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Statin-related muscle complications masquerading as soft tissue sarcomas

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ABSTRACT

Musculoskeletal injuries are a known side effect of long-term statin use. These injuries include sudden, atraumatic muscle rupture which can cause extremity hematomas that motivate patients to seek evaluation and physicians to send referrals for oncologic workup. We discuss two cases where malignancy was suspected rather than statin-induced muscle injury. Using these cases as examples, we discuss subtleties between the two diagnoses so that muscle rupture may be considered prior to subspecialist referral. This paper aims to serve as a reminder and guide for physicians who encounter long-term statin users with nonspecific, improving musculoskeletal symptoms and hemorrhagic MRI findings that lack nodular or mass-like enhancements. While referral to orthopedic oncology is always encouraged in cases of uncertainty, it may not always be necessary.

Introduction

Statins are considered first-line pharmacologic therapy for reducing low-density lipoprotein cholesterol levels. While their efficacy in reducing major adverse cardiovascular events and mortality has been consistently demonstrated, adverse effects are frequently reported [1]. Of these, statin-associated muscle symptoms (SAMS) are the most prevalent, accounting for up to 72 % of all statin-associated adverse events. Acute musculoskeletal injuries, including tendinous complications, acute muscle strains, and grade III muscle ruptures, are less robustly documented but important SAMS [2–4].

These injuries often present with a sudden onset of muscle pain and swelling, unilateral extremity fullness on physical examination, and hemorrhagic findings on MRI studies. When there is a recent history of an inciting trauma, the evaluating physician may be highly suspicious of a muscle strain or rupture irrespective of their consideration of SAMS as the underlying cause. Alternatively, in cases without a history of an inciting trauma, neoplasm often replaces acute muscle injury as the suspected etiology. Despite their similarities, there are key differences between the presentations of statin-induced muscle ruptures and hemorrhagic neoplasms that can help differentiate them - especially in patients on long-term statins who likely carry a higher risk for SAMS than they do for cancer.

Two patients were referred to a tertiary orthopedic oncology office with the aforementioned nonspecific symptomatology and advanced imaging findings. Both were ultimately diagnosed with muscle rupture secondary to statin use. We present these cases to highlight the nuances between muscle rupture hematomas and hemorrhagic soft tissue sarcomas. Recognition of these subtleties can help avoid unnecessary interventions and a multi-office-visit-workup that culminates in an oncologic referral.

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Case reports

Patient 1

A 73-year-old female taking 0.5 mg rosuvastatin every other day for greater than 1 year who had a sudden onset of pain, swelling, and ecchymosis over her left lateral thigh atraumatically. She was first evaluated in the Emergency Department and admitted to the hospital for vascular workup. At that time, CT angiogram and interventional radiology angiography did not demonstrate an active

