

Clinical Reasoning: A 36-Year-Old Man With Asymmetric Muscle Weakness

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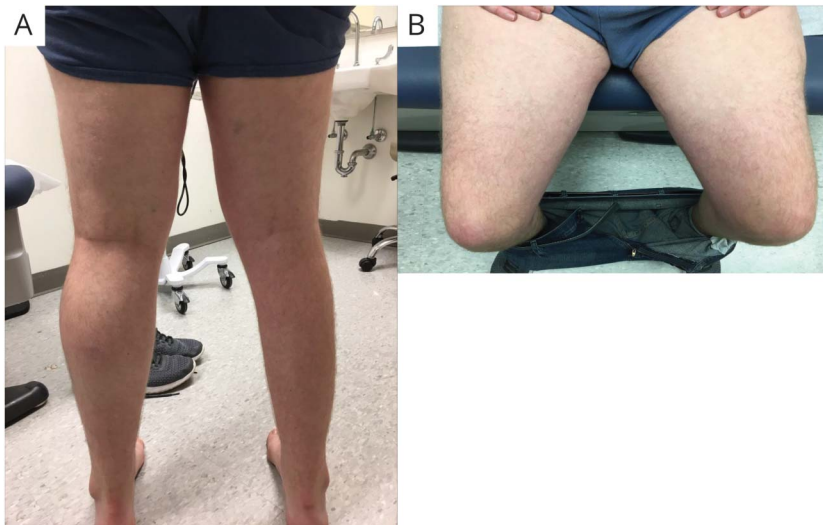
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Section 1

A 36-year-old White man with no relevant medical history was referred to our clinic for evaluation of progressive muscle weakness of both lower limbs. He reported difficulty climbing stairs and standing up from a chair progressing over the prior 2 years. He preferred to lead with his left leg when climbing stairs because of more significant weakness of the right leg. He denied upper extremity weakness, abnormal sensation, muscle cramping, contractures, myalgias, change of urine color, skin rash, dysphagia, dysarthria, dyspnea, or exposure to new medications or toxins. He denied a family history of similar conditions. Neurologic examination was remarkable for asymmetric lower extremity muscle weakness. Muscle atrophy was noted in right quadriceps femoris, hamstrings, and posterior calf (Figure 1). The Medical Research Council grade was 4/5 for bilateral hip flexion, abduction, and adduction. There was asymmetric weakness of knee extension (4-/5 right and 4/5 left), knee flexion (4-/5 right and 4+/5 left), and ankle plantar flexion (4/5 right and 5/5 left). Foot dorsiflexion was normal bilaterally. He had a mild Trendelenburg gait. He did not have scapular winging, scoliosis, or percussion or grip myotonia. The remainder of neurologic examination was normal, including deep tendon reflexes. Previous evaluation at an outside facility revealed elevated serum creatine kinase (CK) 4,283 unit/L. Prior

Figure 1 Bilateral Lower Extremities of the Patient



(A) Muscle atrophy noted in right hamstrings and calf muscles. (B) Muscle atrophy noted in right quadriceps.

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electrodiagnostic testing including nerve conduction studies (NCS) and needle electromyography (EMG)—reported findings of myopathy. Muscle biopsy was subsequently performed in left quadriceps femoris and reportedly revealed rare inflammatory cells; additional details were not available for review. He had been taking prednisone (40 mg/d) for 8 months

and oral methotrexate (15 mg/wk) for 2 months followed by azathioprine (50 mg/d) for 6 months, which did not improve his symptoms. An electrocardiogram (ECG) was normal.

Question for Consideration:

1. What is the differential diagnosis for this presentation?

GO TO SECTION 2

Section 2

Based on the elevated serum CK level and electrodiagnostic studies, myopathy was considered as the etiology for his slowly progressive muscle weakness. The distribution of weakness will be a key for further etiologic delineation. Although proximal lower extremity weakness (“limb-girdle pattern”) is the most common for myopathy, his presentation is unique in its relative asymmetry. Asymmetric proximal myopathy can be seen in sporadic inclusion body myositis (sIBM), caveolinopathy and limb-girdle muscular dystrophy (LGMD) type R2 (dysferlinopathy) and R12 (anoctaminopathy), and facioscapulohumeral dystrophy (FSHD). sIBM was considered to be unlikely given the absence of deep finger flexor weakness and the relatively early onset compared with sIBM which typically presents after the sixth decade.¹ Caveolinopathy is caused by the variations in the *caveolin 3* gene characterized by mild-moderate proximal weakness that can present asymmetrically.² It is also associated with exercise-related muscle cramps and calf hypertrophy that was not present in this case.² Dysferlinopathy presents with 2 different phenotypes including LGMD type R2 and Miyoshi myopathy

