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Case Report
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When Rehabilitation is not the Answer: A Case Report of Statin Use

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Abstract

An 85-year-old male with hypertension and hyperlipidemia, who was previously independent, was started on simvastatin for treatment of hyperlipidemia in January 2018. In March 2018, he developed weakness and declined in function. He had decreased exercise tolerance, increased fatigue, deconditioning, and ambulatory and ADL dysfunction, and saw his primary care doctor in May 2018, at which time he was admitted to the hospital with concerns of adult-onset muscular dystrophy. He diagnosed with rhabdomyolysis and elevated liver enzymes and was treated with intravenous fluids. Over the next three months, the patient's symptoms and elevated CK persisted. He was admitted to the hospital twice more and had multiple clinic appointments before immune-mediated necrotizing myositis due to statin was suspected and ultimately diagnosed with left bicep biopsy. Patient was admitted a final time for treatment with prednisone and IVIG. His symptoms progressively improved, and he was able to ambulate over 150 feet after 5 doses of IVIG. This patient suffered a prolonged period of debility due to the delay in diagnosis and treatment. This case demonstrates the importance of continuing the diagnostic evaluation when the current diagnosis does not fully explain the symptoms and when symptoms do not improve with treatment.

Keywords: Statin; Myositis; Immune-mediated; Necrotizing

Introduction

As physiatrists, by the time we see inpatients, be it on consult or in an inpatient rehabilitation unit, a diagnosis has already been determined. You are there to evaluate and treat the sequelae of the patient's condition, be it a stroke, brain injury, spinal cord injury, or other neurological condition. We often see patients with functional decline due to debility. However, when symptoms cannot be fully explained by a patient's diagnosis and does not improve, it is imperative to question the diagnosis. Here, we discuss a case of an elderly patient thrice diagnosed with rhabdomyolysis secondary to statin use that did not improve with treatment or rehabilitation and suffered a prolonged period of debility before being found to have necrotizing myositis.

Case Presentation

Our patient is an 85-year-old male with a history of hypertension and hyperlipidemia treated with amlodipine-benazepril 5 mg to 10 mg daily and simvastatin 80 mg daily. Prior to March 2018, he was independent for all activities of daily living and was able to walk ten to twelve blocks independently with no assistive device. He lived alone, although his son and daughter visited daily to help with home management and cooking. He was started on the Statin in January 2018 and began developing symptoms of weakness and decline in function in March 2018. He saw his Primary Care Provider for his weakness on May 8, 2018 and was sent to the hospital the next day for evaluation for possible late-onset adult muscular dystrophy. His Statin was stopped at that visit. He was admitted for decreased exercise tolerance, increased fatigue, deconditioning, and ambulatory and ADL dysfunction, found to have abnormal lab values. Significant laboratory values are shown in (Figure 1). Abnormal values included an ALT of 289, AST of 385, and CK of 11,040. He was treated for rhabdomyolysis, elevated LFTs, failure to thrive, and dehydration with intravenous fluids. He was seen by gastroenterology and nephrology as well, and he was discharged on May 15, 2018 with a decreased CK of 4,789. Throughout his hospital stay, per records, he had no pain and continued to have generalized weakness. No specific strength testing was documented. He was discharged to home with the following diagnoses: Statin adverse reaction, Myalgia caused by Statin, Rhabdomyolysis, and Transaminitis.

Upon returning home, that patient suffered a mechanical fall and returned to the emergency

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room the next day, May 16, 2018. He was noted to have edema of the left lateral malleolus but no restricted range of motion of the ankle. His CK was 6782. His AST and ALT were trending down. Physical therapy was consulted and recommended less than three hours of therapy per day after evaluating the patient. He again received intravenous fluids. He had no pain and no dark or tea-colored urine. No signs of volume overload were noted. He was discharged to a skilled nursing facility with the above diagnoses in addition to fall in home, left foot pain, and ambulatory dysfunction.

The patient returned to his primary care provider's office for schooled follow-up on June 11, 2018. He had been discharged to home from the skilled nursing facility. He did not have another fall at home but was still weak and he and his son described his overall health status as poor. No neurologic exam was documented, but blood work was sent. CK was 6,491. ALT was 165 and AST was 234. TSH, CBC, and BMP revealed no abnormalities.

Due to the persistent CK elevation, our patient's primary care provider instructed the patient and his son to return again to the emergency room. Global weakness but no myalgia was noted. Intravenous fluids were again the primary treatment. Nephrology was consulted and recommended ANA, ESR, and consideration of a rheumatology consult if the patient's symptoms do not improve. A low vitamin D level of 16.2 was found and supplementation with 8000 units of cholecalciferol daily was started. The patient was discharged on June 18, 2018 after several days of hydration with a CK of 3144, ALT of 103, and AST of 138. He was able to ambulate 350 feet with a rolling walker and go up and down 4 steps with bilateral rails at a supervision/set-up level with physical therapy, so he was discharged home. He was told to follow-up in a rheumatology clinic, but the clinic associated with the hospital he had been admitted to be unable to accept new patients. Therefore, he needed a referral from his primary care provider and came to our institution.

He was seen in our institution's rheumatology clinic on July 10, 2018. At this time, he was noted to have a poor appetite, weight loss of five pounds in the last two months, dyspnea with walking half a block, weakness of the legs, hand left greater than right pitting ankle edema. He was unable to stand from a seated position. His proximal bilateral upper extremity strength was documented as a 5-minus out of 5. His proximal bilateral lower extremity strength was documented as a 4-minus out of 5. Distal strength in all extremities was 5 out of 5. Laboratory values from July 3rd included an AST of 229, ALT of 190, CK of 6,397, and CRP of 7.4. Because the patient was also noted to have a loss of height, a DEXA scan was done with results significant for osteoporosis. Weekly alendronate and a calcium and vitamin D supplement were started. Ultimately, the patient was referred to neurology for an EMG and or muscle biopsy to rule out inflammatory myositis.

