its excellent soft-tissue characterization, is the preferred imaging modality for investigation [3].

The clinical and imaging features of our patient were consistent with those in the literature. The diffuse lipomatous infiltration of muscle was likely a long-standing disease and the acute symptoms were more likely to be related to the muscle tear than to the underlying denervation. The more prominent focal edema and contrast enhancement surrounding the muscle tear were more likely to be related to muscle injury than to denervation, where a more diffuse edema would be expected. Any possible causality between the denervation pseudohypertrophy and the muscle tear had not been

reported in the literature. The electromyographic abnormalities were compatible with a neurogenic disease related to lower motor neuron dysfunction. The electromyography revealed functional abnormalities of muscles, such as the bilateral vastus lateralis and right paraspinal muscles, which were not evident on MRI. The bilateral electrophysiological abnormalities were consistent with a polyneuropathy, which was probably related to diabetes. Lumbosacral polyradiculopathy and plexopathy were also possible causes of polyneuropathy and had been excluded by MRI in our patient.

Correct diagnosis of denervation pseudohypertrophy has an important role in further management. It guides the direction of further investigations toward any local or systemic disease affecting the nervous system. Besides helping to make the correct diagnosis of denervation pseudohypertrophy, MRI also has an important role in investigating any underlying pathology of the nervous system [12].

Conclusion

MRI is a useful investigation tool for a painful swollen leg, especially when ultrasound findings are inconclusive. It provides important information for the correct diagnosis and guidance for further investigations to confirm the diagnosis and study the underlying causes.

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