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Rhabdomyolysis in An Elderly Patient Receiving High-Intensity Statin and Trimethoprim/ Sulfamethoxazole after Bilateral Percutaneous Transluminal Angioplasty: A Case Report and Literature Review

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Abstract

Rhabdomyolysis, a devastating complication associated with statins, has been identified as a potentially fatal clinical entity. We presented the clinical presentation of an elderly male who suffered from chronic limb ischemia. Vascular duplex illustrated critical stenosis over bilateral lower extremities. Two-staged percutaneous transluminal angiography by local ballooning was performed to achieve adequate reperfusion. High dose atorvastatin was added after the procedure, conjunctionally with trimethoprim/sulfamethoxazole (TMP/SMX) against Stenotrophomonas strain over gangrene. Nevertheless, acute renal failure complicating metabolic acidosis and imbalanced electrolytes developed. Comprehensive workup rendered critical rhabdomyolysis with high McMahon score at 13. Drug related was favored after ruling out other etiologies. Statin was halted, and TMP/SMX was substituted with quinolone. Serum level of creatinine kinase was eventually normalized one week later, and kidney function was restored. Although rare, statin-related rhabdomyolysis is more common in elderly patients with comorbidities or polypharmacy. Administrating statin in individuals with labile host factors should be prudent and based on individualized considerations. TMP/SMX inhibits the statin catabolism only at excessively high serum concentration, while skeletal muscle injury secondary to TMP/SMX was reported predominantly in immunocompromised subjects. Once rhabdomyolysis has resolved, resuming lipid-lowering agents is recommended to prevent further cardiovascular events, particularly in high-risk populations.

Key Words: angiography, rhabdomyolysis, statin, TMP/SMX

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Introduction

Statin related myopathy has been well established, but progression to rhabdomyolysis is seldom encountered. The definition of statin-related rhabdomyolysis varies, while elevated serum creatinine kinase level more than ten times of the upper normal limit was the most widely applied criterion for diagnosis.[1] According to epidemiological statistics, the overall incidence of statin-related rhabdomyolysis was less than 0.1%.[2] A retrospective analysis was conducted upon 871 reports of rhabdomyolysis secondary to statin in 2.5 years, and atorvastatin was accounted for 12.2% of the cases.[3] Pharmacological study has addressed that reduced isoprenoids and antagonized guanine nucleotide-binding proteins by statin are the major mechanisms that bring about rhabdomyolysis.[4] Progressive skeletal muscle injury is nevertheless associated with high risk of renal replacement therapy and all-cause mortality. As the prevalent use of statin and adjuvant medications against comorbidities, recognition of such complication and prompted corresponding managements are pivotal to improve outcomes.

Case report

An 82-year-old man presented with bilateral leg pain persisting for three months. Aggravated claudication severely limited his daily ambulation. The pain was exacerbated by physical movements and partially ameliorated at rest. There was also accompanying persistent erythematous change and local swelling over lower extremities. The wound condition remained poor, occasionally accompanied by pus discharge. The patient has otherwise no remarkable underlying history except hypertension without follow-up. He is a never-smoker and denied ever exposure to alcohol, betel nuts, or illicit drugs. He had

