Clinical implications and current perspectives of statin-induced rhabdomyolysis syndrome – case presentation

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Abstract
Though rare, statins can produce serious adverse effects with clinical implications that urge prompt intervention. However, in high-risk patients that require intense hypolipemiant treatment, such situations can be challenging and require complimentary therapies. We report the case of a 82-year-old hypertensive female patient admitted for diffuse myalgia, mainly in the lower limbs, fatigue and shortness of breath. The patient is known with a recent myocardial infarction (MI) treated by primary stent implantation. The electrocardiogram and transthoracic echocardiography confirmed the recent MI, with non-dilated left ventricle mildly reduced ejection fraction. Initial laboratory studies revealed elevated NT-proBNP, moderate renal impairment and increased serum levels of creatine kinase (CK), CK-MB fraction and transaminases. After stopping statin and receiving supportive treatment, the patient's paraclinical test results and symptoms improved: CK levels and transaminase dropped significantly and both myalgia and general fatigue resolved mostly within 4 days. PCSK9 inhibitor has been introduced with favourable results at follow-ups. Even though statins are effective and safe, they may still generate potential dangerous adverse effects in rare cases. Statin dose adjustment or replacement and adding other lipid lowering therapies represent current therapeutical options, especially in high-risk populations.

Keywords
statins, hypercholesterolemia, myocardial infarction, statin-induced myopathy, rhabdomyolysis, PCSK9 inhibitors.

Rezumat
Deși rare, statinele pot produce efecte adverse grave, cu impact clinic major care impune intervenția promptă. Cu toate acestea, la pacienții cu risc cardiovascular înalt care necesită tratament hipolipemiant intensiv, astfel de situații pot fi dificile, fiind necesare terapii complementare. Raportăm cazul unei paciente hipertensive în vârstă de 82 de ani, internată pentru mialgie difuză, în principal la nivelul membrelor inferioare, oboseală și dispnee. Pacienta este cunoscuta cu un infarct miocardic (IM) recent tratat prin implantare primară de stent. Electrocardiograma și ecocardiografia transtoracică au confirmat IM recent, cu fracție de ejecție ușor redusă a ventriculului stâng. Analizele de laborator au evidențiat NT-proBNP crescut, insuficiență renală moderată și niveluri serice crescute ale creatinkinazei (CK), fracțiunii CK-MB și transaminazelor. După oprirea statinei și primirea tratamentului suportiv, rezultatele testelor paraclinice și simptomele pacientei s-au îmbunătățit: nivelurile CK și transaminazelor au scăzut semnificativ și atât mialgia, cât și oboseala generală au fost ameliorate după 4 zile. Inhibitorul de PCSK9 a fost introdus în tratament, cu rezultate favorabile. Chiar dacă statinele sunt eficiente și sigure, ele pot genera efecte adverse periculoase în cazuri rare. Ajustarea sau înlocuirea dozei de statine și adăugarea altor terapii hipolipemiante reprezintă opțiuni terapeutice curente, în special la populațiile cu risc foarte înalt.

Cuvinte cheie
statine, hipercolesterolemie, infarct miocardic, miopatie indusă de statine, rabdomioliză, inhibitori de PCSK9.

Background

Many studies proved the benefits of the use of statins in the treatment of hypercholesterolemia and in primary or secondary prevention of cardiovascular (CV) events such as myocardial infraction (MI), acute ischemic stroke or peripheral artery disease, by having the capacity of stabilisation and regression of atheroma plaques. Still, although treatment benefits of statin use are a fact, the risk of adverse effects cannot be ignored when prescribing the drug [1].

Statin-associated muscle symptoms are reported in 10-25% of patients receiving statin therapy and include muscle pain and weakness. Statin-induced myopathy, which is accompanied by increases in creatine kinase levels above 10 times the upper limit, is rare (occurs in less than 0.1% of patients taking statins) [2]. Rhabdomyolysis is the worst form of myopathy, being even rarer and is characterized by dissolution of striated muscle fibres, resulting in leakage of muscle enzymes, myoglobin, potassium, calcium and other intracellular constituents, accompanied by a critical increase in sarcoplasmic calcium and intracellular damage by activation of proteases and phospholipases. It can potentially result in dramatic, even life threatening, consequences such as electrolytic disorder which may cause arrhythmias (hyperkalaemia

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and hypocalcaemia), acute renal failure (caused by intraluminal myoglobin, haem protein nephrotoxicity and renal vasoconstriction) and compartment syndrome due to inflammation [2,3,4]. Several coexisting conditions such as impaired hepatic and renal function, hypothyroidism, diabetes mellitus, concomitant medications, either myotoxic or involved in the statin metabolism, consumption of alcohol or grapefruit juice, a personal or family history of hereditary muscle disorders, can increase the risk of developing statin induced myopathy [3,5].

