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A case of myositis with immunological background associated with statin use

Case Report

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Abstract: Statins might cause and/or aggravate the immune-mediated myositis in patients on long-term, stable treatment. We provide a case of polymyositis with an immunological background and gastrointestinal and urinary manifestations in patient on long-term, stable atorvastatin treatment for the past six years. The diagnose of polymyositis was established based on clinical symptoms and signs, electromyography and laboratory test results (elevated aspartate aminotransferase 279 U/L, reference range 0–40 U/L; alanine aminotransferase 198 U/L, 0–33 U/L; lactate dehydrogenase 2200 U/L, 103–227 U/L; creatine kinase 7820 U/L, 15–84 U/L; and positive antinuclear antibodies test, titer of 1:160, with suspect antisynthetase antibodies). Polymyositis was probably related to atorvastatin treatment (Naranjo score, 5). Other probable causes of the myositis were rejected. Coricosteroid therapy, methotrexate and supplementation with vitamin D did not improve the condition. The patient remained bedridden and died two months after the hospital discharge due to the acute myocardial infarction.

Keywords: *Myositis • Atorvastatin • Vitamin D*

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1. Introduction

Hydroxy-methyl-glutaryl Co-A reductase (HMGCR) inhibitors or statins are lipid-lowering agents. Statins inhibit synthesis of mevalonic acid, which leads to up-regulation of low density lipoproteins (LDL) receptors, increase in the rate of removal of LDL from plasma, decrease in the amount of total cholesterol and decrease in serum LDL levels [1]. In addition, statins have a strong efficacy in reducing cardiovascular events and death in secondary prevention due to their pleiotropic actions as well [2]. This group of drugs is widely used and often well-tolerated. On the other hand, adverse effects of statins could have serious impact and form a significant barrier to therapy adherence. A variety of muscle-related side effects could occur [3-4].

Statins are a well recognized cause of different types of myotoxicity: asymptomatic elevations of creatine kinase, myalgias, autoimmune myopathy, muscle necrosis or rhabdomyolysis. Statins could induce fatal rhabdomyolysis, the reported incidence is 1.5 deaths per 10 million prescriptions. However, the mechanism(s) of statin myotoxicity are unclear. The possible mechanisms include reduction in small guanosine triphosphate-binding proteins, increased lipid myopathy, decreased

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sarcolemal cholesterol and reduced intramuscular coenzyme Q10 [5]. It is well known that the highest potency statins, such as rosuvastatin and atorvastatin, show higher muscle adverse event rates [3].

Statin-induced myopathy often occurs during the first six month of drug using with moderately severe symptoms. The majority of patients with these adverse effects are older than 80 years. The multiple risk factors for statin-induced myopathy could be divided into two groups: patient-related (for example, small body size, age, female sex, genetics, co-morbidities such as renal or hepatic dysfunction, diabetes mellitus, and hypothyroidism) and drug-related (for example, transport, metabolism via CYP system and interactions of statins) [6].

There are many different symptoms in myopathy induced by statins: fatigue, muscle pain, muscle weakness, muscle tenderness and tendon pain. The muscle symptoms could be proximal or generalized, and can be made worse by exercise. Statins-caused myopathic symptoms resolve within a few months of discontinuation of the drug. However, symptoms associated with autoimmune myopathy induced by statins could persist or progress even after drug discontinuation [7]. Gastrointestinal manifestations in polymyositis induced by statins are rare [8].

A case of 67-year-old woman with statin-induced autoimmune myopathy that had developed after 6 years of statin use, with gastrointestinal and urinary manifestations, is presented here [6].

2. Case report

A 67-year-old woman was admitted to the Institute of Rheumatology in Belgrade due to pronounced weakness of muscles of shoulder and pelvic belt and neck extensors, weakness in the leg muscles and loss of upright posture of the body. The patient was placed in a semi-upright sitting position (45-60 degrees) and her mobility was restricted (Figure 1).

She had weakness of neck muscles with subsequent difficulties in holding up her head (head drop). She could not sit without the neck support. Also, weakness of neck muscles impaired the ability to lift her head while in bed.

Deterioration occurred one week before the admission to the hospital, but the symptoms had begun and progressively developed a year ago. She did not have muscle pain, difficulty breathing and difficulty swallowing, nor any joint complaint.