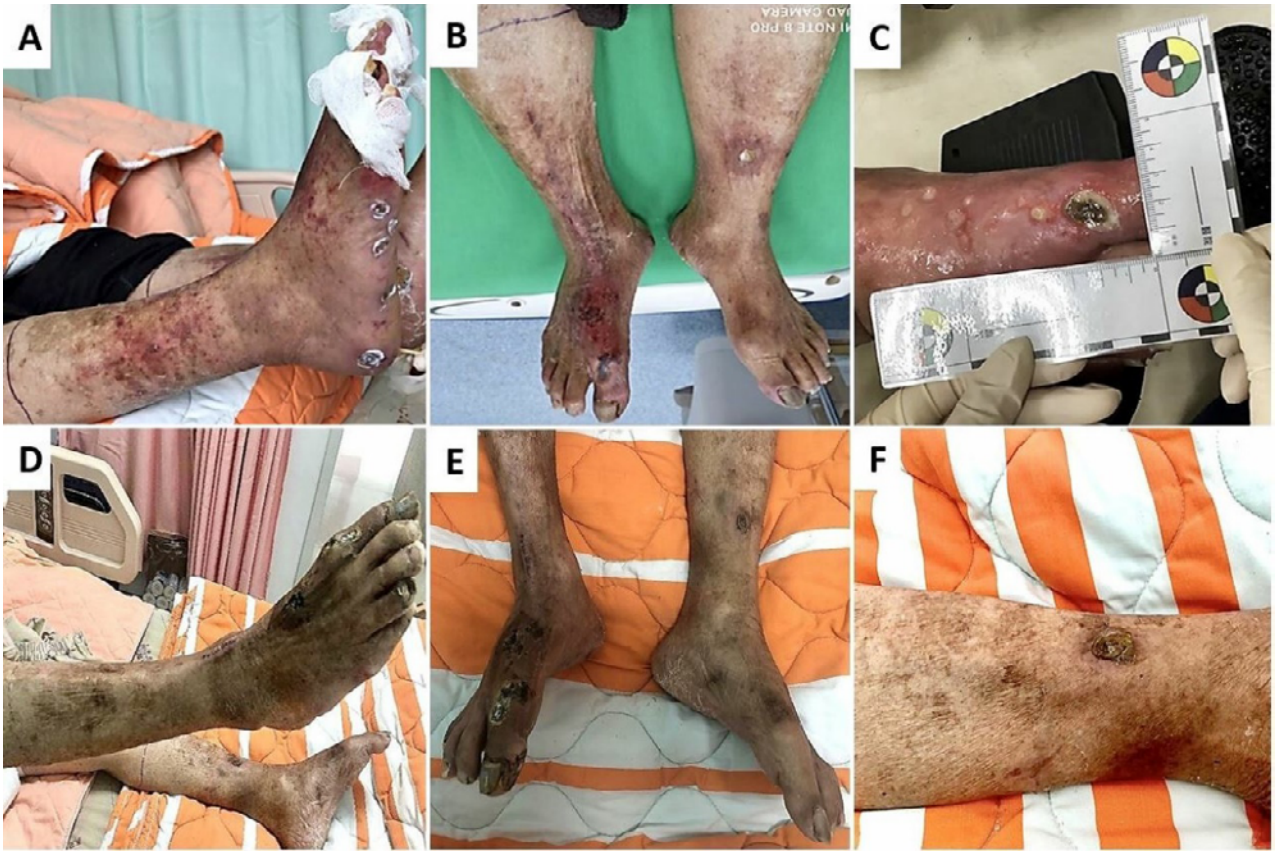

Figure 1. Wound condition of bilateral legs (A) Before angioplasty (B) After angioplasty

retired from his job as a mechanic in an automobile factory two decades ago. There were no remarkable clusters of systemic diseases in his family.

Due to persistent symptoms in both legs, the patient underwent hyperbaric oxygen therapy three times at another hospital yet with minimal improvement. He thus presented to our institution for evaluation of alternative interventions. Upon encounter, the patient was afebrile yet emaciated. Physical examination demonstrated blisters formation and several ulcerated wounds. The distal extremities were cold and pulsations were hardly palpable (Figure 1 ABC). Vascular doppler illustrated critical stenosis over bilateral popliteal artery, anterior tibial artery, and posterior tibial artery (Figure 2). Peripheral artery occlusive disease at Fontaine stage IV/Rutherford category 5 was rendered. Angiography showed diffuse chronic total occlusion (Figure 3 AB). Two staged

