Infantile-onset *LMNA*-associated Muscular Dystrophy Mimicking Juvenile Idiopathic Inflammatory Myopathy

To the Editor:

Juvenile idiopathic inflammatory myopathy (JIIM) refers to a group of rare chronic autoimmune conditions. Juvenile dermatomyositis (JDM) is the most common JIIM. The hallmarks of JDM are characteristic cutaneous features and proximal muscle weakness; however, adermatitic forms have been described. Polymyositis presents with both proximal and distal muscle weakness, muscle atrophy, and similar degrees of dysphagia, arthritis, and contractures[1]. Although magnetic resonance imaging (MRI) is widely used, muscle biopsy remains a critical tool in the diagnosis of JIIM, especially in atypical cases[1].

Recently, *LMNA*-associated congenital muscular dystrophy (LMNA-CMD) has been reported as a novel and severe form of laminopathy with secondary inflammatory changes mimicking inflammatory myopathies[2,3]. Mutations in the *LMNA* gene encoding lamin A/C are responsible for multiple disease phenotypes[4]. Some of them may present early in life as a congenital muscular dystrophy[2,3].

Patient. We report the case of a 26-month-old girl, first child of non-consanguineous parents, who was referred to our department based on a history of progressive muscle weakness with raised creatine kinase (CK) and a muscle biopsy showing marked inflammation. There was no family history of neuromuscular or autoimmune diseases. She was born by normal uncomplicated delivery; no reduced fetal movements were described by the mother during pregnancy. By 1 year of age, she was crawling and cruising around the furniture. From the age of 1, she developed gradual motor regression, with progressive proximal and distal muscle weakness predominantly involving the lower limbs. When seen by us, she was only able to commando-crawl; there was no head drop, her neck flexors were spared, and she had normal cognitive function. She had mild contractures of her knees and ankles with no foot deformity. She had no nailfold capillary changes, nasopharyngeal or skin involvements, respiratory symptoms, or failure to thrive. CK ranged from 738 IU/l to 2700 IU/l. Autoantibodies, including myositis-associated autoantibodies, were negative.

A quadriceps biopsy showed marked focal pathology in a group of fascicles with abnormal variation in fiber size, internal nuclei, split fibers, whorled fibers, necrosis, and regeneration, accompanied by florid interstitial inflammation with a pattern composed of CD4+/CD20+ predominant perimysial/perivascular foci of inflammation. HLA (MHC-I) was patchily upregulated in this area. Other features of JDM, such as perifascicular atrophy, capillary complement deposition or capillary dropout, and endothelial tubuloreticular inclusions were absent (Figure 1). Immunostaining for various dystrophy-associated sarcolemmal and basal lamina proteins was normal. The JDM biopsy score was high at 23/27[5]. In the correct clinical context, these appearances could support a diagnosis of JIIM.

Muscle MRI revealed a loss of muscle bulk and selective signal change involving quadriceps, adductors, gluteal muscles, and biceps femoris, with relative sparing of rectus femoris, gracilis, sartorius, semimembranosus, and semitendinosus muscles, and no fascial involvement. There were small effusions in the hips, knees, and ankle joints. Appearances suggested an inflammatory myopathy with wasting (Figure 2). Although consistent with JIIM, the pattern of muscle involvement was unusual, because muscle involvement in JIIM tends to be diffuse with edema in the myofascia, subcutaneous tissue, and skin[1,5].

Given the following unusual JIIM clinical features — a very young age of onset, absence of rash, the pattern of proximal muscle weakness, with significant involvement of the lower limbs compared to the degree of involvement of the neck flexors, the MRI findings of selective muscle

