Hydroxychloroquine and Colchicine Induced Myopathy

To the Editor:

Hydroxychloroquine and colchicine neuromuscular toxicity is well documented. The largest literature review on colchicine myopathy was conducted by Wilbur and Makowsky in 2004 where a database search found 75 cases. Most patients presented with proximal muscle weakness. A wide range of treatment durations were noted (from 4 days to 11 yrs) with cumulative daily doses of 1.4 ± 0.96 mg. The toxicity became apparent in the majority of cases after changes in recent disease states such as decline in renal function, initiation of dialysis, or solid organ transplantation. A second myotoxic agent such as prednisone, lipid lowering agents, or cyclosporine were common. We report a case with a stable glomerular filtration rate of 36.7 ml/min/1.73 m².

A 66-year-old woman was admitted to the hospital after being unable to stand after a minor fall. She had a 12 year history of seronegative rheumatoid arthritis (RA) treated with hydroxychloroquine 200 mg bid since diagnosis. The patient complained of progressive proximal upper and lower extremity painless muscle weakness since being discharged from the hospital for a bladder suspension surgery 4 weeks before. Her hospitalization was complicated by a postoperative gout flare of multiple metatarsophalangeals on the right, during which she was given colchicine as an inpatient and continued until presentation. She reported having similar mild symptoms of weakness for the previous 12 months also.

Examination revealed the patient was 5 ft, 6 in, weighing 230 lbs with upper and lower extremity; proximal and distal muscle weakness with the most prominent weakness noted with hip flexor strength graded 3/5. She was unable to transfer without assistance. Quadracep deep tendon reflexes were +1 bilaterally with unobtainable bicep and tricep reflexes. No sensory deficits were noted. Scattered Heberden and Bouchard nodes noted along with near anklyosed left 3rd proximal interphalangeal and right 5th metacarpophalangeal joints. Bilateral wrist range of motion was limited in flexion of 45°. No synovitis was evident by palpation. Chest examination was clear and cardiac examination revealed no murmurs or rubs. Skin examination was negative for Gottron’s, Shawl, and V signs or a heliotrope rash. Capillaroscopy displayed no dilations or dropouts.

Further investigations revealed an elevated creatinine kinase (CK) of 343 u/l and electrocardiograph with RBBB and premature atrial complexes unchanged from 3 years prior. Complete blood cell count, liver function tests, electrolytes, and urine analysis were normal. Antinuclear antibodies, extractable nuclear antigen, rheumatoid factor, and cyclic citrullinated peptides, Lyme antibody, and antineutrophil cytoplasmic antibodies were all negative along with negative hepatitis C, hepatitis B, and HIV antibodies. CA-125 was 22 U/ml (range 0-35 U/ml) and thyroid-stimulating hormone normal. Mildly low vitamin D(OH) of 29 ng/ml was noted (upper level of normal 31 ng/ml). Cerebrospinal fluid showed normal glucose (62 mg/dl) and protein (26.1 mg/dl). Magnetic resonance imaging (MRI) of cervical, thoracic, and lumbar spine were essentially normal minus a nonenhancing 5 cm syrinx cavity at T6-T8. Electromyography of lower extremities demonstrated rapid recruitment, myotonic discharges, small to moderate polyphasia. MRI of the lower extremities did not reveal muscle edema or inflammation on T2, STIR (short tau inversion recovery) signals. Biopsy of left vastus lateralis lacked any inflammatory changes but did show numerous swollen axons suggestive of acute axonal neuropathy and vacuoles.

Despite negative MRI and muscle biopsy, polynuromyositis was diagnosed and the patient was initiated with 80 mg of prednisone with a subjective improvement of 50% in strength within 48 h; however, she developed complete heart block requiring emergent pacemaker placement and transfer to our tertiary care center. Transthoracic echocardiogram did not reveal an infiltrating process. Further muscle biopsy studies were done including negative staining of NADH and ATPase for fiber type grouping. Periodic acid Schiff staining showed no evidence of a glycogen storage disease. Oil red O was negative for lipid accumulation within muscle fibers. Electron microscopy showed vacuole changes of curvilinear bodies consistent with hydroxychloroquine myopathy (Figure 1) and whorled membranous bodies consistent with colchicine myopathy (Figure 2). Hydroxychloroquine and colchicine were discontinued with a rapid taper of prednisone. Eight weeks later the patient returned to the hospital with an infected pacemaker lead and swollen left wrist. Aspiration revealed a negative culture but polarized microscopy revealed calcium pyrophosphate dihydrate crystals. She was successfully treated with an intraarticular injection of methylprednisolone. Her strength had returned to baseline with a normal CK of 29 u/l.