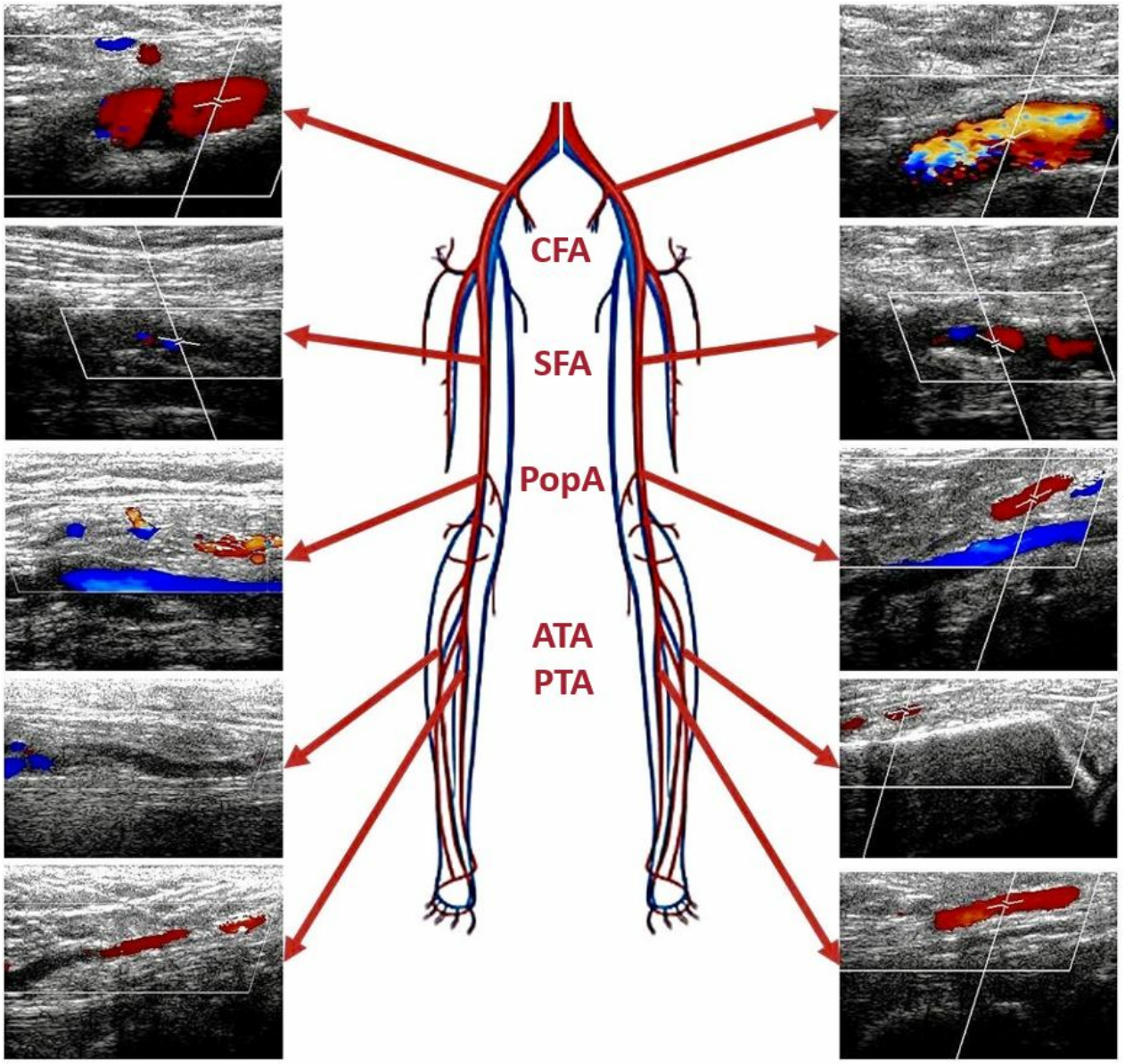

Figure 2. Vascular doppler showed bilateral CFA and middle SFA biphasic or triphasic flow pattern. Monophasic flow was noted over bilateral PopA, left distal ATA, and PTA. CTO was illustrated over right ATA and PTA. CFA, common femoral artery; CTO: chronic total occlusion; SFA, superficial femoral artery; PopA, popliteal artery; ATA, anterior tibial artery; PTA, posterior tibial artery

