Commentary

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MADD is a heterogeneous metabolic disorder that can induce limb-girdle weakness with onset ranging from infantile to adult age. It is caused by defects in fatty acid oxidation in the respiratory chain. Multiple genes can be involved including electron transfer flavoprotein (ETF), ETF dehydrogenase, and riboflavin transporter and metabolizing (riboflavin kinase and flavin adenine dinucleotide synthase) genes. The essential vitamin riboflavin is taken up from the blood by transporters and metabolized into flavin mononucleotide and flavin adenine dinucleotide. These serve as cofactors for dehydrogenases. Not all forms of MADD are responsive to riboflavin treatment, and genetic testing may confirm MADD in riboflavin-insensitive patients. Cardiomyopathy may occur irrespective of age of disease onset. In this patient, serum cTnT was increased without proven cardiac or renal dysfunction. The suspected source of cTnT, which is normally only expressed in cardiac muscle, was skeletal muscle, consistent with previous reports on a number of neuromuscular disorders *(1)*. Subclinical cardiac damage as the source for cTnT remains possible in these cases, but a more likely scenario is reexpression of cTnT in skeletal muscle upon damage. The hs-cTnT assay discriminates cTnT from troponin family members using 2 independent antibodies. To assess reexpression in skeletal muscle, sequencing of cTnT cDNA or protein is preferred above using single antibodies. This has shown reexpression of cTnT mRNA and protein in skeletal muscle from Pompe patients without cardiac involvement *(2)*. cTnI is consistently not increased in neuromuscular disease without cardiac involvement, which may be caused by a lack of reexpression of cTnI in skeletal muscle. Release of proteins such as CK and cTnT from diseased muscle is likely due to leaky muscle fibers. This case stresses that results from the hs-cTnT assay should be interpreted with caution in patients with neuromuscular disease.

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References

1. Rittoo D, Jones A, Lecky B, Neithercut D. Elevation of cardiac troponin T, but not cardiac troponin I, in patients with neuromuscular diseases: implications for the diagnosis of myocardial infarction. J Am Coll Cardiol 2014;63:2411–20.
2. Wens SC, Schaaf GJ, Michels M, Kruijshaar ME, van Gestel TJ, et al. Elevated plasma cardiac troponin T levels caused by skeletal muscle damage in Pompe disease. Circ Cardivasc Genet 2016;9:6–13.

Commentary

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The case report details a phenomenon now becoming more appreciated. With early iterations of the cTnT assay, there was cross-reactivity between the tag antibody and skeletal muscle protein that led to false positive increases in patients with renal failure. A more specific tag seemed to solve the problem. However, reports continued to suggest that some patients with skeletal muscle disease and no overt cardiovascular disease had cTnT increases potentially from skeletal muscle. This is difficult to prove because one could argue, as in the case presented, that there could be diffuse myocardial involvement not detected by MRI, which requires confluent necrosis before a signal can be appreciated. On the other hand, a recent report in *Circulation Cardiovascular Genetics (1)* describes a large cohort of patients with Pompe disease, most of which had increased cTnT. It included measurement of the cTnT mRNA from affected skeletal

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muscle and a mass spectrometry analysis, suggesting that there were fragments from cTnT as well. These data, along with the data showing protein binding of the antibodies used in the cTnT assay to a 39.5-kDa protein from skeletal muscle, make a strong case that there are proteins in diseased skeletal muscle that are capable of causing increases of cTnT. How common this is only time will tell, but for now clinicians should be astute to the fact that patients with skeletal muscle disease can have increased cTnT. These increases may be even more common with the high sensitivity assay. To date, the numbers of cases where there has been a rising and/or falling pattern of cTnT, where there could be confusion with acute myocardial injury, have been rare but that does not mean they could not occur in individuals with skeletal muscle disease and critical illness.

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Reference

1. Wens SC, Schaaf GJ, Michels M, Kruijshaar ME, van Gestel TJ, In't Groen S, et al. Elevated plasma cardiac troponin t levels caused by skeletal muscle damage in Pompe disease. Circ Cardiovasc Genet 2016;9:6–13.