Our 85 year-old male was seen in our institution's neurology clinic on July 23, 2018. On exam, his mental status, speech, and cranial nerves were intact. Sensation was intact. Finger-to-nose testing was within normal limits bilaterally. His upper extremity reflexes were a 2+, and lower extremity reflexes were a 1+. Strength testing out of 5 was documented as follows: 5 neck flexion and extension, 3 shoulder abduction, 4 elbow flexion, 5 distal upper extremities except for 4+ finger extensors, 2 hip flexion, 4+ hip abduction, 5 hip adduction, 4+ knee flexion, 5 knee extension, 5 distal lower extremities. Strength was equal bilaterally. The patient was noted to push up with his arms to stand and have a shuffling, unsteady gait. The patient was found to have an elevated SRP antibody titer and sent for direct admission to the neurology floor.

ALT 289
AST 385
Chol 146, Trigly 73, HDL 42, LDL 89
TSH 2.2
HgbA1c 6.0%
CK 11,040
WBC 7.3, HGb 13.0, Plt 231
Cortisol 12.4
Electrolytes were all within normal limits
Cr 0.60, BUN 6

Figure 1: Laboratory results from the patient's first set drawn on May 8, 2018.

On admission, he was started on prednisone and IVIG one dose per day for five days. He also had a paraneoplastic workup done due to the positive anti-SRP, which was negative. He has a muscle biopsy with his left bicep, which confirmed the diagnosis. Results of muscle biopsy in cases of immune-mediated necrotizing myositis are discussed below. The patient was evaluated by PM&R on consult while receiving his 4th dose of IVIG and said to require acute inpatient rehabilitation admission based on his ability to ambulate only 20 feet × 2 with minimal assistance and require moderate assistance for lower extremity ADLs such as dressing. He was noted by physical therapy to have decreased speed and step length, decreased arm swing, and lateral sway with gait. He had 4 out of 5 strength of the shoulder abductors and 2 out of 5 strength of the hip flexors bilaterally. His strength was 5 out of 5 distally in all extremities. He still had 1+ ankle edema, left greater than right. The rest of his exam was consistent with his exam in neurology clinic above. The day after his 5th dose of IVIG, the patient ambulated 200 feet × 2 with no assistive device with physical therapy. The following day, his shoulder abduction strength was noted to be 4+ out of 5, improved from previous. His hip flexion strength had improved to 3 out of 5. He was discharged to home with home care including physical and occupational therapy as he no longer required inpatient rehabilitation.

Discussion

Perhaps another diagnosis was not considered because our patient already had a rare diagnosis. Rhabdomyolysis occurs in about 0.4/10,000 patient years, while myalgias and cramps are much more common as they occur in 9% to 20% of Statin-users [1]. Most myopathy events associated with Statin use resolve completely in the weeks to months after discontinuation of the Statin [2]. Autoimmune myopathy does not resolve with the cessation of Statin use, however [3]. Necrotizing autoimmune myopathy can also masquerade as muscular dystrophy, leading to a delay in diagnosis [4]. As in our case, diagnosis has been delayed by many months in other documented cases of Statin-induced necrotizing myopathy [5].

The disease occurs in patients over 18 years of age as a sub acute or insidious onset of symmetric proximal more than distal weakness [5]. Sixty percent of patients with necrotizing autoimmune myopathy develop auto antibodies against Signal Recognition Particle (SRP) or 3-Hydroxy-3-Methylslutaryl-CoA-Reductase (HMGCR) [4,6]. CK is often markedly elevated (>4,000) [7]. Biopsy shows necrotic, regenerative, atrophic, and irregularly shaped myofibers with scarce inflammation, mainly composed of macrophages [4,8]. Irritable myopathy on EMG, muscle edema on MRI with diffuse or patchy

increased signal, or myositis-specific antibodies detected in the serum must be present for diagnosis [5,9]. Irritable myopathy on EMG is characterized by spontaneous fibrillation potentials, positive sharp waves, and insertion irritability [9]. When caused by Statin use, response to treatment is generally favorable [3]. It can occur even in low-intensity Statin use, such as simvastatin 20 mg for 5 years [10]. The Statin must also be discontinued. Statins can be found in certain food, which can explain a case in an individual not on Statin medication [11].

Regarding the treatment, our patient experienced a very positive response to 5 doses if IVIG administered over 5 days. Although this is not the only effective treatment, some reports suggest that it may be the most effective treatment [9]. One case series suggested that Intravenous Immunoglobulin (IVIG) monotherapy could be adequate for a specific subset of patients [12]. It has also been suggested that IVIG be included in all treatment schemes [8]. Rituximab treatment has also been reported in a case with dramatic improvement status-post treatment with prednisone and multiple immunosuppressant's' before it [13]. One report described treatment with prednisone, azathioprine, and methotrexate [10].

Conclusion

Statins are used by about a quarter of the US population [14]. Statin-associated autoimmune myopathy has been described more recently in case reports and series [15,16] since the report of its association with HMGCR was published in 2010 [17]. The incidence has been estimated to be 2 to 3 cases in 100,000 Statin-exposed patients overall or 2 cases per million per year [14,18]. Our case serves as an example of why this, albeit rare, disease should not be ignored by physiatrists.

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