Limb-girdle Muscular Dystrophy Type 2A with Muscular Eosinophilic Infiltration in a Chinese Patient

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To the Editor: Limb-girdle muscular dystrophy type 2A (LGMD2A) is a group of progressive muscle diseases with autosomal recessive inheritance. The common myopathological changes consist of muscular changes such as muscle necrosis and regeneration, as well as interstitial proliferation and abundant lobulated fibers. An interesting yet unresolved phenomenon of LGMD2A patients is that some of them demonstrate muscular eosinophilic granulocyte infiltration with or without peripheral eosinophilia. Although cases of LGMD2A have been reported in China, eosinophilia has never been found. Here, we report a Chinese LGMD2A patient with muscle eosinophilic infiltration.

The patient was a 31-year-old man born to nonconsanguineous parents. He came to our clinic because of progressive lower limb weakness for 8 years and upper limb weakness for 3 years. He first noticed leg weakness when climbing hills 8 years ago. Around that period, he also found that he had an abnormal walking posture with protruding back. Since 3 years ago, he developed difficulty standing up from squatting position and climbing stairs, as well as lifting heavy items. The symptoms were progressive. Upon his first visit, he was unable to climb two floors. His weight did not show any notable fluctuation since disease onset. None of his family members showed similar symptoms.

On physical examination, he demonstrated a normal cognitive function. Muscle strength was graded according to the Medical Research Council scale: neck flexors 4/5, neck extensors 5/5, bilateral shoulder abductors 3−/5, left elbow flexors/extensors 4+/5, right elbow flexors/extensors 4−/5, bilateral hip flexors/extensors 3−/5, bilateral wrist flexors/extensors, knee flexors/extensors, and ankle dorsiflexors/plantar flexors 5−/5. There was no extraocular, facial, or bulbar muscle weakness. Bilateral quadriceps atrophy was noted.

Laboratory tests revealed normal blood routine, erythrocyte sedimentation rate, and C reactive protein levels. He had an elevated creatine kinase level of 3566 U/L and lactate dehydrogenase level of 383 U/L. Electromyography revealed myopathic changes including motor unit action potentials with short duration and small amplitude and increased polyphasic potentials.

On muscle biopsy, hematoxylin and eosin (HE) staining showed the presence of hypercontractive fibers, scattered small focal necrosis, and regeneration. There were eosinophils as well as lymphocyte infiltrates in endomysium, both in close proximity to regenerative muscle fibers and small vessels [Figure 1]. The structure of intermyofibrillar network as shown by nicotinamide adenine dinucleotide tetrazolium reductase (NADH-TR) staining was mildly disorganized. Immunostaining targeting inflammatory cells revealed that they were mainly consisted of CD68+ macrophages and a few CD8+ T cells, CD4+ T cells, and CD20+ T cells. MHC-I immunostaining was negative in muscle fibers. Immunohistochemistry targeting dystrophin; α-, β-, γ-, and δ-sarcoglycans; and dysferlin was unremarkable.

Two missense mutations were identified in *CAPN3* gene. The c.2120A>G mutation was reported in Japanese population and the c.2371G>A in Spanish people. According to the 2015 ACMG standards, both were deemed as "likely pathogenic" variants.

This study was approved by the Ethics Committee of Xiangya Hospital.

More than 500 disease-related mutations spanning the whole length of *CAPN3* have been identified in LGMD2A so far, causing either significantly decreased expression or defective autolytic function of the calpain 3 protein. Calpain 3 is a calcium-dependent protease, whose biological functions include sarcomere assembly and remodeling, muscle membrane, and triad integrity maintenance, as well as participation in cell apoptosis. Previous experimental studies have found that the possible pathogenesis of LGMD2A involves increased myonuclei apoptosis, impaired muscle adaption, and faulty myogenesis.

Patients with LGMD2A typically present with pelvic-girdle weakness from childhood to young adulthood. Although scapular winging can often be found, objective upper limb weakness develops in later disease stage. Creatine kinase level is elevated to variably extent, but rarely exceeds 10,000 U/L. It is noteworthy that a small portion of patients present with hyperCKemia with no or minimal muscle weakness. A characteristic but not specific

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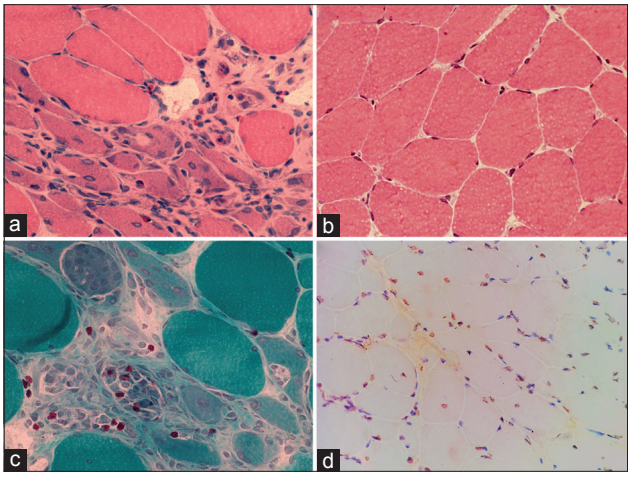

Figure 1: Images of biceps brachii biopsy demonstrating intramuscular eosinophils. (a) Infiltration of eosinophils and mononuclear cells on H and E staining; (b) H and E staining of a normal muscle; (c) eosinophils stained bright red on modified Gomori trichrome; (d) scattered endomysial macrophages as illustrated by immunohistochemistry against CD68 molecules (a-c, ×400); (d, ×200).

myopathological changes of LGMG2A is abundant lobulated fibers, as best shown by NADH staining. The number of lobulated fibers also has a tendency to correlate with disease duration and severity.

In contrast to the American and European population, LGMD2A seems not to be the most popular subtype of LGMD in China. Moreover, peripheral and/or intramuscular eosinophilia as a feature of LGMD2A in Caucasian patients has never been found in previous reports in China.[1,2] Krahn *et al.* have noted that both circulating and muscle eosinophilia tend to be more prominent in LGMD2A children than in adults,[3] thus proposing that eosinophilic infiltration is the early or even primary event of pathogenesis. Yet our case, together with some other previously reported cases with pronounced intramuscular eosinophilia in developed stages of disease, argues against this theory.[4] The underlying mechanism of eosinophilia in LGMD2A remains elusive. As calpain 3 is highly expressed in T lymphocytes, it is suggested that its deficiency may cause defective function of T cells and finally lead to eosinophilia.[5] It is worth mentioning that other members of the calpain family, including calpain 1 and 2, participate in the apoptosis of eosinophils, and that calpain 14 is also involved in eosinophilic esophagitis. It is reasonable to infer that calpain 3 may be implicated in eosinophilia process through similar mechanism.

In conclusion, we report a Chinese LGMD2A patient with prominent intramuscular eosinophilia. The presence of peripheral and intramuscular eosinophilia can be an indicator of multiple diseases including Churg–Strauss syndrome, eosinophilic myositis, parasitic myopathy, and LGMD2A.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form(s), the patient(s)/patient's guardians has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients/patient's guardians understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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