SERONEGATIVE IMMUNE-MEDIATED NECROTIZING MYOPATHY

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Introduction

- Immune-mediate necrotizing myopathy (IMNM) is an infrequent subtype in the inflammatory myositis spectrum of diseases. It is characterized by severe proximal muscle weakness, and rhabdomyolysis from myonecrosis with sparse inflammatory infiltrates at muscle biopsy.
- Autoantibody serology has aided in three subcategories: anti-hydroxy-3-methylguataryl CoA reductase (HMGCR), anti-signal recognition particle (SRP), and seronegative.

Case Presentation

A 79-year-old male presented with a two-week history of progressively worsening difficulty walking, poor appetite, and weight loss. His medical history includes remotely treated prostate and laryngeal cancers, hypertension, and dyslipidemia. He does not endorse any infectious symptoms before the onset of these symptoms. On presentation, decreased power was noted in the proximal muscles of the bilateral lower (2/5) and upper extremities (4/5) and icterus.

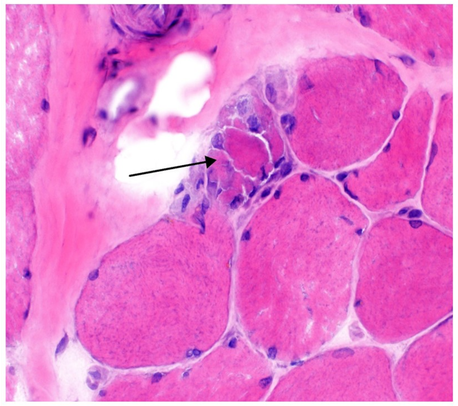
Initial laboratory work revealed elevated creatinine kinase (22806), BUN (64), creatinine (3.43), potassium (5.8), ALT (1100), AST (1694), and bilirubin (4.6).

Clinical Course

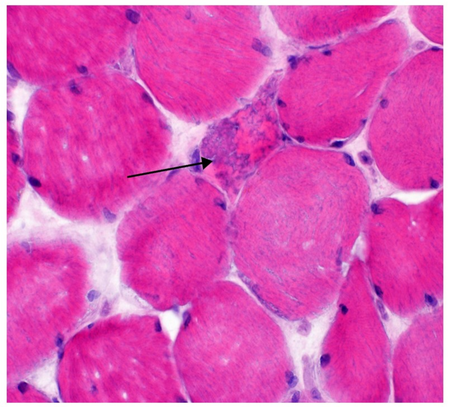
Initially believed to have statin-induced rhabdomyolysis, fluid and bicarbonate infusion were initiated with discontinuation of Atorvastatin. However, there was no improvement in his clinical condition. On day 5, his creatinine kinase trended to 157,580 with worsening renal function and new-onset anuria. Renal replacement therapy with intermittent hemodialysis (HD) was initiated.

MRI of the thighs showed evidence of diffuse myositis and fasciitis. Muscle and renal biopsy, along with further immunological work-up, was ordered. He was commenced on Methyl prednisone for suspected myositis. Renal biopsy showed acute tubular necrosis in the presence of myoglobin casts on underlying diabetic glomerulopathy. Muscle biopsy showed necrotizing myopathy with enhanced MHC and MAC staining on the sarcolemma membranes without any inflammatory cells. Given these results, a five-day IVIG course was added to the steroid course.

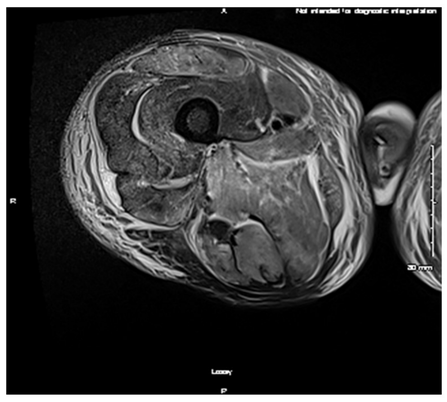
A dramatic drop in CK levels (4359) with significant improvement in the patient's muscle strength was apparent. Labs later revealed negative anti-HMGCR and Anti-SRP antibodies with negative paraneoplastic and myomarker panels. A diagnosis of antibody-negative necrotizing myopathy was made. He was discharged home on a prolonged prednisone taper and intermittent HD from which he was weaned off in mid-January 2023. Atorvastatin was permanently discontinued.

