Chapter 4
A 20-Year-Old Man with Acute Multi-organ Failure and Rhabdomyolysis

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History

A 20-year-old man with no significant past medical history was admitted to intensive care unit (ICU) for fulminant hepatic failure and encephalopathy. The night prior to the admission, the patient went to a nightclub with his girlfriend, where he ingested an unknown amount of "Molly" (purified derivative of 3,4-Methylenedioxy-methamphetamine (MDMA)). Later that evening the patient was noted to become confused and agitated, and he was brought to the emergency room from the night club. Upon arrival, the patient was hypertensive (BP: 218/168 mmHg), tachycardic (HR: 190 beats/minute), febrile (T: 109° F), rigid, diaphoretic and encephalopathic. He was intubated due to poor mental status and for airway protection. He was found to have fulminant liver failure, disseminated intravascular coagulation, and renal failure. He developed clinical seizures, and head CT and brain MRI revealed numerous subcortical punctate hemorrhages. A few days after the admission, he was found to have dark-color urine.

Physical Examination

The patient was not evaluated by a neurology team. According to the notes by ICU physicians, the patient's fever gradually resolved and there was no infection found. He was intubated and sedated. Cranial nerves were unremarkable with equal round and

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reactive pupils. Corneal and gag reflexes were present. Spontaneous breathing was present. Muscle tone was diffusely reduced, but all extremities withdrew to nailbed pressure. Reflexes were 2+ and symmetric. Toes were downgoing bilaterally.

Investigations

Laboratory studies revealed ALT 4885 U/L (1–53 U/L), AST 3128 U/L (1–50 U/L), total bilirubin 6.1 mg/dL (0.1–1.2 mg/dL), LDH 2452 U/L (100–220 U/L), creatinine 5.17 mg/DL (0.7–1.2 MG/DL), and TSH 5.74 uIU/ML (0.34–5.6 uIU/ML). Serum creatine kinase (CK) level rapidly and markedly increased to 156,728 U/L (30–200 U/L) on day 12 post-admission. A right gastrocnemius muscle biopsy was performed on the following day when CK was 214,792 U/L.

Muscle Biopsy Findings

The right gastrocnemius muscle biopsy (Fig. 4.1) shows rare atrophic fibers and one regenerating fiber, which is non-specific and insignificant. There is no evidence of muscle necrosis or inflammation.

Final Diagnosis

Normal gastrocnemius muscle biopsy despite clinical rhabdomyolysis

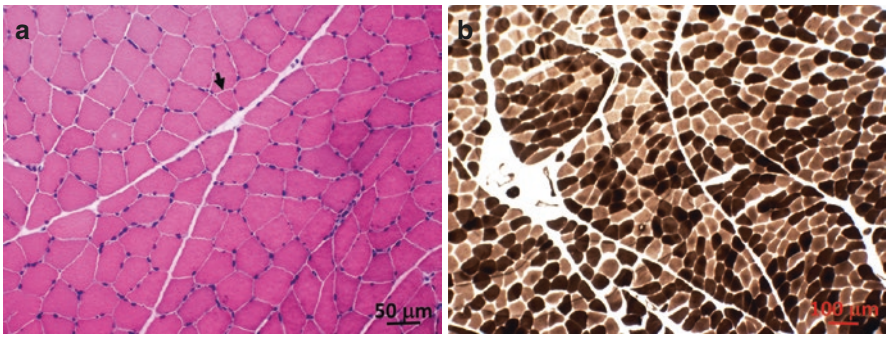

Fig. 4.1 (**a**) HE stain shows a rare atrophic fiber (arrow) but no myofiber necrosis or inflammation. (**b**) ATPase pH 9.4 stain shows normal fiber type distribution with no vacuolar changes to suggest myosin loss

Patient Follow-up

The CK level gradually returned to normal within 4 weeks. His multi-organ failure gradually resolved in 2 months. He was discharged from acute rehab in 3 months. He made a slow recovery over a course of 1 year.