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have similar cardiovascular benefits like statins but are not associated with any increased risk of statin-related side-effects. PCSK9 inhibitors are human monoclonal antibodies that bind with high affinity to human hepatic PCSK9, a protein that degrades LDL receptors before they reach the cell surface, so more LDL cholesterol remains in the bloodstream. So PCSK9 inhibitors prevent the degradation of the beneficial LDL receptor on the hepatocyte cell surface, therefore, lowering circulating LDL cholestrol [6].

Case Report

We describe the case of an 82-year-old hypertensive woman who complains of diffuse myalgia, mainly in the lower limbs, fatigue and shortness of breath, symptomatology with onset 3 weeks before and worsening in the last 3 days.

The patient had a history of a recent hospitalization in the Cardiology department (less than one month ago), when she suffered a right ventricle and inferior MI treated by primary *percutaneous transluminal coronary angioplasty (*PTCA) with drug-eluting *stent (*DES) on the right coronary artery and an episode of periprocedural ventricular tachycardia electrically reduced and prophylactised with amiodarone. Since then, she had been under treatment with Ticagrelor 90 mg b.i.d., Aspirin 75 mg o.d, Rosuvastatin 40 mg o.d., Bisoprolol 2,5 mg o.d, Amiodarone 200 mg o.d and Pantoprazol 20 mg o.d. She declared she had no recent or distant history of alcohol or tobacco consumption. Also, she did not report the use of myotoxic or hepatotoxic drugs nor did she report any personal history of viral episodes or genetic diseases in the family.

On clinical examination she had mild pallor. Her central pulse rate was 70 bpm with a blood pressure of 150/80 mmHg; her precordium examination was normal, except a discrete bilateral leg swelling with pitting edema. She had bilateral pulmonary fine crackles in the basal zone. We noticed an influenced general condition by marked fatigue and weakness in hip flexion and extension, the muscles appeared to be slightly hypotrophic, normotonic and normokinetic. She had close to normal strength against resistance in proximal muscles and her distal muscles had slightly diminished strength. Her tendon reflexes were normal. Her bo*dy mass index* was 22 kg/m^2. The abdominal examination was unremarkable.

Initial laboratory studies revealed increased serum levels of creatine kinase (CK) 3847 U/L and CK-MB fraction 100 U/L, slightly elevated troponin 153 µg/L, lactate dehydrogenase 575 U/L, aspartate aminotransferase (ASAT) 161 U/L), and alanine aminotransferase (ALAT) 219 U/L, with normal hepatic viral markers, suggesting hepatocyte suffering. Also, a mild renal impairment was noticed (creatinine 1.57 mg/dl, urea 74 mg/dl, creatine clearance 31 mL/min/1,73m^2). NT-proBNP was elevated 3169 ng/dl, with normal inflammatory markers. Serum electrolytes, hemoleucogram and thyroid function were normal. LDL cholesterol target has not been yet achieved 79mg/dl, considering her very high cardiovascular risk.

Her electrocardiogram (ECG) revealed sinus rhythm, 63 bpm, intermediate QRS axis, subacute myocardial infarction in the inferior leads, QS morphology in the right limbs and qR morphology in the posterior limbs (figures 1, 2).

The transthoracic echocardiography described nondilated left ventricle, with mildly reduced ejection fraction 45-50% by hypokinesia on basal half of the posterior wall, concentric mild left ventricle hypertrophy, type I diastolic dysfunction, nondilated atria, moderate mitral regurgitation, mildly pulmonary hypertension and normal pericardium.

The Holter ECG monitoring/24 hours revealed: average heat rate 56 bpm (46-101/min); 1800 premature ventricular contractions (PVC) sometimes with a tendency for systematization in bigeminism and doublets; approximately 500 supraventricular premature beats; no pauses longer than 2 seconds; no atrial fibrillation or malignant arrythmias.

Abdominal ultrasound described micronodular liver with dimensions at the upper limit, relaxed gallbladder with small stones. The right kidney has a bumpy outline, with a lower polar cyst.