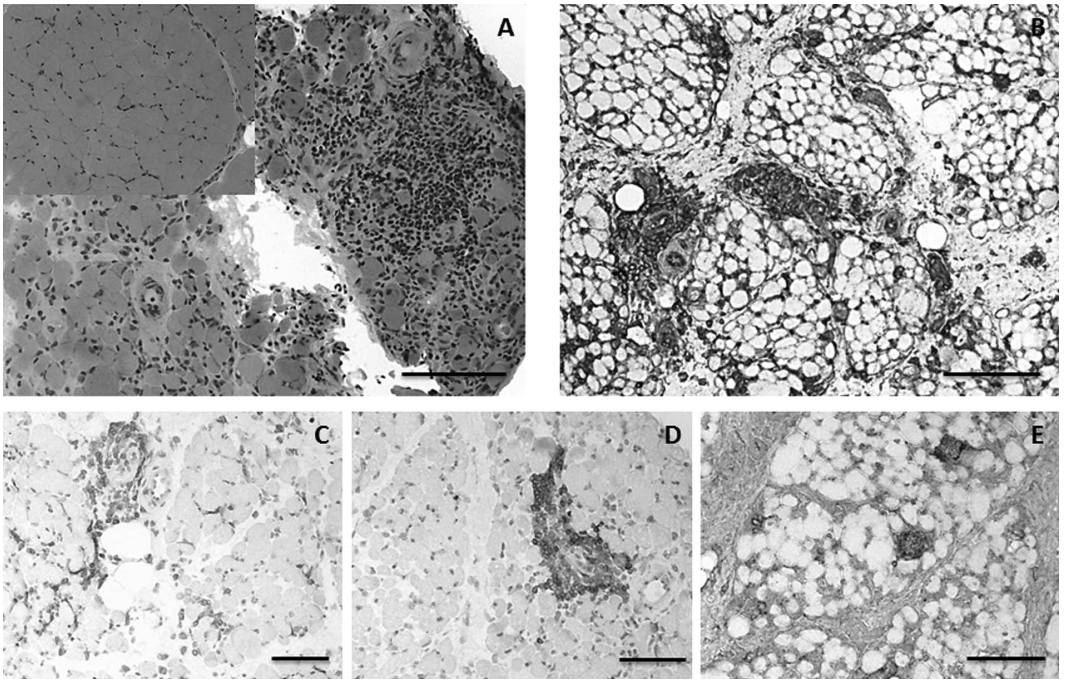

Figure 1. Quadriceps biopsy. A representative area of the left quadriceps biopsy shows florid focal inflammation on a background of marked myopathic changes (A). An adjacent part of the biopsy (A, inset) appears almost completely normal. HLA (MHC-I) is variably upregulated on myofibers in the abnormal part of the biopsy and also highlights the preferential perivascular and perimysial clustering of inflammatory cells (B). The inflammatory infiltrate is predominantly composed of CD4+ T cells (C) and CD20+ B cells (D) around blood vessels. Staining for complement C5b-9 highlights occasional necrotic fibers, but there are no deposits on endomysial capillaries. There is also some nonspecific labeling of the perimysial and endomysial connective tissue (E). A = 500 μm, B–E = 250 μm.

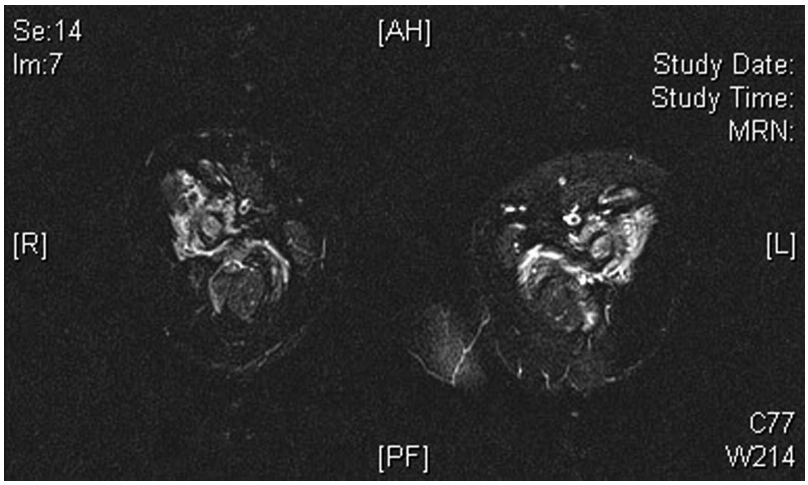

Figure 2. Axial short-tau inversion recovery MRI (TR/TE/TI, 4390 ms/97 ms/190 ms) demonstrates symmetrical abnormality of the thighs. There is, in general, little muscle bulk. Obvious signal abnormality (higher than normal, bright in the image) is seen throughout the quadriceps groups, the semimembranosus, and the long head of the biceps femoris at this level. The signal abnormality is in keeping with edema and suggestive of myositis. MRI: magnetic resonance imaging.

involvement[6], and following multidisciplinary team review — the phenotype was felt to be more consistent with a muscular dystrophy with secondary inflammation, possibly an early-onset laminopathy.