Discussion

This is a striking case of rhabdomyolysis with an exceedingly high serum CK elevation but a normal muscle biopsy. It raises three management quesitons. (1) Was the muscle biopsy indicated? (2) Was it the right time to do a muscle biopsy? (3) Was it the right muscle selected for biopsy?

Rhabdomyolysis is defined as an acute muscle illness with marked serum CK elevation [1]. It results from acute necrosis of skeletal muscle with leakage of muscle constituents into blood circulation. It is a serious condition which can, but not always, cause myoglobinuria and acute renal failure, and even death [1–3]. According to a study of 475 inpatient cases with rhabdomyolysis [2], 60% were multifactorial. A detailed etiology analysis revealed that 46% cases were caused by exogenous toxins, 9% by trauma, 8% by neuroleptic malignant syndrome, 7% by seizures, and 7% idiopathic. About 10% of the cases were caused by underlying myopathies, including idiopathic inflammatory myopathies (27/475), metabolic myopathies (10/475), viral myositis (5/475), muscular dystrophies (3/475), and sarcoid myopathy (2/475). The most common cause of rhabdomyolysis is the exposure to exogenous toxins, including alcohol, illicit drugs, and prescribed medications with myotoxicity, such as antipsychotics, statins, selective serotonin reuptake inhibitors (SSRIs), Zidovudine, and Colchicine, among others. The purpose of a muscle biopsy in this setting is to determine whether the patient has an underlying myopathy that may require a specific treatment. Rhabdomyolysis itself does not need a muscle biopsy to confirm. In regard to the case presented here, the patient was known to suffer from the MDMA toxicity. MDMA is an amphetamine derivative. It is a popular recreational drug for adolescents and young adults who have misbelieve that the drug is safe. MDMA has unpredictable toxicity which can be life-threatening and fatal. Acute toxicity is caused by its sympathomimetic effects and serotonin syndrome, which can manifest hyperpyrexia, hypertension, encephalopathy, cerebral hemorrhage, hyponatremia, seizures, multi-organ failure, muscle rigidity and rhabdomyolysis [4] as seen in this case. The cause of rhabdomyolysis in this case is clear, which is the acute MDMA toxicity, given the history of presentation and the lack of a past medical history. Therefore, a muscle biopsy is not indicated, especially in the acute setting.

In general, a muscle biopsy should not be done at the peak of CK elevation during rhabdomyolysis, because the biopsy at this time point is most likely to show massive myofiber necrosis which can obscure the pathology of underlying myopathy.

Muscle biopsy is not needed in the majority of the rhabdomyolysis cases, as an inciting cause other than a primary myopathy can be identified and controlled in these cases. If a primary myopathy is of concern, a muscle biopsy should be done after the resolution of rhabdomyolysis, which may take a few weeks [5]. A muscle biopsy should be considered if CK level does not return to normal in the absence of a known cause, which may suggest an underlying primary myopathy, or if rhabdomyolysis is recurrent, which is commonly seen in metabolic myopathies. Patients with metabolic myopathies often report exercise intolerance, and rhabdomyolysis is usually triggered by strenuous physical activity.

