


Letter to the Editor: New Observation

Failure of Hematopoietic Cell Transplantation in Immune-Mediated Necrotizing Myopathy

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Immune-mediated necrotizing myopathy (IMNM) is a severe, inflammatory myopathy requiring early, aggressive immunosuppressive therapy.¹ No clinical trials exist to guide IMNM management. Suggested agents include corticosteroids with one of methotrexate, rituximab or intravenous immunoglobulin (IVIg).¹ In refractory cases of inflammatory myopathy, autologous hematopoietic cell (“stem cell”) transplantation (autoHCT) may be trialed. To our knowledge, autoHCT has not been used for refractory anti-3-hydroxy-3-methylglutaryl-CoA reductase (anti-HMGCR) IMNM. We report a failed case of autoHCT for anti-HMGCR IMNM.

A previously healthy female, originally from Nepal, with no prior statin exposure, presented at age 27 years with fatigue, proximal weakness and ambulation difficulties. Family history was negative for autoimmune or muscle disease. Creatine kinase (CK) was > 10 000 U/L (normal < 200) at presentation. Electromyography suggested an irritable myopathy. Rheumatologic markers (including ANA, ENA, anti-dsDNA, AMA, ASMA, RF, anti-CCP, scleroderma and Sjogren’s testing), local myopathy panel (including autoantibodies to myositis-related antigens Mi-2, Ku, PM/Scl-100, PM/Scl-75, Jo-1, PL-7, PL-12, Ro-52, OJ, EJ and signal recognition particle [SRP]), myotonic dystrophy and FKRP/calpain genetic testing were negative. Left biceps biopsy, at age 28 years, demonstrated significant fibrosis, atrophy and only rare foci of endomysial/perimysial lymphocytic infiltration consistent with an inflammatory myopathy or muscular dystrophy.

Therapy with prednisone and IVIg was started given inflammatory features on muscle biopsy. Prednisone caused significant weight gain with minimal benefit. Methotrexate 15 mg weekly and mycophenolate mofetil 1000 mg twice daily were not tolerated due to cytopenia and liver dysfunction, respectively. Rituximab 2 g (in equally divided doses, 2 weeks apart) every 6 months and IVIg 2g/kg/month were started at age 30 years, at which point she was wheelchair dependent. There was improvement with this regimen between the ages of 30 and 34 years to a point of independent ambulation; however, a plateau was reached followed by mild worsening.

HMGCR antibody returned high-positive at age 36 years suggesting IMNM. Lower extremity MRI demonstrated severe muscular atrophy of the pelvic girdle, thighs and to a lesser degree gastrocnemius. Edema was present suggesting active myositis. Left deltoid biopsy at age 37 years revealed frequent abnormal sarcolemma complement deposition, consistent with acute IMNM. There was, however, a lack of significant acute myofiber necrosis possibly due to the various immune therapies received. Although muscle histology did not meet strict pathologic criteria for IMNM, IMNM was highly likely given extreme CK elevation, positive HMGCR antibody, muscle edema on MRI and the response to IVIg and rituximab.

IVIg was replaced by plasma exchange therapy (weekly for 1 month and then twice weekly for another month) with significant improvement at age 37 years. On this treatment, motor grades (Medical Research Council grade out of 5) were 4+ neck flexion (2 at age 29 years), 4+ bilateral shoulder abduction (2 at age 29 years), 4+ right and 5 left elbow flexion (3 bilaterally at age 29 years) and 2 hip flexion (unchanged), with normal strength in other muscle groups.

Given the immune-responsiveness, she was referred to hematology for consideration of autoHCT, completed at age 38 years. Stem cell mobilization was achieved with cyclophosphamide 2.5 mg/m² + granulocyte-colony stimulating factor. Conditioning consisted of cyclophosphamide 200 mg/kg and thymoglobulin 4.5 mg/kg. Immediately following transplant, CK normalized. Motor power was dramatically improved at 2 months post-transplant with 5/5 strength in upper extremity muscle groups and neck flexion. Hip flexion remained 2/5. After 2 months, the CK began to rise, suggesting early relapse. By 3 months post-transplant, there was clear clinical and biochemical relapse with 4- neck flexion, 4- shoulder abduction, 4- elbow flexion and 4 elbow extension and ongoing HMGCR antibody positivity. Rituximab and IVIg were restarted.

Few cases of autoHCT for refractory inflammatory myositis are reported, mostly for dermatomyositis or polymyositis, with sustained responses from between 12 and 36 months post-transplant.^{2–4} A successful case of anti-SRP IMNM with positive

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effects up to 3 years post-transplant has been reported. Sustained effectiveness of autoHCT in these cases may be due to the time at which autoHCT was completed.⁵ On MRI, there was only evidence of muscle edema and no clear fatty replacement of tissue, suggesting earlier autoHCT in the anti-SRP case compared to our study where autoHCT was completed 10 years after symptom onset.⁵ AutoHCT may be ineffective after years of disease duration, supported also by failed autoHCT in a case of dermatomyositis with prolonged disease duration.⁶ Interestingly, a case series of five patients with severe refractory IMNM treated with high-dose cyclophosphamide therapy without stem cell rescue is reported. Two out of five patients demonstrated a substantial response, both were anti-SRP positive. Perhaps anti-HMGCR patients are less responsive to high-dose cyclophosphamide and autoHCT. More cases are required to understand treatment responsiveness.

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