Genetic analysis. Genetic analysis revealed a heterozygous mutation in exon 1 of the *LMNA* gene NM_170707.3:c.91_93delGAG;pGlu31del. This is a novel in-frame mutation and has not been previously reported, to our knowledge. It is likely pathogenic because this sequence variant is predicted to cause the deletion of a highly conserved amino acid in the lamin A/C

Table 1. Comparison of clinical characteristics, imaging, and muscle biopsy findings between patients with LMNA-CMD, JIIM, and our case.

Characteristic	Our Patient's Presentation	Infantile-onset LMNA-associated Muscular Dystrophy[2,3,7,8]	JIIM[1,9,10]
Proximal muscle weakness	+	+	+
Neck extensors involvement	–	+	–
Neck flexors involvement	–	+	+/–
Contractures	+	+	+/– [1]
Muscle edema	–	–	+
Skin disease	–	–	+/–
Skin ulceration	–	–	+/–
CK levels	738–2700 IU/l	Levels to 2878 IU/l reported[7,9].	Levels can vary from mild/moderate increase to high.
Histopathological analysis of muscle biopsy[2]	See text body.	Variable pathology; dystrophic to nonspecific myopathic; often focal; whorled fibers, rounded atrophic fibers; prominent interstitial inflammation in some cases.	Diagnostic features: perifascicular atrophy, capillary pathology including complement deposition and capillary dropout, predominantly interstitial inflammation CD4/CD20++; electron microscopy tubuloreticular endothelial inclusions.
Muscle MRI	Loss of muscle bulk with relative sparing of rectus femoris, gracilis, sartorius, semimembranosus, and semitendinosus muscles. No muscle edema, fascial involvement, or subcutaneous inflammation.	Often diffuse involvement of thigh muscles with relative sparing of sartorius, gracilis, and rectus femoris. Diffuse or selective muscle involvement of vastus lateralis, vastus intermedius, and vastus medialis have also been described.	Diffuse or patchy muscle involvement. Muscle edema, myofascial, and subcutaneous tissue involvement. Loss of muscle bulk if myopathy with wasting.
Cardiac and respiratory involvement	No.	Life-threatening cardiac arrhythmias. Progressive restrictive respiratory failure.	Myocardial inflammation, dilated cardiomyopathy. Left ventricular diastolic dysfunction, often subclinical. Cardiac systolic dysfunction. ILD.

LMNA-CMD: *LMNA*-associated congenital muscular dystrophy; JIIM: juvenile idiopathic inflammatory myopathy; CK: creatine kinase; MRI: magnetic resonance imaging; ILD: interstitial lung disease.

protein, and a pathogenic mutation involving deletion of the adjacent codon has been described in patients with Emery-Dreifuss muscular dystrophy[7]. Family genetic studies support that mutation segregates with disease, because it was only found in the father as a low-frequency somatic mutation.

Treatment and followup. A short course of oral steroids resulted in transient clinical improvement with improved crawling. At the age of 5 years, she can bottom shuffle, has lower limbs contractures, and head drop. The cardiac and respiratory function studies remain normal.

Discussion. This report highlights the need to consider the recently described infantile-onset LMNA-CMD as a differential diagnosis in patients presenting to the pediatric rheumatologists with muscle weakness in infancy or early childhood and significant inflammation in their muscle biopsy. It appears from previous reports that LMNA-CMD has a distinct clinical phenotype, with head drop and contractures. In the case of our patient, neck muscle weakness was not present at presentation, but later in the course of the disease. The presence of contractures can be a key in differentiating the 2 conditions because they are an extremely rare feature of JIIM (Table 1).

Similar MRI and muscle biopsy's abnormalities have been reported in infantile-onset LMNA-CMD[2,3,8,9]. The frequency of inflammatory changes is higher in patients with infantile-striated muscle laminopathy[2]. Muscle MRI of lower legs are informative because patients with LMNA-CMD show characteristic involvement of the posterior calf muscles[11].

Combined appraisal of the clinical features, imaging and pathology, and increasing awareness of the clinical phenotypes of LMNA-CMD can prevent a potential misdiagnosis of JIIM and avoid life-threatening cardiac and respiratory complications associated with laminopathy.