On admission, internist examination revealed auscultatory seldom late-inspirium both-sided basal lung breaks. A systolic murmur was present, heard best at Erb's point. Her arterial pressure was 115/80 mmHg, and heart rate was 76/min. Her body weight was 65 kg, height was 1.70 m, and body mass index 22.5 kg/m^2. There was no skin rash.

Patient had pulmonary tuberculosis 36 years previously. (Figure 2).

Her past medical history was significant for hypertension (over 30 years), hyperlipoproteinemia (6 years), ischemic heart disease and blepharospasm. Her daily home drug regimen included ramipril 5 mg b.i.d., bisoprolol 2.5 mg q.d., aspirin 100 mg q.d., pentaerithritol tetranitrate 40 mg b.i.d., and atorvastatin 20 mg q.d. Atorvastatin has been used for the treatment of hypercholesterolemia during the last six years, in a stable treatment regimen. In the last 3 years, botox was administered for the treatment of blepharospasm once every 6 months. The last injection of botox, used in the treatment of blepharospasm, was administered three

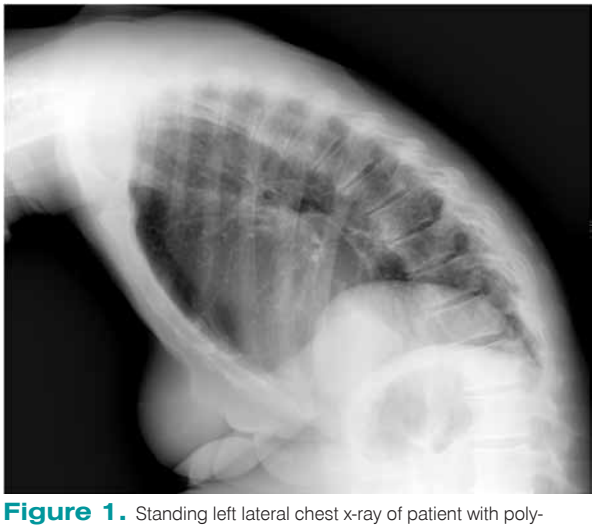

Figure 1. Standing left lateral chest x-ray of patient with polymyositis and restricted mobility showing her semi-upright position.

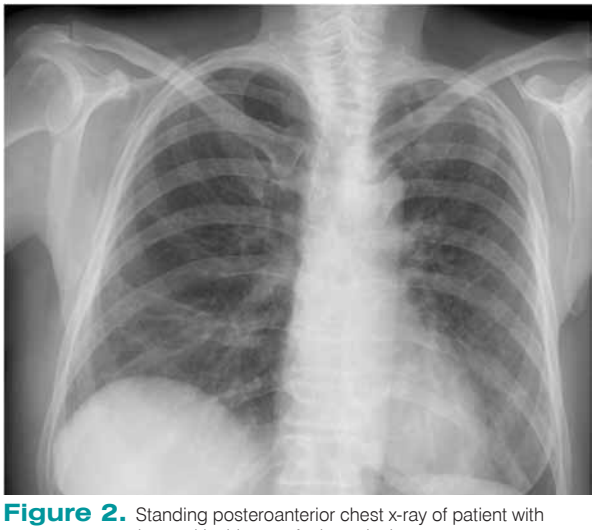

Figure 2. Standing posteroanterior chest x-ray of patient with polymyositis: history of tuberculosis.

months before the admission. There was no history of any food and drug allergy.

On the day of admission to the Institute, the serum creatine kinase (CK), lactate dehydrogenase (LDH), aspartate transaminase (AST) and alanine transaminase (ALT) were significantly elevated (Table 1).

In addition, vitamin D3 level was somewhat below the normal range (72.3 ng/ml; the normal range of 25-hydroxy-cholecalciferol: 75-185 ng/ml). Also, positive antinuclear antibodies test, titer of 1:160, with suspect antisynthetase antibodies was detected, while the anti-Jo1 antibodies test was negative (not shown in the table). Other hematologic and serum biochemical tests were within the reference range, including the erythrocyte sedimentation rate (ESR), which was 14 mm/h, and WBC (except day 14 increase of up to 12.9 x10^9/L).

The urinalysis tests were within the reference range (not shown).

