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X-linked Emery-Dreifuss muscle dystrophy manifesting with adult onset axial weakness, camptocormia, and minimal joint contractures

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Abstract

Emery-Dreifuss muscular dystrophy is an early-onset, slowly progressive myopathy characterized by the development of multiple contractures, muscle weakness and cardiac dysfunction. We present here the case of a 65 years-old male patient with a 20 years history of slowly progressive camptocormia, bradycardia and shortness of breath. Examination showed severe spine extensor and neck flexors muscle weakness with slight upper limbs proximal weakness. Cardiologic assessment revealed slow atrial fibrillation. Whole body MRI demonstrated adipose substitution of the paravertebral, limb girdles and peroneal muscles as well as the tongue. Emerin immunohistochemistry on patient muscle biopsy revealed the absence of nuclear envelope labeling confirmed by Western Blot. Genetic analysis showed a hemizygous duplication of 5 bases in exon 6 of the *EMD*, *emerin*, gene on the X chromosome. This is an unusual presentation of X-linked Emery-Dreifuss muscular dystrophy with adult onset, predominant axial muscles involvement and minimal joint contractures. Diagnosis was prompted by the analysis of emerin on muscle biopsy.

Keywords:

EMD gene, emerin, Emery-Dreifuss muscular dystrophy, muscular dystrophy, muscle biopsy, emerin immunohistochemistry, whole body MRI

Introduction

Emery-Dreifuss muscular dystrophy (EDMD) is an early-onset, usually in the first decade, slowly progressive myopathy [1]. EDMD is mainly caused either by mutations in *EMD* gene encoding emerin in X-linked EDMD (X-EDMD) [2], or mutations in *LMNA* gene encoding lamins A and C in autosomal dominant and recessive forms [3]. EDMD clinical presentation includes the classical triad of symptoms with early joint contractures involving Achilles, elbows and the neck tendons, progressive muscle weakness and wasting beginning in the humero and peroneal regions, and cardiac disease combining cardiac arrhythmias, conduction defects and cardiomyopathy [4,5]. Mean age of onset is reported to be 5.6 years (4.2–6.9) in EDMD patients carrying an out of frame *emerin* gene mutation [6]. In another large published series of 20 *emerin* mutated patients, Astejada et al [7] found a higher range of age of onset (10.1 ± 9.5 years old) distributed along the first and second decades of life. Symptoms of onset were usually joint contractures before the development of any significant muscle weakness, lower limb muscle weakness, or isolated heart conduction blocks.

We report herein a man with X-linked EDMD showing unusual age of onset and muscle phenotype. Muscle immunohistochemistry allowed orientating the genetic screening toward the *EMD* gene.

Case report

The proband is a 65 years-old man of North African origin, born to non-consanguineous parents, diving instructor. He had slight sport difficulties since childhood and he used orthopedic insoles. His mother wore a corset in adulthood and died at 65 years of unknown cause. The patient developed asymptomatic sinus bradycardia detected from 25 years of age. From age 45, he progressively showed camptocormia during walking, dyspnea on exertion, and difficulties in carrying heavy weights. For example he needed help to lift an oxygen bottle out of the water. His first physical examination at 65 years revealed a waddling gait, hyperlordosis, camptocormia with progressive worsening during walking, and slight elbow (**Figure 1A**) and neck contractures (**Figure 1B**). Additional features included mild facial weakness consisting of incapacity to swell cheeks and eversion of lower lip, scapular winging (**Figure 1C**) and atrophy of the biceps brachii and left calf. Manual muscle testing showed a mild proximo-distal upper limb weakness involving wrist extensors, elbow flexors and extensors, shoulder flexors, and interossei muscles (graded 4/5 on MRC scale). There was marked axial weakness involving trunk flexors and extensors, with difficulties in rising up from supine position.