with primarily distal weakness.³ LGMD type R2 is characterized by slow progression of predominantly proximal muscle weakness, and atrophy that can present in an asymmetric distribution with disease onset is in the adolescence or early adulthood.⁴ Diagnosis requires the genetic test for *DYSF* gene and immunohistochemical analysis for sarcolemmal dysferlin immunoreactivity. Finally, FSHD is also unlikely given the absence of scapular winging and facial and truncal weakness.

In light of the differential diagnosis discussed above, we conducted electrodiagnostic testing (NCS/EMG) that revealed abundant fibrillation potentials and positive sharp waves along with many small, stable polyphasic motor unit potentials with early recruitment in the left vastus lateralis muscle. These findings are consistent with active myopathy with muscle membrane irritability. There was no evidence for sensorimotor polyneuropathy.

Questions for Consideration:

1. What findings might you suspect on muscle biopsy?
2. What is the next step in evaluation?

GO TO SECTION 3

Section 3

The muscle biopsy specimen was reviewed (Figure 2). H&E staining revealed marked variation in fiber diameter with many atrophic fibers including nuclear clumps and scattered hypertrophic fibers up to approximately 150 micrometers in diameter. There was a marked increase in internal nuclei, but no degenerating or necrotic fibers. There was mild to moderate fibrosis and fat infiltration. There was no inflammation or necrotizing vasculitis. Amyloid deposition was observed in blood vessels with Congo red and in blood vessels and endomysium under thioflavin T stain. A peptide profile was performed that included serum amyloid P component, apolipoprotein A4, and apolipoprotein E, and it did not identify a specific amyloid type. Based on these findings, we proceeded with molecular genetic testing that demonstrated a homozygous pathogenic variation ANOS c.191 dup. This result confirmed the diagnosis of anoctaminopathy.

Discussion

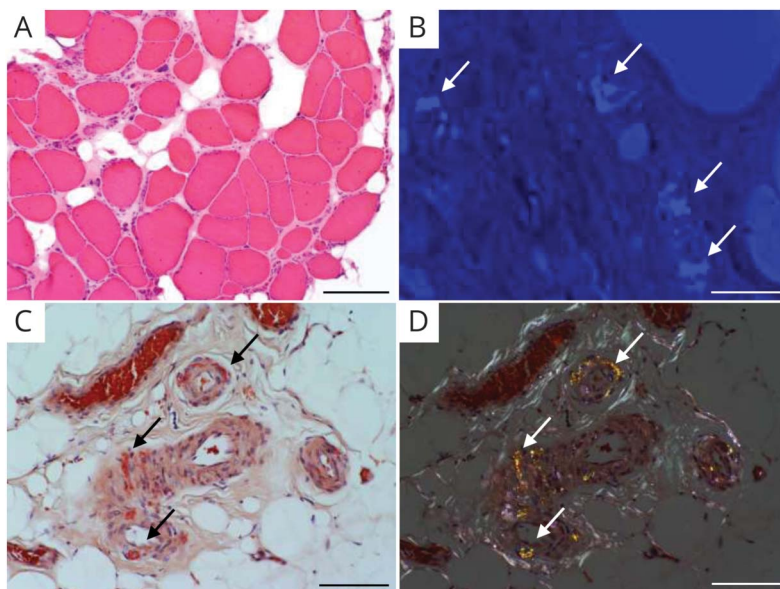
ANOS-related myopathy (i.e., anoctaminopathy) is a slowly progressive autosomal recessive disorder associated with variations of the ANOS gene. ANOS encodes the anoctamin-5 protein, a calcium-activated chloride channel associated with membrane-repair machinery that is highly expressed in skeletal and cardiac muscle and bone.⁵ The most common variation is c.191dupA which is a founder variation in Northern European patients.⁶ The mean age at onset in LGMD type R12 is from the early 20s to 50s with a minimum prevalence of 0.27/100,000 among general population in Northern England.⁷ The prevalence seems to have regional differences. For example, in a cohort study in Denmark, the prevalence of