Electromyoneurography (EMNG) results indicated myopathic findings in proximal muscles (a decrease in duration of the action potential and a reduction in the area to amplitude ratio of the action potential). The electroneurographic test data were within normal range (Figure 3).

Based on symptoms and signs, laboratory and EMNG results, the diagnosis of polymyositis was established. The treatment was initiated with intramuscular methylprednisolone 1 mg/kg/day (60 mg daily). Use of atorvastatin was stopped.

The patients' condition deteriorated and she subsequently developed urinary retention, abdominal distension and constipation within the first seven days

Table 1. Selected laboratory parameters during corticosteroid therapy (patient with polymyositis)

Parameters (normal range)	Methylprednisolone therapy						
	Before	I.m. 1 mg/kg/day	Bolus I.v 1000 mg/day (3 days)		I. m. 1 mg/kg/day		Po. 0.5.mg/kg/day
	The hospital day						Follow-up
	1st	3th	7th	9th	14th	20th	
Urea (2.5-7.5 mmol/L)	5.26			15.35	9.15	10.89	
AST (0-40 U/L)	279		187	185	150	96	42
ALT (0-33 U/L)	198		171	173	208	164	92
GGT (5.9-25 U/L)	24			81		66	
Uric acid (150-360 mmol/L)	524				486	485	
LDH (103-227 U/L)	2200	2030	1314	1448	1640	1300	672
CK (15.0-84.0 U/L)	7820	6870	3004	2773	2720	1553	540
Cholesterol (3.63-5.75 mmol/L)	6.38						9.0
Triglycerides (0-2.28 mmol/L)	3.01						4.3
25(OH)D3 (75-185 ng/ml)	72.3						

Follow-up one month after hospital discharge; i.m. – intramuscular; i.v. – intravenous; p.o.- per os; 25(OH)D3–25-hydroxy-cholecalcipherol. Other parameters measured (for example, serum creatinine, glucose, and others were within normal range).

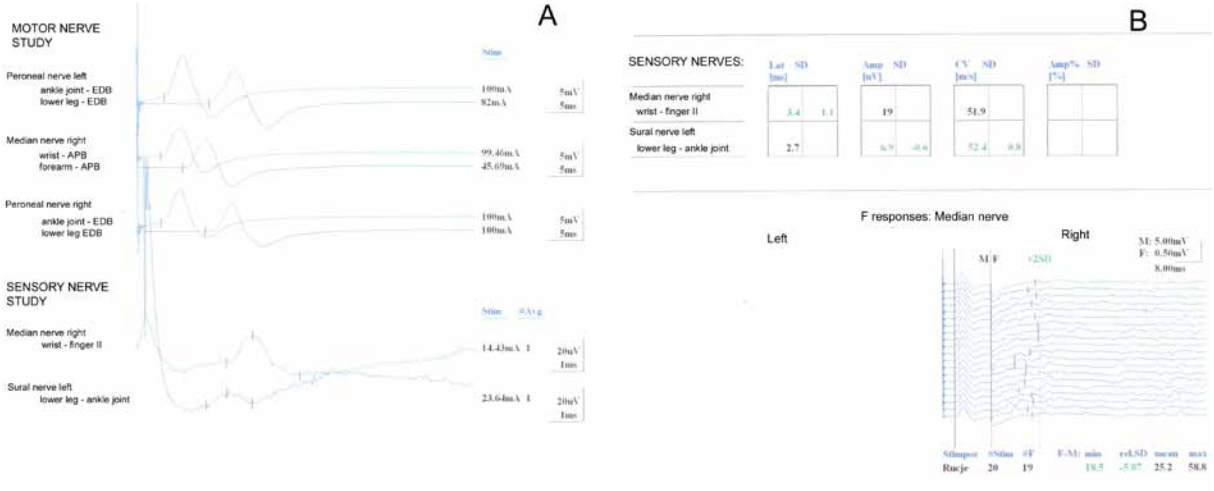

Figure 3. Electromyoneurography (EMNG): typical finding of polymyositis with stronger affected proximal muscles of the lower extremities, without any sign of disturbances of innervation (Panels A and B).

in the hospital. Standard abdominal *x*-ray examination disclosed dilated loops of small bowel (Figure 4), but no obstructing lesion was located.

Detailed examination did not reveal secondary causes of myopathy. There were normal blood levels of all tested tumors markers. A chest *x*-ray examination and abdominal and pelvic ultrasound examination showed no evidence of malignancy.