CK level was normal (131 UI/L). ENMG needle electrode examination revealed pseudo neurogenic pattern with fast firing rate and high size motor unit potentials in deltoid anterior, brachioradialis, biceps brachialis, and tibialis anterior muscles. Whole body MRI showed marked fat replacement and atrophy of the tongue, trapezius, spine extensors, biceps brachialis, semi-tendinous and semi-membranous, medial gastrocnemius (Mercuri score 3) and soleus (Mercuri score 4) muscles. Fat replacement was also present but less severe in teres major, anterior serratus, deltoid and latissimus dorsi (Mercuri score 2) (**Figure 2**). EKG revealed spontaneously slow atrial fibrillation, with a mean heart rate of 45 b.p.m, without QRS enlargement and cardiac electrophysiology but displayed nodal conduction block without infrahisian conduction delay. Left ventricular dimensions and systolic function were normal on echocardiography and both atria were dilated. Forced vital respiratory capacity (FVC) was normal (100%).

A deltoid muscle biopsy showed nonspecific muscle abnormalities including a moderate number of fibers with internalized nuclei, rare atrophic fibers (**Figure 3A and B**) and absence of type 2B fibers demonstrated by immunofluorescence studies using myosin alpha and beta-slow heavy chain, fast 2A heavy chain, and 2X myosin heavy chain (BA-D5, SC-71, and 6H1, Developmental Studies Hybridoma Bank, University of Iowa, Iowa City, USA) that showed the absence of 2X myosin heavy chain expression (**Figure 3C**). A comprehensive battery of immunohistochemical reaction was carried out and immunostaining study using an antibody against emerlin (NCL-Emerin, Novocastra, Newcastle, England) showed a complete absence of the normal nuclear labeling compared to a normal control (**Figure 3D**). Western blot analysis of patient muscle homogenate using monoclonal MANEM8-7B9 anti-emerlin and anti-lamins A/C antibodies confirmed the absence of emerlin compared to a normal control muscle (**Figure 3E**).

Direct sequencing of the *EMD* gene revealed a pathogenic hemizygous duplication of 5 bases c.650_654dup: p.Gln219Trpfs*20, leading to a premature frameshift.

Discussion

The X linked Emery-Dreifuss muscle dystrophy (EDMD) was described as a childhood onset progressive myopathy with early joint contractures, followed within the third decade by supraventricular arrhythmias and cardiac conduction defects potentially evolving toward complete atrioventricular block and sudden death [1,5,8]. The mutated gene, *EMD*, within the Xq28 [2] encodes for a 254-aminoacid protein named emerin, an inner nuclear membrane integral protein.

Mean age of onset is reported to be in the first decades [6,7,9]. Remarkably our patient only reported mild sport difficulties during infancy without any significant contracture. He developed an overt progressive axial weakness of paraspinal muscle leading to camptocormia during walking in adulthood. To our knowledge, both onset and clinical features of our patient are highly unusual. Interestingly camptocormia had never been reported before as a predominant symptom in EDMD [1,7,10,11]. Camptocormia is a frequent symptom in old patients and is frequently related to movement disorders[12]. Rare myopathic form exists, often idiopathic [13]. Concerning the myopathies related to defect in proteins of the nuclear envelope, there is a rare phenotype of severe congenital muscular dystrophy with axial involvement associating dropped head with distal limbs contractures and rigid spine due to *LMNA* gene mutations [10].

In our patient only a careful clinical examination revealed the presence of mild contractures of neck and elbows (Fig. 1), without any spine rigidity. The presence of mild contractures in X-linked EDMD have been previously reported [7,14,15]. However, in EDMD patients the contractures are one of the core clinical features and patients start developing them during childhood beginning from Achilles tendons [5,11] extending to elbows and to spine extensor muscles in the second decade [10]. Rigid spine syndrome (RSS) is the consequence of spinal

contractures [5]. Myopathies with prominent spine contractures are rare in adulthood. Early onset myopathies such as congenital muscular dystrophies (e.g., *LMNA*, *LAMA2* and Collagen VI related myopathies) and rare congenital myopathies such as *SELENON*, *FHL1* related reducing body myopathy, *BAG3* myofibrillar myopathies and *titin* related myopathies) may be associated with RSS [10]. The distribution of spinal rigidity is variable among different entities and can help in the differential diagnosis[10]. However, the absence of prominent contractures and rigid spine did not help to reach the diagnosis in our patient.