We present a case of neuropathy and myopathy in a woman treated chronically with hydroxychloroquine and recently added colchicine. Both...
agents were felt to have a role in her progressive decline, with hydroxychlo-roquine likely inducing a mild myopathy over the previous 12 months. This worsened acutely with the introduction of colchicine, and her symptoms resolved with discontinuation of both of these agents within 8 weeks. She had no other common etiologies to explain her weakness including electrolyte abnormalities, endocrinopathies or drugs including alcohol, glucocorticoids, lipid-lowering agents, antipsychotics, or antiretrovirals. Although she did have a response to prednisone, an idiopathic inflammatory myopathy was not likely to be her underlying diagnosis given her normal MRI, muscle biopsy, and serologies.

Hydroxychloroquine was noted, in one large prospective study of 119 patients, to have toxic myopathy of 1.2% with a prevalence of 6.7%. In that study 111 received chloroquine and 8 received hydroxychloroquine, and interestingly, several patients had “myeloid bodies” (spheromembranous bodies) in addition to curvilinear bodies on biopsy. That observation raises the possibility that chloroquine alone may produce both pathologies, but the report does not specifically address the question of whether those patients were receiving chloroquine monotherapy or a combination of agents. Hydroxychloroquine myopathy is thought to be underestimated with prior reports noting normal CK levels in patients with typical biopsy features of vacuoles and curvilinear bodies. Duration of drug and dose are not well defined in myopathy; onset of symptoms may vary months to years; typical symptoms are nonspecific. With moderate proximal muscle weakness with slightly elevated to normal CK levels. Proximal muscle strength usually recovers slowly and can be incomplete. Involvement with respiratory musculature has been severe, most recently noted by Abdel-Hamid, et al, ultimately leading to death in 2 medically complicated patients. Cardiac toxicity from antimalarials has also been described as conduction abnormalities or as congestive heart failure with biopsy revealing similar vacuole changes in skeletal muscle and myocardium. Without biopsy or resolving arthralgias, possible cardiac involvement is difficult to prove.

The differential diagnosis of vacuoles on light microscopy include metabolic; acid maltase deficiency, phosphofructokinase deficiency, carnitine deficiency, periodic paralyses; inflammatory: inclusion body myositis; infectious: echovirus; neurological: Duchenne’s dystrophy, oculopharyngeal dystrophy, and distal myopathy; toxic: colchicine, hydroxychloroquine, alcohol, glucocorticoids, cyclosporine, any cause of hypokalemia, vincristine, zidovudine.

New light has been shed on the mechanisms of action of both colchicine and hydroxychloroquine. Colchicine has multiple effects including disruption of the innate immunity by suppressing the NALP3 inflammasome-driven caspase-1 activation of interleukin 1β processing and release, and L-selectin expression on neutrophils. Classically, colchicine is known to inhibit microtubule polymerization, which results in impaired lysosomal transport along microtubules. Whorled membranous bodies and spheromembranous bodies, which represent accumulation of tubular profiles and saccoplastic reticulum, can be seen at the electron microscopic level as seen in our patient. Hydroxychloroquine has a lipid soluble hydrophobic region as well as an amine group bearing a net positive charge, which allows the drug to insert into membranes having multiple effects including decreasing Toll-like receptor-9,8,7, and -3 activation. These membranes get autodigested with the histopathological result showing fiber digestion. On the electron microscopic level one can see the distinctive cytosomes with curvilinear profiles as seen with our patient, which are due to enhancement of lipofuscin formation.

Our patient was receiving a combination of hydroxychloroquine and colchicine for the treatment of seronegative RA and gout. RA and gout can occur together albeit rarely, with a review in 2003 collecting only 20 cases. The reason for the lack of coexistence between these 2 diseases is still disputed. Theories of protection from rheumatoid arthritis in patients with gout stem from uric acid’s function as an antioxidant and free-radical scavenger. Interestingly, hyperuricemia seemed to also have a protective effect in RA with an associated quiescent or inactive disease, lower rheumatoid factors, and flares occurring during normalization of urate levels. Data on the association of pseudogout/chondrocalcinosis and RA are scarce, with pseudogout being less common in age and sex matched controls. Given that our patient had a wrist aspiration consistent with calcium pyrophosphate dihydrate, her need for hydroxychloroquine and possibly colchicine are questionable.

In summary, we present a patient taking longterm hydroxychloroquine who developed an acute-on-chronic progressive proximal myopathy with the addition of colchicine. Our patient likely had baseline mild proximal myopathy secondary to hydroxychloroquine with her acute decompensation due to a second myotoxic drug, colchicine. To our knowledge this is the first documented case of a myopathy induced by both hydroxychloroquine and colchicine supported by unique electron microscopy findings. These medications are used to treat a wide variety of rheumatologic disorders and are generally well tolerated. We must, however, be aware of their possible side effects with the possible additive risk of myopathy.

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