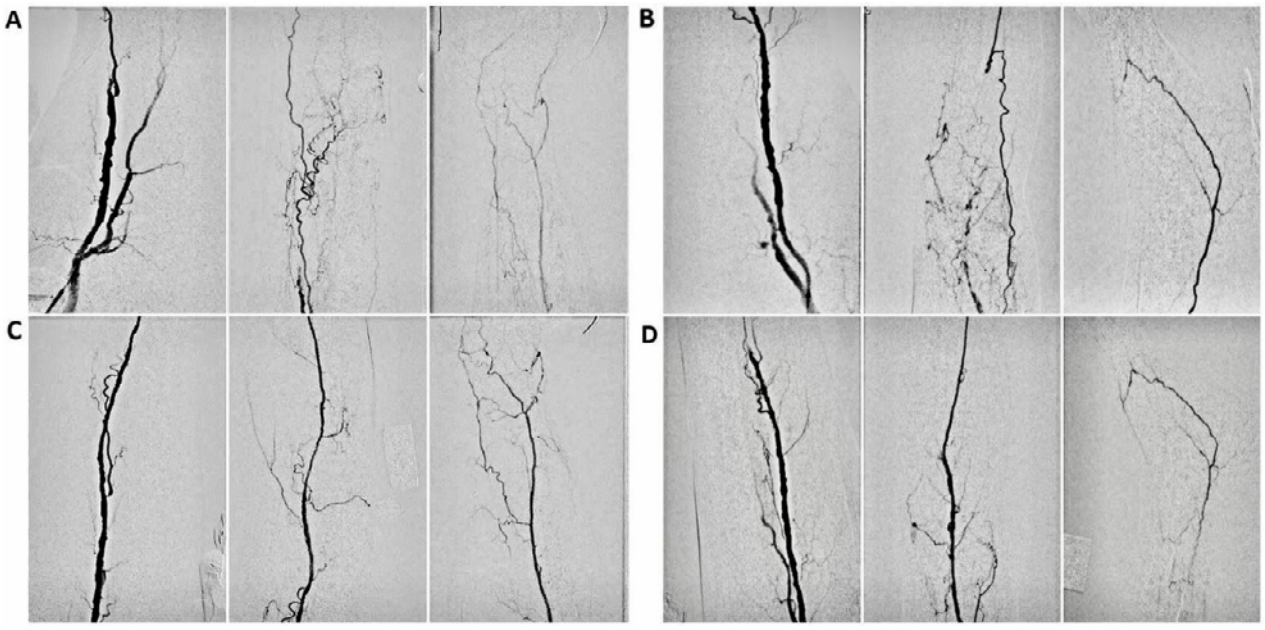

Figure 3. Angiographic findings. (A) Chronic total occlusion over right SFA, PopA, tibioperoneal trunk, ATA, PTA, and 60% stenosis over right peroneal artery. (B) 70% stenosis over left SFA 70% as well as chronic total occlusion over left peroneal artery, tibioperoneal trunk, ATA, PTA, and peroneal artery. (C) Reconstructed flow from right SFA to peroneal artery after angioplasty (D) Reconstructed flow from left SFA to PTA after angioplasty. SFA, superficial femoral artery; PopA, popliteal artery; ATA, anterior tibial artery; PTA, posterior tibial artery

percutaneous transluminal angioplasty (PTA) was performed to restore distal perfusion. First, ballooning was attempted over right peroneal artery, right tibioperoneal trunk, right popliteal artery, and right superficial femoral artery. One week later, the left posterior tibial artery, left tibioperoneal trunk, left popliteal artery, and left superficial femoral artery were revascularized by second-stage ballooning. Final flows of both legs were adequate (Figure 3 CD). After the procedure, dual antiplatelet therapy with aspirin 100 mg daily and clopidogrel 75 mg daily were initiated. Atorvastatin 40 mg daily was also introduced to mitigate thrombotic burden. Further pus culture of both legs yielded wild type Stenotrophomonas maltophilia, and definite trimethoprim/sulfamethoxazole (TMP-SMX) 80/400 mg twice daily was administered accordingly. Rehabilitation commenced seven days after PTA procedure.

