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Amiodarone-induced neuromyopathy in a geriatric patient

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SUMMARY

Amiodarone is an antiarrhythmic medication with many side effects. Neuromyopathy is a rare adverse effect. We present an 87-year-old woman with bilateral leg pain and weakness in the context of amiodarone. She was admitted to the Acute Geriatric Unit in Calgary, Alberta, Canada. On examination, hip flexor and extensor strength were 2/5 bilaterally while knee flexor and extensor strength were 4/5 and 3/5, respectively. Creatine kinase and C-reactive protein levels were normal. MRI of the lumbar spine showed mild central canal stenosis. Electromyography and nerve conduction testing showed a severe axonal length-dependent polyneuropathy of the left lower extremity. There was evidence of myopathic changes to the left iliopsoas muscle. Overall, a neuromyopathic process affecting the lower extremities was supported. After discontinuation of amiodarone, mobility and function significantly improved. Although a rare complication of amiodarone, neuromyopathy should be considered in patients with compatible symptomatology.

BACKGROUND

Prescription medications are prevalent and associated with both common and rare adverse effects. Many can impact the neuromuscular system.¹⁻⁴ Amiodarone is an antiarrhythmic medication with a variety of associated side effects.⁵ Neuromyopathy is a rare adverse effect of this agent characterised by significant proximal and distal weakness, distal sensory loss and diminished muscle stretch reflexes.⁶⁻⁸ The lower extremities are more commonly affected than the upper ones.⁸ Amiodarone is thought to interact with lipid membranes, resulting in complexes resistant to lysosomal digestion.⁵ This leads to cellular vacuoles filled with debris, ultimately cumulating in pathology. We present an 87-year-old woman with bilateral leg pain and weakness in the context of amiodarone therapy. Specifically, we wish to highlight the importance of medication side effects in the geriatric population. Medication side effects can present typically or atypically in this population and rare adverse effects can be more prevalent due to the pharmacodynamics and pharmacokinetics of an ageing body.

CASE PRESENTATION

This patient was admitted to the Acute Geriatric Unit (AGU) in Calgary, Alberta, Canada, for the assessment and management of subacute bilateral leg pain and weakness, which cumulated in complete loss of independent ambulation. Her past medical history

was significant for atrial fibrillation, right frontal cerebrovascular cortical infarction, subcortical lacunar infarctions and well-controlled diabetes mellitus type 2 (haemoglobin A1c was 7.5% within 1 month of presentation). Her atrial fibrillation was initially rate-controlled with a combination of verapamil, metoprolol and digoxin. Prior to AGU admission, these medications were discontinued due to an episode of atrial fibrillation with rapid ventricular response as well as adverse drug reactions and perceived risk with continued use. Subsequently amiodarone was started for rhythm-control with a 200 mg by mouth three times a day dose for 14 days, and then followed by 200 mg by mouth daily. The patient was also anticoagulated with apixaban for her atrial fibrillation.

Shortly after initiation of amiodarone she developed bilateral leg weakness and pain. This pain was progressive and migratory though it was limited to her lower extremities. There were no bowel or bladder complaints. Prior to the initiation of amiodarone, the patient was able to ambulate independently and without a gait aid. When admitted to the AGU, she was a two-person assist for transfers from sit-to-stand and could not ambulate. This was after approximately 2 months of amiodarone therapy.

On physical examination, hip flexor and extensor strength were 2/5 bilaterally while knee flexor and extensor strength were 4/5 and 3/5, respectively. Ankle dorsiflexor and plantarflexor strength were 5/5 bilaterally. Patellar and ankle deep tendon reflexes were absent bilaterally. Vibration sensation was absent to the waist at all levels including the great toe, medial malleolus, knee and pelvis. Pinprick sensation was impaired to the mid-distal level bilaterally. Proprioception was intact in the lower extremities.

INVESTIGATIONS

Laboratory investigations showed unremarkable haematology and routine biochemistry. Creatine kinase and C-reactive protein levels were normal. CT of the lumbar spine showed no lytic lesions, but severe bone demineralisation. MRI of the lumbar spine showed scoliosis with degenerative disc disease and mild central canal stenosis at L1/L2 and L2/L3. Severe central canal stenosis was seen at L3/L4 and L4/L5. The Physical Medicine and Rehabilitation Service performed electromyography and nerve conduction studies. Only the left lower extremity was tested because EMG and nerve conduction studies were terminated prematurely due to bleeding in the context of anticoagulation. Her studies showed no response on superficial



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Case report

peroneal and sural sensory testing, severely reduced amplitude but normal conduction velocity of the extensor digitorum brevis, slightly reduced amplitude of the tibialis anterior and borderline normal amplitude but reduced conduction velocity on tibial motor testing. The overall impression was that the patient had an axonal length-dependent polyneuropathy of the left lower extremity, sensory greater than motor, and this was graded as severe. There was evidence of myopathic changes to the left iliopsoas muscle without frank denervation.