For the establishment of a positive diagnosis, we considered the anamnesis (muscle related symptoms, no alcohol consumption, no use of myotoxic or hepatotoxic drugs, no personal history of viral episodes or genetic diseases in the family). Also, the ECG was stationary with the one from the previous discharge and the CK-MB fraction was < 5% in repeated measures, even though troponin was slightly increased, so a myocardial origin of the dramatic CK elevation was excluded. Also, her thyroid function was normal, the hepatic viral markers were negative and there was no marked inflammatory response and no fever to suggest an inflammatory muscle disease. Therefore, the history of a recent daily use of rosuvastatin in high dose was incriminated for the apparition of myopathy and the elevation of transaminases and CK, CK-MB.

Immediately after, rosuvastatin was stopped and the patient received supportive treatment with moderate-volume intravenous saline liquids administration to maintain an adequate urine output, and carefully monitoring sodium and calcium serum concentrations.

During the four days of hospitalization, muscle cytolysis enzymes started to decrease (CK 3847→1458 U/L, CK-MB 100→77 U/L) and renal function improved (Creatinine 1.57→1.18mg/dl, creatine clearance 31→41 mL/min/1,73m^2). Also, there was a slight improvement of the patient myopathy related symptoms. Also, transaminase and troponin concentrations fell rapidly (troponin 153→31 µg/L, ASAT 219→103 U/L, ALAT 161→103 U/L), suggesting the muscular origin.

The heart failure treatment was adjusted by adding loop diuretic (furosemide 20 mg o.d.), an aldosterone antagonist (spironolactone