However, one week later the patient complained worsening general malaise, diffuse muscle pain, and urine output was plummeted. Biochemical analysis revealed pronouncedly elevated serum creatinine level (0.9 to 2.5 mg/dL), high alanine aminotransferase level (243 U/L), azotemia (blood urine nitrogen at 86 mg/dL), hyperkalemia at 6.5 mmol/L, and metabolic acidosis (venous blood gas pH at 7.293, sodium bicarbonate 15.5 mEq/L). Renal ultrasonography illustrated bilateral kidney atrophy whilst in the absence of hydronephrosis or nephrolithiasis. The urine appeared dark in color. Urine analysis exhibited remarkable microhematuria (occult blood 3+, red blood cell sediment 10~19 per high power field), substantial proteinuria (urine protein-creatinine ratio 4413 mg/g), acidic with pH value at 5.5, but in the absence of crystal. Multistix and sediment examinations were repeated, reporting similar findings. Fractional excretion of sodium was at 6% but under concurrent furosemide use. Surprisingly, diagnostic workup revealed serum level of creatinine kinase (CK) level surged to 11507 U/L (reference range

30-223 U/L). Serum and urine level of myoglobin level were both quantified at >4102 ng/mL (reference range 17.4-105.7 U/L) and 3869.2 U/L (reference range <11.5 U/L). Elevated lactate dehydrogenase at 620 U/L and alanine aminotransferase levels 243 U/L were present concomitantly. McMahon score was at 13 (age >80 years old, elevated serum creatinine >2.2 mg/dL, hypocalcemia <1.87 mmol/L, hyperphosphatemia >5.4 mg/dL, and low serum sodium bicarbonate level <19 mEq/L). Atorvastatin and TMP/SMX were considered as possible culprit medications and thus halted. He has otherwise been exposed to no other substances, and there had been no recent strenuous exercise or trauma. No evidence of crush injury or compartment syndrome was present. Drug-related rhabdomyolysis, in conjunction with other etiologies including contrast nephropathy, dehydration, and TMP/SMX-associated hyperkalemia, was deemed the most likely cause of acute renal insufficiency. After vigorous hydration with crystalloid, urine alkalinization, and electrolytes correction, kidney function was restored effectively and CK level was normalized one week later. Wound condition improved remarkably and distal pulsations remained strong (Figure 1 DEF). The patient was finally transferred to the rehabilitation ward to participate in a reconditioning program.

Discussion

We herein reported a case of drug-related severe rhabdomyolysis, which was considered culprit to atorvastatin. The exact prevalence of rhabdomyolysis secondary to statin is challenging to estimate, but rare occurrence resulted in a paucity of study to investigate disease trajectory. In a large randomized control trial to affirm drug safety, no statin-related rhabdomyolysis was reported.[5] According to anecdotal case reports and corresponding drug labeling, most of the patients were notable for predisposing conditions. Advanced age is considered to potentiate the development of skeletal muscle injury.[6] Untreated contemporaneous hypothyroidism synergistically leads to myopathy.[7] A comprehensive review of case reports also noted common presence of chronic renal disease as pre-existing clinical condition, whereas the mean duration between statin introduction and symptom onset was only nine days.[8] Regarding this patient, there was no significant medical history, the baseline renal function was normal, and statin treatment had only been initiated for one week.

Aside from comorbidities, drug-drug interactions have been identified as contributors to muscle injury associated with statins.[9] The Drug-Induced Rhabdomyolysis Atlas specifically identifies parallel medications that affect the metabolism by cytochrome P450 (CYP3A4 for lovastatin, simvastatin, atorvastatin, and pravastatin; CYP2C9 for fluvastatin), which significantly increases the risk of muscle injury.[10] Common potent CYP3A4 inhibitors include macrolide antibiotics, antifungal azole derivatives, protease inhibitors, and non-dihydropyridine calcium channel blockers. In our case, the patient has been concurrently initiated atorvastatin and TMP/SMX. However, TMP and SMX are recognized as antagonists specifically against CYP2C8 and CYP2C9, respectively. The effect of attenuating CYP3A4 becomes significant only when the steady-state plasma concentrations of TMP/SMX reach 250/500 μM.[11] Given the status of acute renal insufficiency leading to elevated serum level of antibiotics, nevertheless, the effect of TMP/SMX still could not be excluded absolutely. In addition, anecdotal reports have described TMP/SMX itself as a culprit in drug-related rhabdomyolysis, mostly associated with prophylactic use against *Pneumocystis jirovecii* pneumonia or *Toxoplasma gondii* in immunocompromised patients.[12] In this case, addition of TMP/SMX in such dose might synergistically contributes to the onset of rhabomyolysis as well.