DIFFERENTIAL DIAGNOSIS

The opinion of the Attending Medical Team and Neuromuscular Service was that the patient possibly had an amiodarone-induced neuromyopathy. A muscle biopsy was discussed with the patient but after weighing the risks and benefits of the procedure (especially in the context of anticoagulation), it was not pursued. The Attending Medical Team decided that the risk of bleeding outweighed pursuing the procedure, and stroke risk was too high to interrupt anticoagulation. Even though a muscle biopsy was not performed, the clinical history, physical examination and electromyography/nerve conduction studies supported a neuromyopathic process affecting the lower extremities of the patient. Although MRI of the lumbar spine showed central canal stenosis, it is unlikely that clinical findings were due to spinal stenosis. Patients with lumbar spinal stenosis can show spontaneous improvement in pain and health-related quality of life, however acutely losing and/or regaining the ability to walk rarely occurs.⁹ The possibility of diabetic neuropathy causing this weakness and pain was discussed. The physical examination did not completely fit with a stocking and glove pattern of diabetic neuropathy. Moreover, electromyography/nerve conduction studies were not typical of diabetic neuropathy. Medication review confirmed that this patient was not on metformin or statin therapy at the time of symptom presentation. Moreover, this patient had not been on metformin or statin therapy for at least 6 months prior to symptom presentation. This patient's diabetes mellitus type 2 was managed with insulin therapy and sitagliptin. Sitagliptin has not been widely associated with neuromyopathy. On examination, there was no upper extremity weakness to support a diagnosis of polymyalgia rheumatica or polymyositis. Lastly, a vitamin B12 level checked in May 2019 was well above normal range for geriatric patients. Based on the timeline of leg weakness and pain in the context of amiodarone therapy initiation, an amiodarone-induced neuromyopathy was the leading diagnosis.

TREATMENT

On admission to the AGU, amiodarone was discontinued and rate control with a beta-blocker was initiated successfully. With active rehabilitation including strength training, balance exercises, targeted physiotherapy and functional optimisation by occupational therapists, the patient slowly started to regain lower extremity function. Amiodarone was started in April 2019 and discontinued in June 2019. From June until October 2019, inpatient rehabilitation continued.

OUTCOME AND FOLLOW-UP

By the end of October 2019, the patient, using a four-wheel walker gait aid, was independent with transfers and ambulation. She was discharged home at her pre-amiodarone level of mobility and functional abilities. Follow-up with the patient in March 2020 showed no recurrence of leg weakness or pain.

DISCUSSION

Geriatric patients usually have multiple comorbidities, polypharmacy and complex presentations. Emphasis is placed on generating a broad list of differential diagnoses and then systematically narrowing this list down through clinical reasoning and investigation. We have provided rationale and evidence that the lower extremity neuromyopathy seen in our patient was not due to other underlying medication side effects (such as metformin or statin therapy). Clinical history and examination findings did not support neuromyopathy secondary to diabetes mellitus type 2, spinal stenosis or polymyalgia rheumatica/polymyositis. Common vitamin deficiencies such as vitamin B12 deficiency, were also excluded.

Neuromyopathy is a known but rare complication of amiodarone. It is not as frequently found when compared with other neuromyopathy-causing medications, such as statins.¹⁰ Unusual features in this study were the normal creatine kinase levels and short duration of amiodarone therapy. While supportive if elevated, normal creatine kinase levels do not rule out a myopathic process. In amiodarone neuromuscular toxicity, creatine kinase levels may not correlate with the degree of myopathy.⁵ Furthermore, symptoms of neuromyopathy can develop

Patient's perspective

I felt a variety of emotions during my hospitalisation for leg weakness and pain. Initially, I was angry that I had lost the ability to walk and that this had happened rather suddenly. I felt as if my independence had been taken from me. I was angry with the amiodarone medication itself, as well as with the initial care team that prescribed this medication. Specifically, I was not educated around the indications, risks and benefits of amiodarone and therefore was not aware of neuromyopathy as a potential side effect. Although, this rare side effect may not have been discussed in the initial medication counselling, however even a preliminary risk/benefit discussion would have eased my anger after encountering an adverse medication event. In addition, my family members raised concerns over potential medication side effects when my walking ability was lost. At times, these family members felt like they were not being heard early in the clinical presentation.

Throughout rehabilitation, I experienced points of encouragement and discouragement however as pain slowly started to improve, my outlook brightened. I was able to form a good alliance with the medical and rehabilitation teams and was grateful to the Acute Geriatric Unit and the fine job that was done regarding management.

Learning points

- ▶ Amiodarone has many side effects, including neuromyopathy, which can present as leg weakness and/or pain.
- ▶ Amiodarone-induced neuromyopathy can develop anywhere from a few months to years of amiodarone therapy.
- ▶ A normal creatine kinase does not exclude amiodarone-induced myopathy.
- ▶ After amiodarone is stopped, muscle strength slowly returns and can take up to 6 months for full strength to return.
- ▶ Geriatric patients metabolise medications in different ways. Adverse effects should be considered in patients with compatible symptomatology.

anywhere from a few months to years of amiodarone therapy.¹¹ The short duration of amiodarone therapy does not exclude an amiodarone-induced neuromyopathy. Optimally, a muscle biopsy would have been obtained to confirm causal relationship between amiodarone and lower extremity neuromyopathy in this patient. The Attending Medical Team could not justify subjecting this patient to an invasive and risky procedure when they were already confident that amiodarone was the cause of neuromyopathy. Not only was this leading diagnosis supported by specialists on the Neuromuscular Service, but the timeline of clinical recovery also fit that of an amiodarone-induced neuromyopathy.

The patient returned to her pre-amiodarone mobility and functional abilities. In general, muscle strength gradually improves after amiodarone is discontinued. It can take up to 6 months for full strength to return.⁸ This is consistent with the clinical timeline seen in our patient. Unfortunately, the diagnosis of an amiodarone-induced neuromyopathy was delayed until June 2019. Although a rare complication of amiodarone, this syndrome should be considered in patients with compatible symptomatology.

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