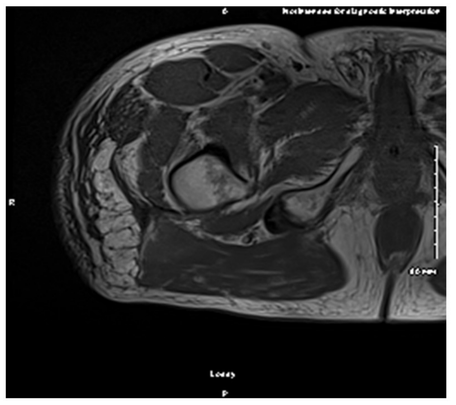


NECROTIC MYOFIBRES WITH MACROPHAGE INFILTRATION

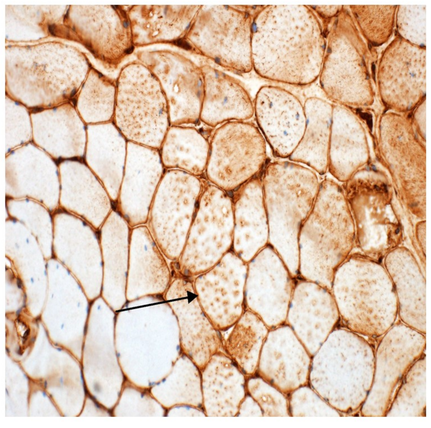


NECROTIC MYOFIBRES





MRI THIGHS: PROMINENT DIFFUSE MUSCLE EDEMA WITH ASSOCIATED FASCIAL AND SUBCUTANEOUS EDEMA



ENHANCED MHC-I STAINING ON SARCOLEMMAL MEMBRANE

Peak CK	**157,580**
ANA	**Negative**
Anti-HMGCR	**Negative**
Anti-SRP	**Negative**
Myomarker panel	**Negative**
Paraneoplastic panel	**Negative**

Discussion

- Seronegative IMNM is a clinicopathological diagnosis characterized by severe proximal muscle weakness and elevated CK. Extramuscular signs in skin, joints, and interstitial lung disease are infrequently present [1]. The rise in CK levels has been consistent with the severity of the disease. This subtype has a greater frequency of underlying cancers, and this was also associated with poorer prognosis.
- MRI is a sensitive diagnostic modality that shows hyperintensities reflecting muscle edema associated with inflammation or myonecrosis. Identification of fatty replacement signifies irreversible damage and poor recovery. This is also a sensitive modality for assessing the extent/severity of the disease, guiding biopsies, and monitoring disease activity [2].
- Muscle biopsy showing prominent muscle necrosis with the paucity of inflammatory cells is a typical finding in IMNM. There is enhanced expression of MHC-I on the sarcolemmal membrane. The absence of perifascicular/endomysial infiltrates, rimmed vacuoles, or tubulofilament-filled inclusions helps differentiate it from polymyositis, dermatomyositis, and inclusion body myositis.
- High-dose corticosteroids, intravenous immunoglobulins (IVIG), and immunosuppressants like Methotrexate and azathioprine are the cornerstone of therapy. No definite treatment strategy has been defined in a prospective study so far.

Conclusion

- Seronegative IMMN is the least recognized and often misdiagnosed as polymyositis or statin-induced myositis.
- Waiting for the biopsy and serology results could potentially delay the onset of therapy and increase the risk of complications. This includes ongoing active myonecrosis, fatty replacement of the muscle tissue, electrolyte derangements, and acute tubular necrosis. Early initiation of steroids with a high index of suspicion and the addition of IVIG or immunosuppressants would be the ideal therapeutic plan for seronegative IMNM.
- Needs age-appropriate cancer screening at the time of diagnosis.

References

1. *Yang, H., Tian, X., Zhang, L. et al. Clinical and pathological features of immune-mediated necrotising myopathies in a single-centre muscle biopsy cohort. BMC Musculoskelet Disord* ***23****, 425 (2022).* https://doi.org/10.1186/s12891-022-05372-z
2. *Fionda, L., Lauletta, A., Leonardi, L. et al. Muscle MRI in immune-mediated necrotizing myopathy (IMNM): implications for clinical management and treatment strategies. J Neurol (2022).* https://doi.org/10.1007/s00415-022-11447-7