Intravenous (i.v.) bolus of methylprednisolone (1000 mg) was administered for three consecutive days, and treatment was continued with intramuscular methylprednisolone 1 mg/kg/day (60 mg daily). The patient responded only partially to corticosteroid treatment. Her gastrointestinal pseudo-obstruction and urinary retention recovered completely. Her CK and LDH levels fell to 2720 and 1640 U/L, respectively, but muscle strength did not improve, and the patient was still immobile 25 days after initiation of steroid therapy. Further corticosteroid treatment was tapered on the hospital release due to pulmonary tuberculosis history in patient´s anamnesis. Accordingly, oral methotrexate (10 mg/week) was initiated.

The treatment on the time of discharge from the hospital included oral methylprednisolone 0.5 mg/kg/day (36 mg daily), methotrexate 15 mg/week, folic acid 5 mg weekly (the day after application of methotrexate), alfacalcidiol 0.5 μg/day and the cardiovascular treatment as previously. However, use of statins was forbidden forever. The rehabilitation and physical therapy was proposed to the patient.

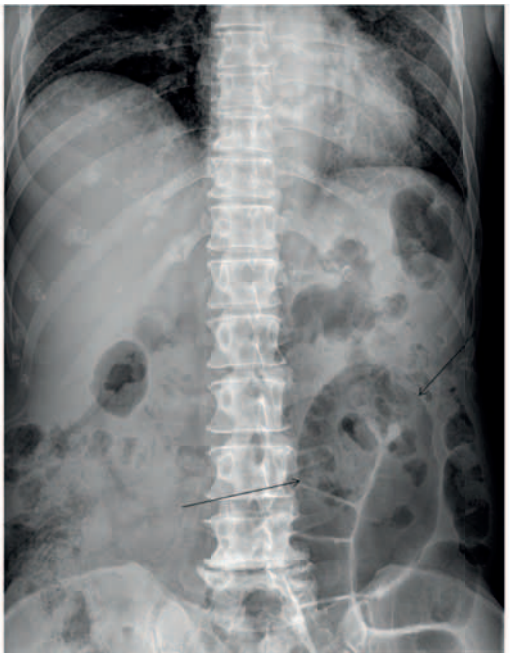

Figure 4. Native abdominal x-ray of patient with polymyositis showing dilated loops of small bowel without obstruction (arrows).

The patient was still bedridden for weeks after discharge from the hospital, but her CK and LDH values were significantly lower (540 and 672 U/L, respectively). Unfortunately, the patient died 2 months after the hospital discharge due to acute myocardial infarction. No autopsy has been performed.

3. Discussion

Here is presented patient with polymyositis probably related to atorvastatin treatment (Naranjo score, 5). The most important properties of presented case are the following:

- delayed onset of the adverse event after prolonged, stable atorvastatin treatment
- development of the autoimmune myopathy, and
- polymyositis with gastrointestinal and urinary manifestations, and borderline serum vitamin D3 level.

Our case fit guidelines for the diagnosis and management of suspected statin-induced myotoxicity [6].

Polymyositis is an inflammatory disease of proximal skeletal muscle that evolves over weeks to months. The patients have moderate to severe muscle weakness presented as difficulty in climbing steps, rising from the chair, lifting objects, combing hair. There are well-defined criteria for diagnosis: clinical, immunopathological, histological and demographic [9]. Myalgia, myopathy, myositis or rhabdomyolisis could be defined based on CK level [10]. In the presented case, patient had high levels of CK and LDH with severe clinical symptoms, which indicated development of myositis, without histological evidence of inflammatory changes. We are aware of the limitations of our study, but our diagnostic criteria do not differ from the most of published cases of statin-induced myopathy, according to Hilton-Jones [11]. In addition to clinical and laboratory examinations, we have assessed the probability of causal relationship between the suspected drug and adverse event described. The Naranjo score for this particular case is 5; i.e., the causal relationship could be assessed as probable [12].

Statin-induced myopathy often occurs within first six month of statin use. The present patient used atorvastatin for six years before the developed myositis. This important data makes a decision about the diagnosis difficult, but according to the FDA, in 13.23% of atorvastatin-treated patient's myopathy could occur even after 5-10 years of drug use [13]. Similar symptoms could develop in hypothyroidism or paraneoplastic syndrome. The levels of thyroid hormones (triiodothyronine, T3; thyroxine, T4; thyroid stimulating hormone, TSH) in our patient were within normal range. Also, there were not

abnormal levels of tumor markers; *x*-ray and ultrasound examination showed no evidence of malignancy.