Whole body MRI in EDMD patients has been rarely reported. Mercuri *et al.* investigated nine patients including four with *EMD* mutation and found that especially the medial head of the gastrocnemius muscle had prominent atrophy [16]. In a Spanish study conducted in 42 EDMD patients including 10 X-linked EDMD, the MRI or CT scan (from trunk to feet) showed fatty infiltration in paravertebral, glutei, quadriceps, biceps, semitendinosus, semimembranosus, adductor major, soleus, and gastrocnemius but peroneus muscle was involved in 88% of patients with mutations in the *EMD* compared to only 40% of patients with mutation in the *LMNA* gene [17]. Whole body MRI of our patient showed marked symmetric fatty replacement and atrophy of the tongue, trapezius, all the spine extensors, biceps brachialis, semitendinous and semimembranosus, medial gastrocnemius and soleus as previously described [16]. To a lesser extent, we also noted fatty infiltration in teres major, anterior serratus, deltoid and latissimus dorsi. In contrast, alterations of glutei, adductor major, quadriceps and biceps of the thighs, and peroneous muscles were only subtle, compared to what reported [17]. Previous studies of whole body MRI in *LMNA/C*-EDMD revealed distinctive patterns helping distinguishing *LMNA/C*-EDMD with rigid spine presentation [18,19]. As a whole, our patient showed a pattern evocative of laminopathy with a lesser atrophy compared to younger *LMNA/C* patients.

According to the online UMD-EMD database (see <http://www.umd.be/EMD/>), at least 230 male patients (156 families) carrying 103 *EMD* different mutations have been reported. The majority (66.6%) harbor truncating mutations (out-of-frame large or small deletions/insertions, nonsense mutations) causing absent or rarely faint emerlin (out-of-frame large or small deletions/insertions, nonsense mutations) with western blot studies. The mutation harbored by our patient is a 5 nucleotides (TGGGC) duplication introducing a frameshift after aminoacid 218, was already reported in 6 affected individuals from 3 families of German, Japanese and Israeli origin [20-22]. None of them had camptocormia. These patients presented a typical EDMD phenotype with elbows and ankles contractures [20] in association with stiff neck in one case [22]. Cardiac involvement was always present, varying from 1st degree to complete atrio-ventricular block requiring pacemaker with supraventricular arrhythmias and heart dilation. It is noteworthy that any muscular condition associated with cardiac arrhythmias in early adulthood should guide to diagnosis of conditions affecting the nuclear membrane and other arrhythmogenic cardiomyopathies. Among the 6 reported patients, 2 had muscle biopsy that, similarly to our patient, showed non dystrophic findings including atrophic muscle fibers [22], type grouping and type 1 fiber predominance [20] with absent emerlin [21]. Of note we describe the absence of type 2B fibers that was not reported previously. This finding is difficult to explain and could be secondary to the absence of emerlin. Concordantly, it was a comprehensive battery of immunohistochemical reactions that allowed to reveal the absence of emerlin thus suggesting *EMD* molecular study. One could argue that facing a non-specific myopathy a large gene panel would have been performed before proposing a muscle biopsy. However muscle specific study should have been performed to validate the pathogenicity of the known *EMD* mutation in such an atypical case.

In conclusion, this observation enlarges the clinical spectrum of X-linked EDMD by reporting a patient with adult onset axial weakness, camptocormia, and very mild contractures. Muscle biopsy followed by emerlin immunohistochemistry directed *EMD* gene sequencing.

We stress the importance of a systematic diagnostic algorithm including muscle biopsy and muscle imaging in patients presenting myopathies with atypical clinical features.

Abbreviations:

CK : creatine kinase

EDMD: Emery-Dreifuss muscular dystrophy

ENMG: electroneuromyogram

MRC: Medical Research Council

RSS: Rigid spine syndrom

Vs: versus

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Figures legends

Figure 1. Patient's pictures.

A. Mild elbow contractures (arrows). **B.** Mild neck contractures (arrow). **C.** Scapular winging.

Figure 2. Whole body muscle MRI. Axial sections of the 3 points DIXON sequence fat images from head to calves (A to J). Coronal T1 weighted sections of the face (K) and of the thoraco-lumbar muscles of the back (L). Masticatory muscles are well visible and preserved but the tongue is partly fatty infiltrated (white long arrow, A and K). Muscles of the back in cervical, thoracic and lumbar areas are heavily fatty infiltrated (black discontinuous arrows). In thighs and legs the posterior compartments are predominantly affected with atrophy and fat infiltration especially of the semi-tendinous and the semi-membranous (ST/SM) in thigh and gastrocnemius medialis (GCM) and soleus (Sol) in leg.