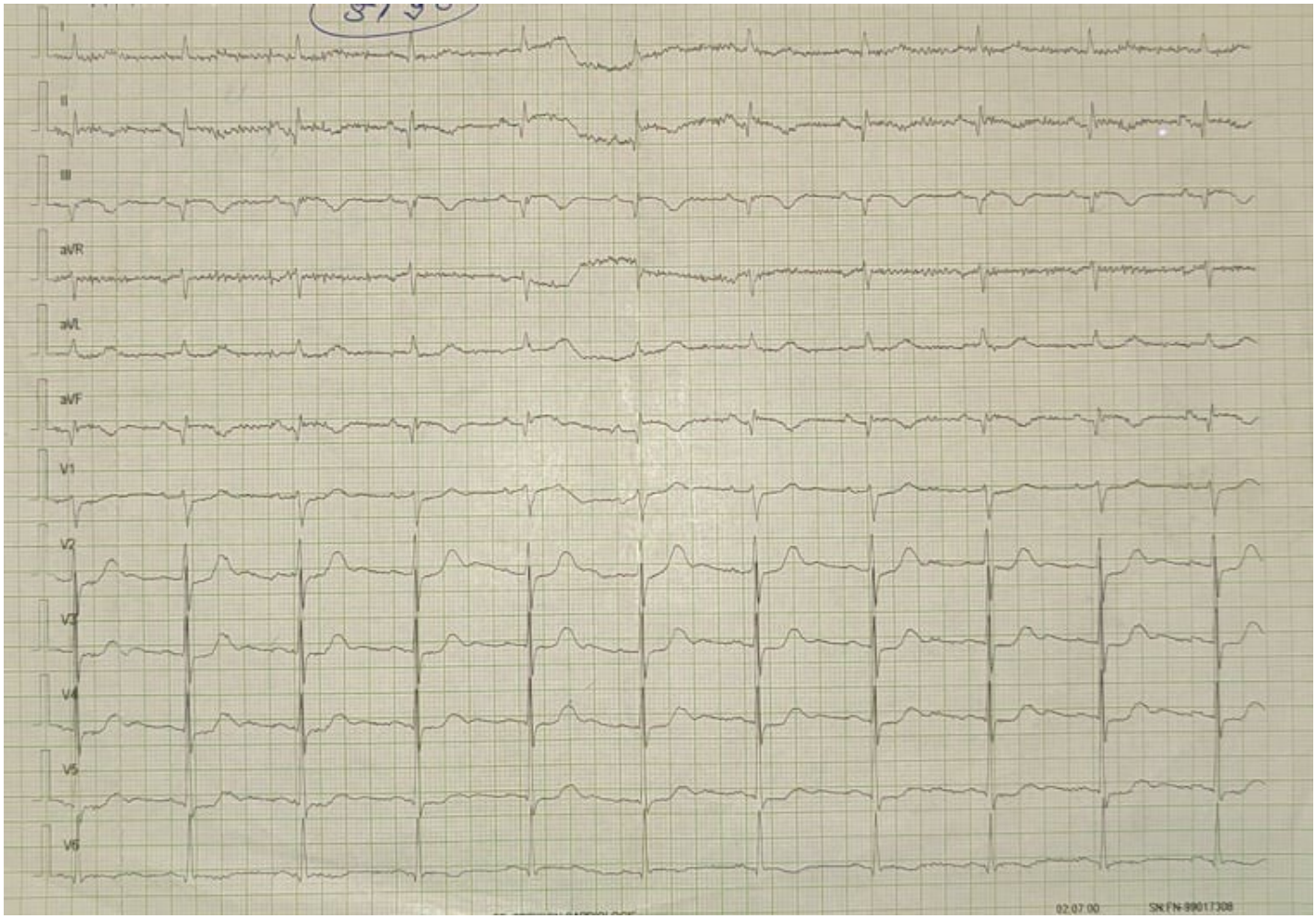


Figure 1 - ECG on admission: sinus rhythm, 63 bpm, subacute myocardial infarction in the inferior leads.

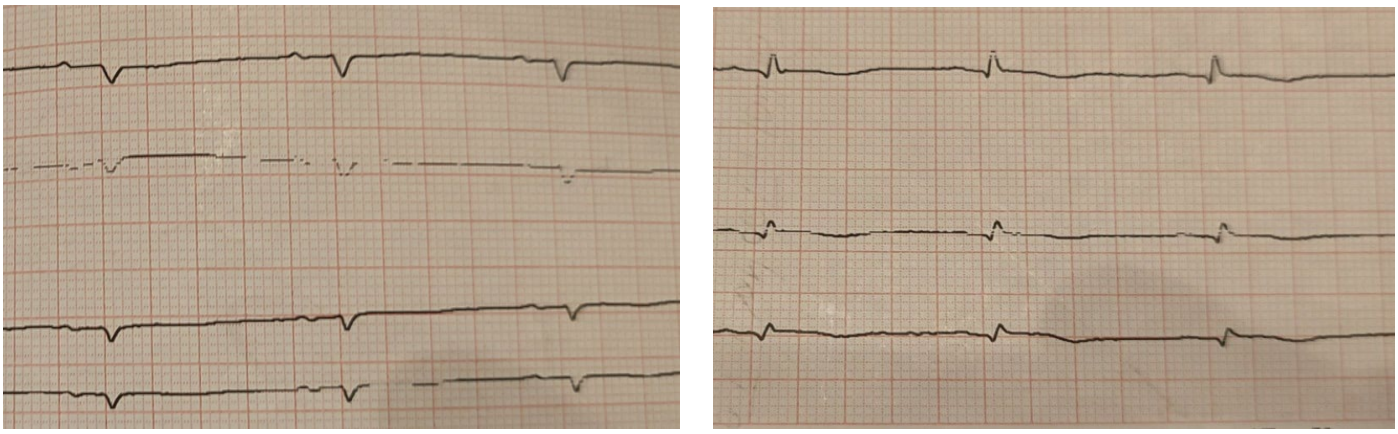


Figure 2 - ECG on admission: right limbs and posterior limbs.

25 mg o.d.), and a renin angiotensin aldosterone system inhibitor (ramipril 2,5 mg o.d.), with no renal alteration.

Therefore, on the discharge, the recommended home treatment included: Ticagrelor 90 mg b.i.d., Aspirin 75 mg o.d., Bisoprolol 2,5 mg o.d, Spironolactone 50 mg and Furosemide 20 mg o.d, Ramipril 2,5 mg o.d, Amiodarone 200 mg o.d and Pantoprazol 20 mg o.d.

Moreover, considering the very recent history of a myocardial infarction treated by primary stent implantation, a lipid-lowering

medication for secondary CV prevention was mandatory. So, considering the 2019 ESC guidelines of dyslipidaemia, the target of a LDL cholesterol below 55 mg/dl was not achieved, so there was a need for a better lipid lowering option [1]. Therefore, given the patient's statin intolerance and the need for a lipid-lowering medication for secondary prevention of an acute cardiovascular event, the therapy with alirocumab 75 mg subcutaneous injection every 14 days was recommended.