Acute renal insufficiency is the most prominent complication of rhabdomyolysis. Direct injury of *myoglobin* and oxidative injury bring about acute tubular necrosis.[13] Fluid resuscitation to facilitate *myoglobin*

clearance remained as the mainstay treatment. Cohort study suggested early and vigorous crystalloid supplementation was associated with more favorable prognosis.[14] Additional mannitol to augment urine output and urine alkalinization with sodium bicarbonate nevertheless failed to decrease the rates of kidney failure, dialysis, and all-cause mortality.[15] However, the evidence was primarily established on population with traumatic cause. Generalization to patients with drug-related rhabdomyolysis warranted further investigations. Hemodialysis serves as the ultimate measure to rescue acute renal injury. Specific high-flux hemofiltration was demonstrated to remove *myoglobin* more effectively,[16] whilst randomized control trial revealed pronouncedly higher mortality.[17] Continuous renal replacement therapy was associated with no remarkable outcome benefit as well especially in the absence of hemodynamic compromise.[18] For prognostication, McMahon score was established to predict risk of acute kidney injury and dialysis.[19] Our case presented with high score but hemodialysis was not mandated, potentially due to early recognition and prompt elimination of triggering factor.

Finally, effective management of lipid burden remained crucial in individuals with high cardiovascular events but experienced statin-related adverse events. A recent retrospective study demonstrated no significant increase in statin discontinuation when a drug-drug interaction is present.[20] Nevertheless, determining whether to resume statin treatment in this population poses a clinical conundrum. Current guidelines still recommended resuming statin therapy to protect against future cardiovascular events.[21] Skeletal muscle injury is still possible to develop after reinitiation of statin if in the absence of clinical parameters that could be modified. Therefore, either decreasing the dose or shifting to another statin are viable alternatives to prevent recurrence of rhabdomyolysis and promote patient adherence.[22] For statin-intolerant individuals confirmed by rechallenge, GAUSS-3 (Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects-3) study proposed switching statin to proprotein convertase subtilisin/kexin type 9 inhibitors is a safe and effective approach to orchestrate serum cholesterol level.[23]

In conclusion, statin-related rhabdomyolysis is a rare yet catastrophic complication. Very elderly patients with predisposing factors are particularly susceptible to drug-induced skeletal muscle injury. Introducing statin in these individuals hence involves a personalized and cautious assessment of the potential benefits and risks. Fluid replenishment to augment urine output and management of complications secondary to acute kidney insufficiency are key aspects of treatments. Once rhabdomyolysis is ameliorated, re-evaluation of cardiovascular risk and resuming lipid-lowering agents are endorsed to improve overall prognosis.

Disclosure

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年邁患者雙側下肢動脈血管成形術後使用 statin 與 trimethoprim/sulfamethoxazole 致橫紋肌溶解症：病例報告與文獻回顧

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摘要

橫紋肌溶解症是使用 statin 嚴重且潛在致命的併發症，本文報導一位嚴重血管性跛行的年邁男性，血管超音波顯示雙下肢嚴重狹窄，曾嘗試高壓氧療法但無改善，後續透過兩階段氣球擴張術完成經皮血管成形，術後給予高效力 statin，又因膿瘍培養出嗜麥芽窄食單胞菌，而注射 trimethoprim/sulfamethoxazole (TMP/SMX) 治療，然而卻導致急性腎衰竭合併代謝性酸中毒及電解質失衡，系統性詳檢結果為嚴重橫紋肌溶解症 (McMahon 13 分)，在排除其他成因後，診斷為藥物相關，因而暫停給予 statin，並使用　諾酮藥物替代 TMP/SMX。一週後血漿肌酸磷化酶濃度及腎功能皆恢復正常，病人最後轉至復健科行肌力訓練。statin 導致之橫紋肌溶解症雖罕見，但在伴隨共病症及多重用藥的年邁病人上，風險仍高，目前尚無臨床試驗提供此類病人使用 statin 的證據，因此需謹慎處方且納入個人化考量。而 TMP/SMX 惟在極高劑量才會阻滯 statin 代解，其所導致的橫紋肌溶解症，絕大多數亦只被報導在免疫不全的病人發生。一旦橫紋肌溶解症獲得緩解，尤其針對高風險患者，建議評估恢復使用降脂肪藥物，以避免後續心血管事件發生。