Figure 3. Deltoid muscle biopsy study and protein studies.

A. HE. Some fibers harbor internalized nuclei. **B. NADH** staining showing the presence of few atrophic fibers and small disorganization of the structure. **C.** Immunofluorescence analysis using myosin alpha and beta-slow heavy chain, fast 2A heavy chain, and 2X myosin heavy chain and merge. The absence of type 2B fibers is demonstrated by the absence of blue staining corresponding to type 2B fibers. Merge image confirm this finding. Magnification 16X. **D. Immunohistochemical analysis** with an anti-emerin antibody showing complete absence of nuclear staining. In the insert box it is represented a normal nuclear emerin staining on a control muscle. **E. Western Blot studies** on muscle homogenate. C: control. P: patient. Note the complete absence of emerin band at the normal molecular weight (35 kDa) in patient's muscle. The LMNA/C, lamins A/C, bands are normally present in both patient and control. Myosin is used a loading control.

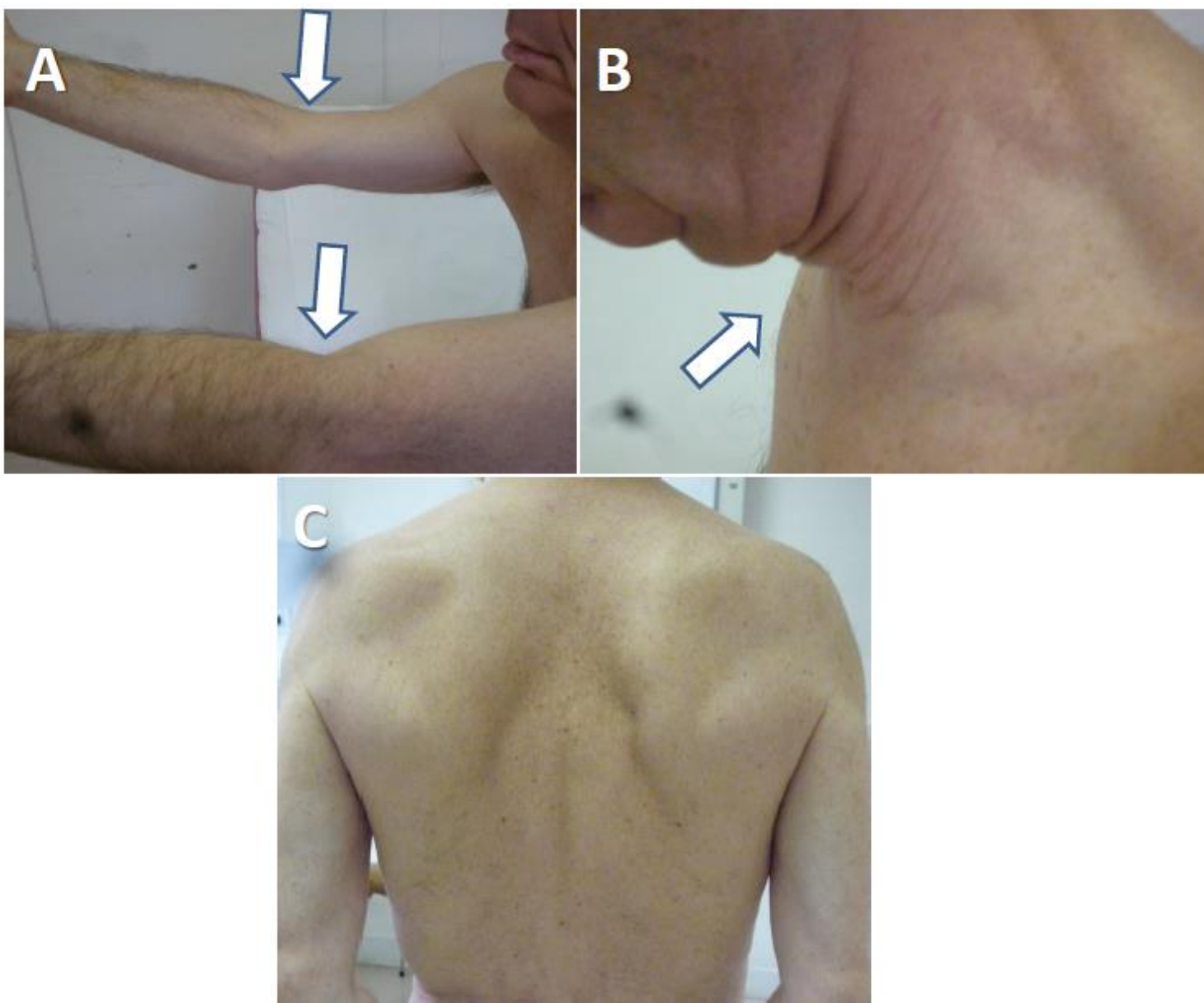


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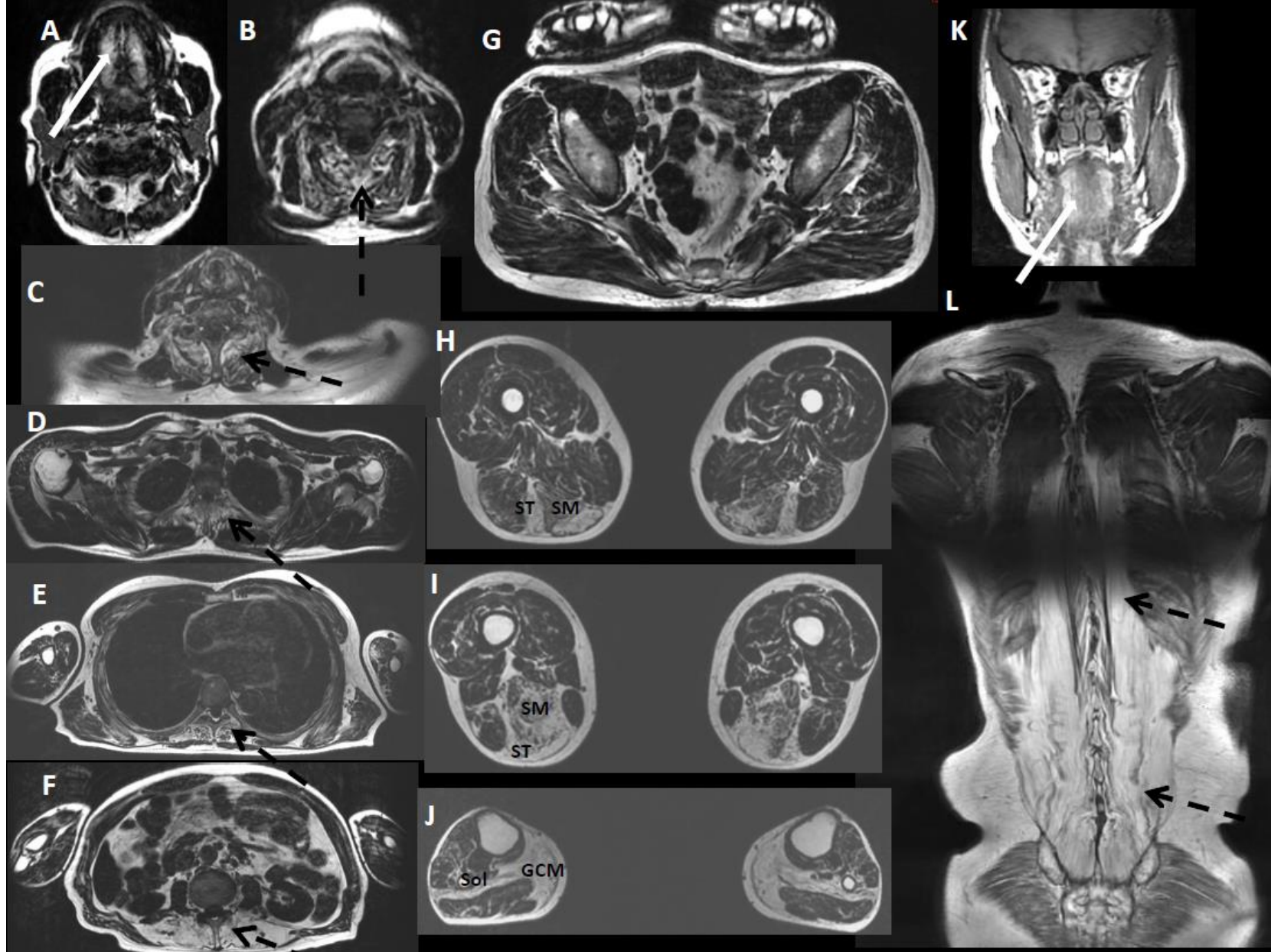