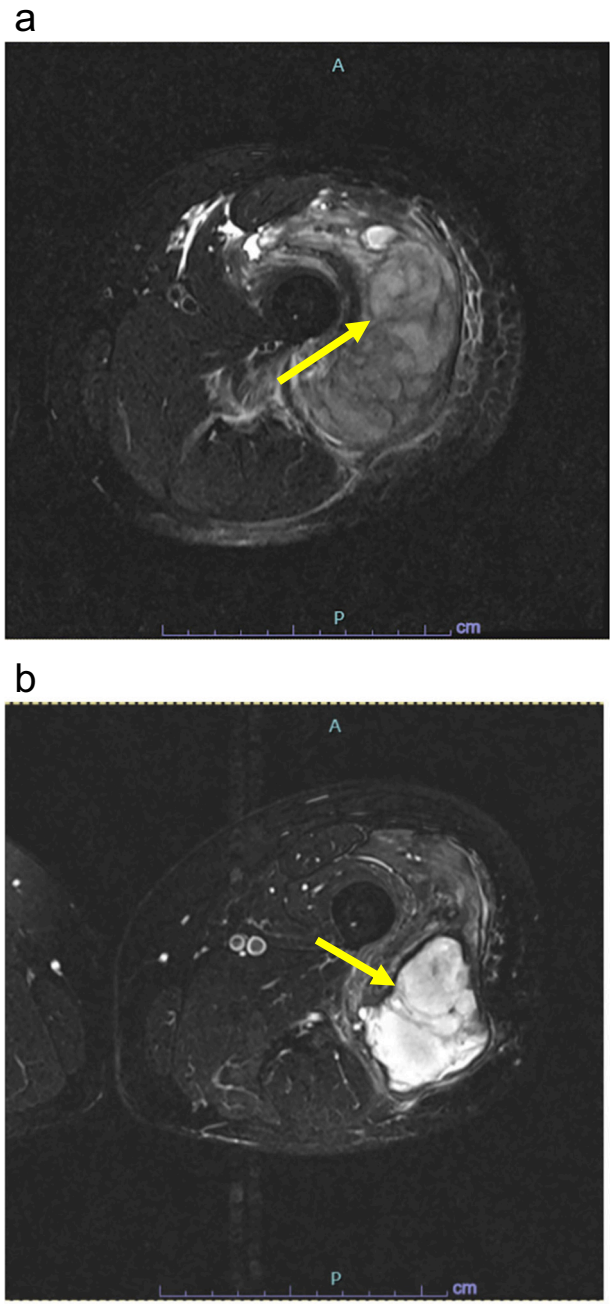

Fig. 1. A: Initial MRI demonstrated extensive increased signal on T2 sequences (yellow arrow) throughout the quadriceps musculature with surrounding soft tissue stranding and inflammation. Size of 9.7 cm × 6.8 cm × 21.4 cm.
B: Repeat MRI 27 days later with a more loculated appearance of more intense T2 signal (yellow arrow) within the quadriceps muscles, with less diffuse edema in the surrounding tissue which demonstrates peripheral enhancement on contrast studies. Size of 8.41 cm × 5.5 cm × 15.3 cm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

bleed. MRI demonstrated a left thigh hematoma and she was discharged home for outpatient workup (Fig. 1A). Despite improvement in symptoms at outpatient orthopedic follow up, the patient was referred to orthopedic oncology secondary to suspicion for underlying malignancy. MRI at that time (27 days after initial evaluation) revealed that the hematoma within the quadriceps muscle had decreased in size compared to previous and was without solid masslike enhancement (Fig. 1B). Repeat MRI studies three months later demonstrated near complete resolution of the hematoma and she reported clinical improvement to her baseline ambulation and pain status.

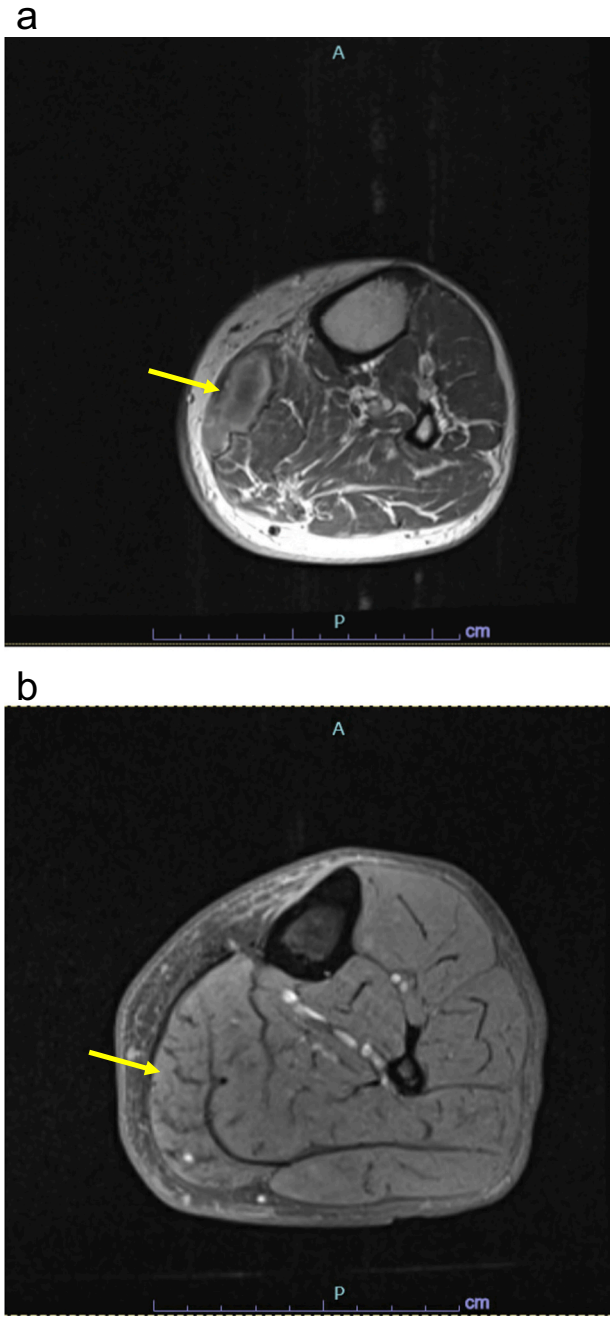

Fig. 2. A: Deep to the fascia the medial calf 13.3 cm × 2.5 cm × 5 cm size well-circumscribed area of increased signal on T2 (yellow arrow) with peripheral enhancement on contrast studies with some surrounding soft tissue edema.
B: Demonstrates resolution of the lesion previously appreciated on prior MRI described in panel A. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Patient 2

A 79-year-old male taking 10 mg atorvastatin daily for greater than 1 year who had an atraumatic onset of left knee pain and swelling. Prior to his referral to orthopedic oncology he was evaluated twice by an outpatient orthopedist and once in the emergency department. Workup during those visits included a venous duplex US and MRI studies. Imaging results revealed a lesion that prompted his referral to orthopedic oncology (Fig. 2A). At that time, about 1 month after his initial injury, his pain and range-of-motion difficulties had resolved. Repeat MRI studies 4 months after onset showed near-complete resolution of the previously described fluid collection (Fig. 2B).