At the one month follow up examination, the patient declared no muscle related symptoms and improvement of effort dyspneea. The biological tests improved significantly: CK, CK-MB, ASAT, ALAT and creatinine clearance were all within normal ranges. LDL cholesterol was 65mg/dl, so PCSK9 inhibitor dose has been doubled. Re-administration of a lower-dose statin was also considered but considering the initial severity of symptoms, the age and the good response at PCSK9 inhibitor, we decided to postpone it.

Discussion

Even though statin-associated muscle symptoms are reported in 10-25% of patients, statin-induced myopathy (creatine kinase levels above 10 times the upper limit) occurs in less than 0.1% of patients taking statins while rhabdomyolysis (the destruction of striated muscle cells) is even rarer [2,5].

Statin-associated muscle symptoms may represent the major reason for statin discontinuation. However, in some double-blind trials, patients could not distinguish between muscle pain associated with statins and symptoms associated with placebo [7]. Thus, the pain can either have other causes than statin treatment or it could be the nocebo effect in terms of statin intolerance, meaning that the patients often report subjective side effects of medication after learning about those side effect as muscle pain [7]. Still, regardless of the cause of these muscular pains, they must be taken into consideration. If the pain is severe, the statin should be stopped and later be resumed at a lower dose or with another statin [1,5]. Physician must identify those at increased risk of developing real and serious side effects. A careful attention should be given to the patients who have risk factors such as alcohol use, advanced age (> 80 years), female gender, Asian ethnicity, neuromuscular, kidney, or liver conditions, those who exercise excessively or who are grapefruit juice consumeres [5]. Still, there are acute events such as acute ischemic stroke or myocardial infraction when a high-dose statin is indicated in order to reduce the CV risk [1]. In those situations, many patients are old and are not accustomed to high doses, so careful monitoring of CK levels is recommended [1,5].

The mechanisms behind muscle related side effects have not been fully elucidated. Statin therapies have HMG-CoA reductase inhibition effects (inhibition of cholesterol biosynthesis), but statin toxicity may be caused by alteration of ubiquinone metabolism, which depends on cholesterol biosynthesis via mevalonate. So, statins may also lower levels of ubiquinone, an essential compound for mitochondrial energy production and maintenance of the cell wall integrity. Therefore, ubiquinone deficiency associated with statin therapy can lead to apoptosis of muscle cells [4,5].

Through the same mechanism, statins can also lead to hepatocellular injury by modifying the hepatocyte membrane lipid composition, leading to increased permeability and leaking of the liver enzymes. This leads to asymptomatic rises in aminotransferase activity (>3 times the upper normal limit), but with no histopathology changes or liver toxicity, in the absence of other biological or morphological changes [4,5].

In some very rare cases, an autoimmune myopathy can develop in some patients, also causing muscle weakness, but with evidence of muscle-cell necrosis on biopsy and the presence of autoantibodies against HMG-CoA reductase. In contrast to most patients who have the classical side effects, those with statin associated autoimmune myopathy may have progressive weakness that must be controlled with immunosuppressive therapy [8].

In the therapeutic management of statin-induced myopathy the most important step is identification and withdrawal of the potential causative agent or the suspected coexisting precipitating factor. The diagnosis is established following the patient's history and the exclusion of other possible causes of increased muscle enzymes as mentioned before. An ECG is mandatory for the exclusion of a myocardial origin of CK and troponin elevation (CK-MB fraction is below 5% from total CK in case of rhabdomyolysis and above 5% in cardiac origin) [9].

The therapeutic management of such a condition includes mainly supportive treatment with prevention of possible complications such as renal and cardiac complications. In case of severe renal damage by acute tubular necrosis because of the nephrotoxic myoglobin, continuous hemofiltration or haemodialysis may be required [4,9].

Alternative treatment strategies should be provided for lowering LDL cholesterol. PCSK9 inhibitors have similar CV benefits like statins but are not associated with any increased risk of statin-related side-effects. Thus, PCSK9 inhibitors can be recommended as a first-line lipid-lowering treatment for patients with statins intolerance or resistance, as recommended by the ESC Guidelines [1].

Conclusions

Statins have remarkable effects in reducing CV risk and mortality. However, even though the risk of myopathy is low, statins can still produce potential dangerous adverse effects. Patients should be advised to report any muscle related symptoms to quickly adjust the dose or replace the drug.

Since the benefits significantly outweigh the risks, patients should not be left untreated for fear of potential side effects and most of them present a good adherence to statin treatment. However, in case of clear signs or symptoms, alternative treatment strategies for lowering LDL cholesterol should be considered.

Conflicts of interest

none declared.

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