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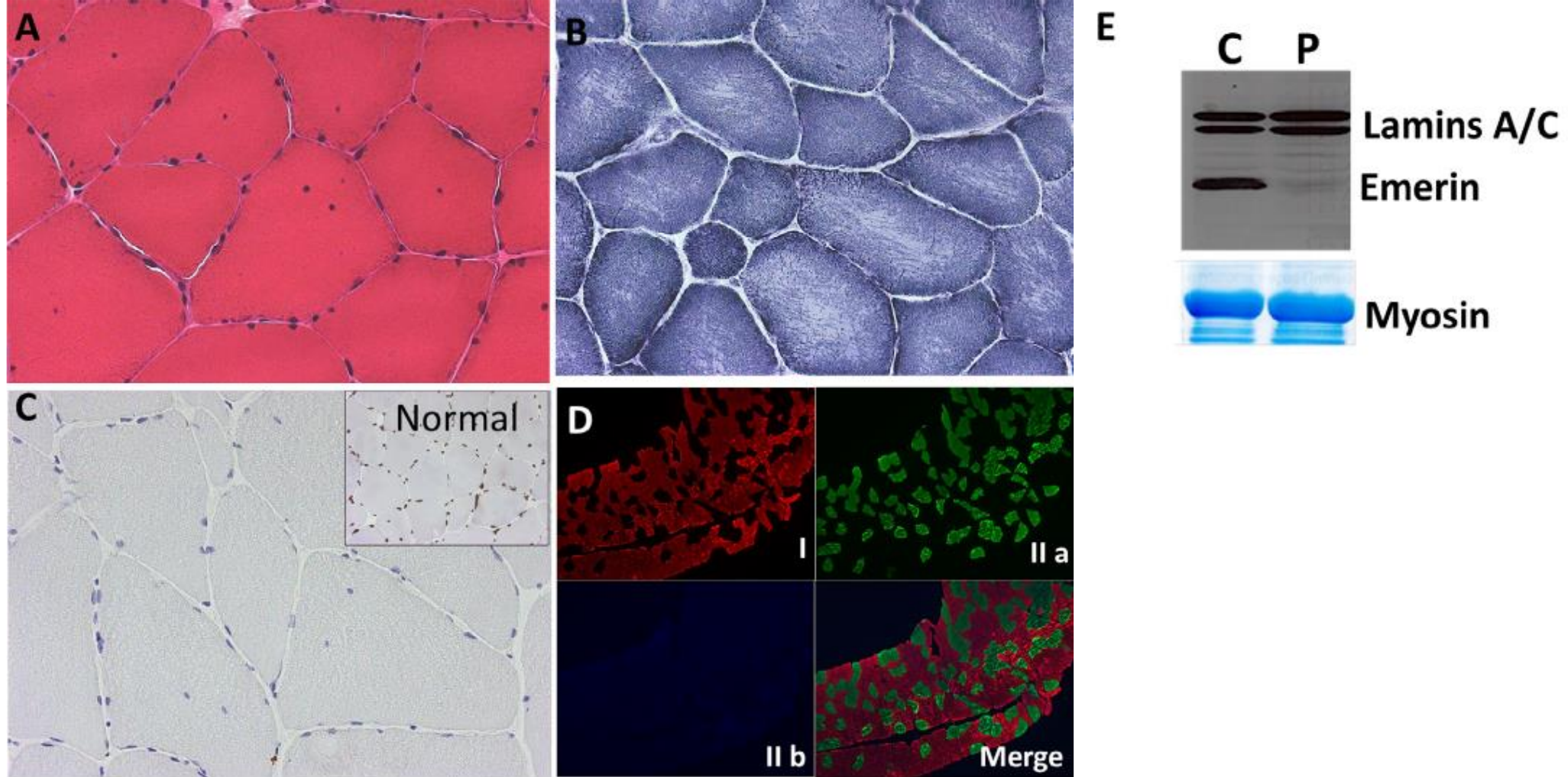


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