ELENA MORAITIS, MBBS, Clinical Research Fellow, Rheumatology Department, Great Ormond Street Hospital for Children, and Infection, Inflammation and Rheumatology Section, University College London (UCL) Institute of Child Health; A. REGHAN FOLEY, MD, Clinical Research Fellow, Dubowitz Neuromuscular Centre, Medical Research Council Centre for Neuromuscular Diseases, UCL Institute of Child Health, Great Ormond Street Hospital for Children; CLARISSA A. PILKINGTON, MBBS, BSc, MRCP, Consultant Pediatric Rheumatologist, Great Ormond Street Hospital for Children; ADNAN Y. MANZUR, MBBS, DCH, FRCPCH, Consultant Neurologist Dubowitz Neuromuscular Centre, UCL Institute of Child Health, Great Ormond Street Hospital for Children; ROSALINE QUINLIVAN, BSc (hons), MBBS, DCH, FRCPCH, FRCP, MD, Consultant Neurologist, Dubowitz Neuromuscular Centre, UCL Institute of Child Health, National Hospital for Neurology and Neurosurgery, Great Ormond Street Hospital for Children; THOMAS S. JACQUES, PhD, MRCP, FRCPath, HEFCE, Clinical Senior Lecturer/Hon. Consultant Paediatric Neuropathologist, UCL Institute of Child Health, Great Ormond Street Hospital for Children; RAHUL PHADKE, MBBS, MD, FRCPath, Consultant Neuropathologist, National Hospital for Neurology and Neurosurgery, University College London Hospitals National Health Service Foundation Trust, Dubowitz Neuromuscular Centre, Great Ormond Street Hospital for Children, and Department of Molecular Neuroscience, UCL Institute of Neurology; SANDRINE COMPEYROT-LACASSAGNE, MBBS, MSc, Consultant Pediatric Rheumatologist, Great Ormond Street Hospital for Children, London, UK. Address correspondence to Dr. E. Moraitis, Rheumatology Department, Great Ormond Street Hospital for Children, Great Ormond Street, London, WC1N 3JH, UK.
E-mail: elena.moraitis.13@ucl.ac.uk

REFERENCES

1. Feldman BM, Rider LG, Reed AM, Pachman LM. Juvenile dermatomyositis and other idiopathic inflammatory myopathies of childhood. Lancet 2008;371:2201-12.
2. Komaki H, Hayashi YK, Tsuburaya R, Sugie K, Kato M, Nagai T, et al. Inflammatory changes in infantile-onset LMNA-associated myopathy. Neuromuscul Disord 2011;21:563-8.
3. Quijano-Roy S, Mbieleu B, Bönnemann CG, Jeannet PY, Colomer J, Clarke NF, et al. De novo LMNA mutations cause a new form of congenital muscular dystrophy. Ann Neurol 2008;64:177-86.
4. Genschel J, Schmidt HH. Mutations in the LMNA gene encoding lamin A/C. Hum Mutat 2000;16:451-9.
5. Wedderburn LR, Varsani H, Li CK, Newton KR, Amato AA, Banwell B, et al; UK Juvenile Dermatomyositis Research Group. International consensus on a proposed score system for muscle biopsy evaluation in patients with juvenile dermatomyositis: a tool for potential use in clinical trials. Arthritis Rheum 2007; 57:1192-201.
6. Davis WR, Halls JE, Offiah AC, Pilkington C, Owens CM, Rosendahl K. Assessment of active inflammation in juvenile dermatomyositis: a novel magnetic resonance imaging-based scoring system. Rheumatology 2011;50:2237-44.
7. Menezes MP, Waddell LB, Evesson FJ, Cooper S, Webster R, Jones K, et al. Importance and challenge of making an early diagnosis in LMNA-related muscular dystrophy. Neurology 2012;78:1258-63.
8. Carboni N, Mura M, Marrosu G, Cocco E, Marini S, Solla E, et al. Muscle imaging analogies in a cohort of patients with different clinical phenotypes caused by LMNA gene mutations. Muscle Nerve 2010;41:458-63.
9. Pasqualin LM, Reed UC, Costa TV, Quedas E, Albuquerque MA, Resende MB, et al. Congenital muscular dystrophy with dropped head linked to the LMNA gene in a Brazilian cohort. Pediatr Neurol 2014;50:400-6.
10. Martin N, Krol P, Smith S, Beard L, Pilkington CA, Davidson J, et al; Juvenile Dermatomyositis Research Group (JDRG). Comparison of children with onset of juvenile dermatomyositis symptoms before or after their fifth birthday in a UK and Ireland juvenile dermatomyositis cohort study. Arthritis Care Res 2012;64:1665-72.
11. Mercuri E, Counsell S, Allsop J, Jungbluth H, Kinali M, Bonne G, et al. Selective muscle involvement on magnetic resonance imaging in autosomal dominant Emery-Dreifuss muscular dystrophy. Neuropediatrics 2002;33:10-4.

J Rheumatol 2015;42:6; doi:10.3899/jrheum.140554