The blood level of vitamin D3 in our patient was borderline, i.e., somewhat below the reference range from our laboratory (see above). Accordingly she was supplemented with vitamin D (alfacalcidiol). Correction of serum 25-(OH) levels from 22 to 43 ng/ml leads to improvement of clinical symptoms of myopathy in statin intolerant patients, according to the results of a double-blind study in patiens with myositis-myalgia [14]. However, there are few studies that describe resolution of statin-induced myositis-myalgia by correcting serum 25 (OH) vitamin D deficiencies. Also, one could argue that interaction between vitamin D deficiency and statins could produce symptomatic myositis-myalgia in statin-treated patients [14].

Our patient started with vitamin D supplementation. In this way, we excluded D3 hypovitaminosis as a cause of myopathy. Although alfacalcidiol was added in low doses as supplement therapy, there was a parallel, sustained decrease of serum AST, ALT, LDH and CK concentrations until the 30th day of follow-up. The atient's condition did not improve (she died bedridden) despite normalization of serum enzyme levels. The possible influence of vitamin D supplementation on the statin-induced myositis in this particular case remains to be clarified.

Urinary and gastrointestinal manifestations in polymyositis induced by statins are rare (with the exception of pharyngeal dysphagia). Our patient developed urinary retention and atonic small bowel with abdominal distention and constipation. There are a few case reports of pseudo-obstruction in patients with polymyositis [15-17]. According a study that included 441 reports from FDA and 121052 atorvastatin users, urinary retention as adverse effect of atorvastatin occurs in 0.36% of drug-users. Most patients developed moderate to severe urinary retention during first 6 months of atorvastatin use (more than 50%) and only 3.7% of patients developed an observed adverse effect of medication during 5 to 10 years of drug use. There are important data that the most of patients with urinary retention as adverse effect of drug had co-morbidities such as multiple sclerosis, gastro-oesophageal reflux diseases, or diabetes mellitus. On the other hand, approximately 7% of atorvastatin-used patients developed constipation in period 5-10 years after atorvastatin introduction [13].

Statin-induced myopathies could be associated with autoimmune or connective tissue disorders [7]. Our patient was antinuclear antibody (ANA)-positive, anti-Jo1 antibodies negative, but anti-HMGCR antibodies were not measured (see Table 1). It is well known that these antibodies might be associated with antisynthetase syndrome, as well as some other antibodies, e.g., anti-PL-7, anti-PL-12 [18]. However, we could not clarify the possible cause-effect relationship between statin use and the immunological findings presented. In addition, the false positive ANA test could be found in 5-10% of patients without connective tissue disorders, especially in elderly and women [19]. We could hypothesize that either statin might cause the muscle injury, which triggers antibody production, or statin just aggravates the primary immunological disorder. There are several articles describing association between statins and autoimmune ANA and anti-Jo positive myopathy [20-22]. Also, there is a review suggesting that statins might cause or provoke an immune-mediated myopathy [7].

The patient died due to acute myocardial infarction. Although cardiovascular manifestations constitute a major cause of death in myositis, it is not clear if the cause of her death was resulted from myositis or her initial heart condition [23]. Of note, her serum cholesterol and triglyceride concentrations significantly increased after the cessation of atorvastatin therapy (follow-up, Table 1). Accordingly, the patient had multiple risk factors for cardiac death: long-term hypertension, hypercholesterolemia and the advanced age.

During hospitalization, she received high doses of corticosteroid therapy. It is well known that a high dose of corticosteroids worsens cardiovascular diseases [24]. Accordingly, given the serious condition of the patient and the association of several risk factors for sudden cardiac death, we could not determine the cause of the occurrence of myocardial infarction.

In conclusion, we provide the evidence that statins might cause and/or aggravate the immune-mediated myositis in a patient on the long-term, stable treatment. The probable cause of the therapy outcome in this particular case was the late visit to the general practice doctor in the primary care (one year after the appearance of symptoms).

4. Acknowledgment

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Conflict of interest statement

Authors state no conflict of interest.

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