It is surprising that the muscle biopsy in this case was unrevealing even the biopsy was done on the day when the patient's CK level was exceedingly high (>200,000 U/L). The importance of choosing a right muscle for biopsy cannot be overemphasized. Muscles are not equally affected by a disease process. While the majority of myopathies predominantly affect proximal limb muscles, a few preferentially affect distal limb, trunk, or facial muscles. The yield of a muscle biopsy is not 100%, and sampling error occurs frequently. In order to minimize the sampling error and increase the yield of a muscle biopsy, it is crucial to target a muscle for biopsy. Muscle selection can be challenging and should be done by treating neurologist not surgeon. The selection should be based on the pattern of clinical weakness, electromyography (EMG) findings, and/or muscle imaging findings [5, 6]. In a chronic myopathy, one should choose a muscle which is weak but not severely weak (MRC >3) for biopsy. If a muscle is severely weak and atrophic, the biopsy may show end-stage fibrofatty tissue replacement with limited number of myofibers available for evaluation, which is non-diagnostic. If a myopathy is acute or subacute when muscle chronic changes have not developed, one may choose a more severely affected muscle for biopsy to catch primary muscle pathology. Since the majority of myopathies predominantly affect proximal limb muscles, deltoid, biceps, and quadriceps muscles are most commonly chosen for biopsy, and these muscles have sufficient norms established for comparison with respect to myofiber size and fiber type percentages [7, 8]. If a myopathy predominantly affects distal limb muscles, tibialis anterior and gastrocnemius muscles may be selected for biopsy if they are affected. EMG is very useful not only to diagnose and characterize a myopathy but also to help select a muscle for biopsy. One should not choose a muscle that had recent injection, trauma, or needle EMG examination for biopsy to avoid confounding "needle myopathy" [9]. Since muscle involvement is often symmetrical in a myopathy, needle EMG of limb muscles is usually done on one side, and the muscle for biopsy is selected from the other side. It is worth mentioning that EMG can be normal in a mild myopathy, and some myopathies may have focal or asymmetrical limb muscle involvement. In these settings, skeletal muscle MRI and ultrasound can be useful in targeting a radiologically affected muscle or muscle area for biopsy.

Pearls

1. Understanding muscle biopsy indications is important to avoid unnecessary biopsy.
2. Choosing a right muscle for biopsy is critical, as muscle disease does not affect every muscle equally. Muscle selection should be carefully done by treating neurologist not surgeon, and should be based on clinical weakness, EMG findings, and/or muscle imaging findings.
3. The purpose of a muscle biopsy in a patient with rhabdomyolysis is to determine whether there is an underlying primary myopathy that may require specific management.
4. The most common cause of rhabdomyolysis is exogenous toxin exposure. An underlying primary myopathy is only found in 10% of inpatient cases of rhabdomyolysis. Therefore, the majority of patients with rhabdomyolysis do not need muscle biopsy.
5. A muscle biopsy should be considered in a patient with rhabdomyolysis if CK level does not return to normal without a known cause, which may suggest the presence of an underlying primary myopathy, or if rhabdomyolysis is recurrent, which is commonly seen in metabolic myopathies. A muscle biopsy should be done after rhabdomyolysis is resolved; it should not be done in the acute phase of rhabdomyolysis.

References

1. Gabow PA, Kaehny WD, Kelleher SP. The spectrum of rhabdomyolysis. Medicine (Baltimore). 1982;61(3):141–52.
2. Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: an evaluation of 475 hospitalized patients. Medicine (Baltimore). 2005;84(6):377–85.
3. Ward MM. Factors predictive of acute renal failure in rhabdomyolysis. Arch Intern Med. 1988;148(7):1553–7.
4. Davies N, English W, Grundlingh J. MDMA toxicity: management of acute and life-threatening presentations. Br J Nurs. 2018;27(11):616–22.
5. Nance JR, Mammen AL. Diagnostic evaluation of rhabdomyolysis. Muscle Nerve. 2015;51(6):793–810.
6. Dubowitz V, Sewry CA, Oldfors A. The procedure of muscle biopsy. In: Muscle biopsy: a practical approach. 4th ed: China: Saunders/Elsevier; 2013. p. 2–15.
7. Schiaffino S, Reggiani C. Fiber types in mammalian skeletal muscles. Physiol Rev. 2011;91(4):1447–531.
8. Staron RS, Hagerman FC, Hikida RS, Murray TF, Hostler DP, Crill MT, et al. Fiber type composition of the vastus lateralis muscle of young men and women. J Histochem Cytochem. 2000;48(5):623–9.
9. Engel WK. Focal myopathic changes produced by electromyographic and hypodermic needles. "Needle myopathy. Arch Neurol. 1967;16(5):509–11.