Discussion

While statins are generally well-tolerated, many users develop SAMS. Although the true prevalence is difficult to discern due to the spectrum of associated muscle adverse events and differences between analytical and anecdotal findings, there is consensus that statin formulation and dose influence risk. For example, the risk of myopathy is higher in statins metabolized by cytochrome P450 CA4 (lovastatin, simvastatin, atorvastatin) and exacerbated with higher doses [11,12]. A meta-analysis including over 100,000 patients did not find an increase in SAMS after 1-year of treatment indication that long-term therapy was not a significant risk factor [13]. Ensuring patients are on safe statin regimens by considering formulation, dose, and co-morbidities is an important first step in preventing associated SAMS. When injury is inevitable, however, consideration of the etiology prior to oncologic mechanisms is crucial.

Although muscle rupture hematomas associated with statin-use have been documented [4–6], they are relatively rare and present differently than the SAMS that are more commonly seen in clinical practice and more substantially reported on. Because of this, clinical suspicion for statin-induced hematoma requires active consideration of the etiology and knowledge of the presentation nuances of other differential diagnoses, including soft-tissue neoplasms with hemorrhagic components.

Soft tissue sarcomas with telangiectatic changes (STST) define a variety of high-grade soft tissue sarcomas with hemorrhagic changes. These changes exist on a spectrum and include masses that undergo such extreme hemorrhaging that they present clinically as fluctuating masses that may be confused with hematomas [7]. Many case reports have described similarities between benign hematomas and STST. Most of them focus on cases of tumors masquerading as benign hematomas in comparison to our two cases which focus on the opposite diagnostic error.

Without a history of an inciting trauma, it can be difficult to distinguish benign hematomas from STST; In addition to consideration of statin use, symptom course and MRI subtitles may aid in their differentiation. Most high-grade soft tissue sarcomas present as painless, gradually enlarging masses [7]. With telangiectatic changes, however, they can present with pain secondary to the intratumoral bleed and the resulting rapid stretching of surrounding tissues which further explains their confusion with benign hematomas. Importantly, without combination treatment, STST symptoms are non-resolving and gradually worsen [7,8]. Both patients presented with an atraumatic onset of pain and swelling to their lower extremity. They reported radial improvement of their symptoms in the weeks following onset without any treatment or intervention. Improvement of symptoms without treatment should increase suspicion for benign vs. malignant etiologies. Given the subjective nature of symptomatology, however, MRI remains the gold standard for evaluating soft tissue lesions.

The difficulty in discerning between benign hematomas and STSTs on MRI studies arises because both can contain blood filled areas. These areas display various low to iso signal intensities without enhancement on T1 images. Key differentiation, therefore, comes from T2 weighted images where sarcomatous parts of lesions enhance while hemorrhagic areas do not [9]. Nodular or masslike enhancement seen on T2 images following contrast administration is suggestive of neoplasms, whereas a lack of enhancement essentially excludes this diagnosis [10]. Additionally, the size of the lesion can help to steer clinical suspicion. STST lesions typically have a long-to-short axis ratio of 2:1 or less while intramuscular hematomas typically expand along musculotendinous compartments with gravity and have a ratio greater than this [8]. Neither of the presented cases had imaging findings that showed nodular or mass-like enhancement. They were evaluated with serial imaging that showed a decrease in size over time that corresponded with improvement in associated pain, swelling, and ecchymosis.

In the presented cases and those similar, providers may be eager to refer patients to orthopedic oncology so as to not miss a diagnosis or delay treatment of a possible malignancy. We suggest that despite well-intentions, this thought process can potentially expose patients to anxiety-provoking referrals and unnecessary procedures. Instead, muscle rupture secondary to statin use can be considered and referral to orthopedic oncology may be delayed when the patient's symptoms have been improving since onset and MRI studies lack nodular or mass-like enhancement.

Conclusion

Physicians should be aware of the association between statin-use and muscle rupture. These statin-associated muscle injuries are less common and less documented, and as a result less likely to be connected to statin-use upon primary evaluation. Because of this, early suspicion for a statin-associated adverse event may be missed if not actively considered. Additionally, optimizing patients' statin regimen with consideration of both formulation and dose can prevent injuries in the first place. This paper aims to serve as a reminder and guide for physicians who encounter long-term statin users with nonspecific, improving musculoskeletal symptoms and hemorrhagic MRI findings that lack nodular or mass-like enhancements. While referral to orthopedic oncology is always encouraged in cases of uncertainty, it may not always be necessary.

Declaration of competing interest

None.

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