ANOS deficiency was estimated at 1:100,000.⁸ In the United States, ANOS deficiency comprises around 7.2% of genetically confirmed LGMD cases.⁷

It can present with asymmetric muscle weakness and atrophy especially in thigh muscles with a markedly elevated serum CK level (average 4,500 IU/L).⁵ Some patients require assistive devices such as canes or wheelchairs 20–40 years after the onset of initial symptoms.⁶ On the other hand, cases with isolated hyperCKemia without weakness have been reported that are often associated with exercise intolerance and can have calf or thigh hypertrophy.⁹ A large cohort study revealed male predominance in the development of weakness.¹⁰ Muscle weakness and wasting are commonly observed in quadriceps femoris, hamstrings and calves, biceps, or brachioradialis.^{6,11} The distribution of weakness is also characterized by asymmetric involvement.^{6,8} A cohort study of patients from British and German kindreds revealed 90% of the subjects had asymmetric weakness in limbs.⁶ Muscle MRI studies have also demonstrated asymmetric variable fatty replacement and inflammatory changes of adductor magnus, semimembranosus, semitendinosus, and gastrocnemius muscles.¹¹

Muscle biopsies typically show increased fiber size variability and fraction of central nuclei and can also demonstrate necrotic fibers with inflammatory changes.^{6,8} These features could mimic inflammatory/necrotizing myopathy.¹² Clinically, the highly elevated serum CK and false positivity of autoantibodies such as anti-Mi2 alpha or beta can make its diagnosis challenging.¹² As in our case, patients with anoctaminopathy may initially receive immunotherapies before an accurate diagnosis is made. Mild clinical improvement and reduction of CK level after the initiation of corticosteroids have also been reported.¹²

Figure 2 Muscle Biopsy of the Patient



(A) Hematoxylin and eosin–stained sections show marked variation in fiber diameter, with many atrophic fibers and scattered hypertrophic fibers, marked increase in internal nuclei, mild to moderate fibrosis, and fat infiltration. (B) Thioflavin T–stained sections visualized under a DAPI channel show amyloid deposits in vessel walls (white arrows). (C and D) Congo red–stained sections show salmon pink–colored amyloid deposits in vessel walls (black arrows in C). Amyloid deposits show apple–green birefringence under polarized light (white arrows in D). Scale bar = 200 mm in (A) and 100 mm in (B–D).

Cardiac involvement has been commonly reported because ANOS is also expressed in cardiac muscle. Therefore, cardiac monitoring is recommended with regular electrocardiography (ECG) and echocardiography. Cardiac arrhythmias have been reported including premature ventricular complexes, paroxysmal atrial fibrillation, and first-degree atrioventricular block.⁸ In addition, hypertrophied and dilated cardiomyopathy have also been reported.^{13,14} In our case, his ECG was normal, but the patient chose not to proceed with echocardiography.

Of note, this patient's muscle biopsy revealed the deposition of amyloid in blood vessels and endomysium. This reflects another noted feature of anoctaminopathy. The other conditions that can show extracellular amyloid disposition include light chain amyloidosis, hereditary or wild type transthyretin amyloidosis, gelsolin amyloidosis, or dysferlinopathy.¹⁵ The cause for amyloid deposition is still unclear, but a cohort study of 15 patients with anoctaminopathy reported no genotype or phenotypical difference between patients with skeletal muscle interstitial amyloidosis and without it.¹³ All 8 patients with skeletal interstitial amyloidosis in their cohort had no evidence of systemic amyloidosis as in our case. Therefore, anoctaminopathy has been identified as one of the disorders presenting as isolated amyloid myopathy.¹⁵ Compared with systemic amyloidosis, it tends to present at younger age of onset (median, 41.5 vs 65 years) with elevated serum CK values.¹⁵

We report a case with ANOS-related myopathy presenting with asymmetric muscle weakness and significantly elevated serum CK value that initially mimicked inflammatory myopathy. Although it is a rare muscle disorder, anoctaminopathy should be included as a differential diagnosis of asymmetric myopathy.

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Appendix Authors

Name	Location	Contribution
Yohei Harada, MD	Department of Neurology, Duke University Medical Center, Durham, NC	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Shih-Hsiu Wang, MD	Department of Neurology, Duke University Medical Center, Durham, NC; Department of Pathology, Duke University Medical Center, Durham, NC,	Analysis or interpretation of data
Vern C. Juel, MD	Department of Neurology, Duke University Medical Center, Durham, NC	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design

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