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Bilateral multifocal muscular hemorrhage in the triceps surae during antiplatelet therapy: a case report

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Abstract

Hemorrhagic complications are often reported following antiplatelet therapy; however, simultaneous multifocal hemorrhages in both legs are uncommon. The patient was a 75-year-old man diagnosed with ST elevation myocardial infarction who underwent percutaneous coronary intervention in the right coronary artery. He was prescribed oral acetylsalicylic acid and ticagrelor. Three days after initial drug treatment, he complained of bilateral leg pain that was aggravated by walking and moving his ankle across a broad range of motion. No deep vein thrombosis was detected on Doppler ultrasonography; however, muscular hemorrhage was suspected according to musculoskeletal ultrasonography. Multifocal muscular hemorrhage was confirmed in the soleus and gastrocnemius muscles on magnetic resonance imaging. To reduce the risk of bleeding, we changed the medication from ticagrelor to clopidogrel. The patient performed leg elevation exercises, compression, and applied an ice pack. He also performed range of motion exercises and gait training in addition to receiving drug treatment. With these therapies, his pain score improved from 5 to 3 on a visual analog scale, without further complications. Multifocal muscular hemorrhage rarely occurs bilaterally; however, when it does occur, an appropriate treatment plan can be developed based on musculoskeletal ultrasonography.

Keywords

Dual anti-platelet therapy, muscle, hemorrhage, diagnosis, ultrasonography, percutaneous coronary intervention, right coronary artery, triceps surae

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Introduction

Dual antiplatelet therapy (DAPT) is widely used to treat acute coronary syndrome after percutaneous coronary intervention (PCI) with drug-eluting stents.[1–3] Current DAPT guidelines recommend acetylsalicylic acid (aspirin) monotherapy or combining aspirin with a P2Y12 inhibitor.[4,5] Ticagrelor, a direct-acting P2Y12 inhibitor, is often the first medication administered after PCI as it acts faster and has a better antiplatelet inhibitory effect than clopidogrel. However, ticagrelor's pharmacokinetic properties mean that its use is associated with a higher risk of bleeding than alternative drugs.[6–8] Previous studies have reported that prolonged DAPT increases the risk of bleeding; however, the alternative short-duration therapy carries a heightened risk of myocardial infarction and stent thrombosis.[9,10] For this reason, drug substitution should be performed with caution and only under close observation.

The incidence of clinically relevant bleeding in patients who continued DAPT after PCI is 6.2%, while bleeding-related hospitalization occurs in 4.8% of patients.[11,12] In more than half of these cases, bleeding occurred in the gastrointestinal tract.[11] Approximately 12.8% of the bleeding was urogenital, and in 17.6% of the cases, bleeding was not classified.[11] Bleeding occurred most commonly within 30 days post-discharge.[11,12] Anticoagulation therapy has been associated with intermittent spontaneous muscular hemorrhage;[13,14] however, this occurs rarely in patients receiving DAPT. Spontaneous muscular hemorrhage commonly occurs in the rectus sheath or the psoas muscle and rarely in the calf muscles.[15,16] Diagnosis is often delayed because of vague and nonspecific symptoms (e.g., poorly localized pain, tachycardia, hypotension or pallor), leading to inappropriate treatment, and patients ultimately developing a life-threatening condition.[13] We report a rare patient who developed multifocal muscular hemorrhage in bilateral triceps surae. The event occurred during treatment with aspirin and ticagrelor after the patient underwent PCI for ST-elevation myocardial infarction (STEMI).

Case report

The reporting of this study conforms to the CARE guidelines.[17] Institutional approval was obtained from the review board of Jeonbuk National University Hospital (institutional review board (IRB) number 2021-07-017). The need for patient consent was waived by the Jeonbuk National University institutional review board because no information was collected that could identify the patient, and because the report was based on existing data and documentation.

A man in his mid-70s, with a history of diabetes mellitus and hypertension and no remarkable familial medical history or hematologic disorders, was initially hospitalized for severe chest pain. He also had a history of myocardial infarction in 2005 and was prescribed 100 mg aspirin once daily thereafter. He was diagnosed with STEMI and underwent PCI in the proximal segment of the right coronary artery with two everolimus-eluting stents. After the PCI, he was prescribed aspirin 100 mg once daily and ticagrelor 90 mg twice daily. In addition to the DAPT, he was also received metformin, hepatotonics, and antihypertensive and mucosal protective agents.

Three days after PCI, he complained of bilateral leg pain that was aggravated by walking and moving his ankle across a broad range of motion. A consultation at the Department of Rehabilitation Medicine was requested. The patient's physical examination revealed severe tenderness along bilateral gastrocnemius and soleus muscles,

with no palpable mass. However, his pain subsided during knee flexion and ankle plantarflexion. He had a positive Homan's sign, as well as a positive straight leg raise test result in each leg and a negative Thompson test result for Achilles tendon rupture.

Laboratory test results indicated the following: hemoglobin: 102 g/L (reference value: 130–180 g/L); platelet count: 95×10^9/L (reference value: 130–450 $\times 10^9$/L); prothrombin time (PT): 11.9 s (reference value: 9.2–12.6 s); PT international normalized ratio: 1.09 (reference value: 0.88–1.19); and activated partial thromboplastin time: 28.0 s (reference value: 24.8–36.1 s). The following results were also obtained: white blood cell count: 6.89×10^9/L (reference value: 4.8–10.8×10^9/L); high-sensitive C-reactive protein: 300.86 nmol/L (reference value: 0–47.62 nmol/L); d-dimer: 3.644 mg FEU/L (reference value: 0–0.98 mg FEU/L); and estimated glomerular filtration rate (eGFR): 23.4 mL/min/1.73 m^2. Table 1 shows the patient's routine blood test results at the consultation.

Diagnostic musculoskeletal ultrasonography (MSK US) of both calves was promptly performed. This imaging revealed a decreased fibrillary pattern in bilateral soleus muscles, and a hyperechoic lesion in the fascia between the gastrocnemius (GCM) and soleus muscles (Figure 1). To obtain a precise diagnosis, magnetic resonance imaging (MRI) of the right leg, which exhibited severe symptoms, was performed. MRI revealed multifocal muscular hemorrhagic lesions in the soleus and GCM muscles with a small hematoma in the myotendinous junction of the soleus muscle (Figure 2). Venous and arterial Doppler ultrasonography was then performed to detect deep vein thrombosis (DVT). This imaging showed that venous flow from the common femoral vein to the peroneal vein and posterior tibial veins was patent and without thrombosis or stenosis.

Table 1. The patient's blood laboratory test results.

Blood test (normal range)	Value
RBC (4.7–6.1 $\times 10^{12}$/L)	3.27
Hemoglobin (130–180 g/L)	102
Hematocrit (0.42–0.52 L/L)	0.29
MCV (80–94 fL)	87.5
WBC (4.8–10.8 $\times 10^9$/L)	6.89
Platelet count (130–450 $\times 10^9$/L)	95
PT (9.2–12.6 s)	11.9
INR (0.88–1.19)	1.09
aPTT (24.8–36.1 s)	28.0
Fibrinogen (1.91–4.71 g/L)	3.3
D-dimer (0–0.98 mg FEU/L)	3.644
ESR (<9 mm/hour)	47
High-sensitivity CRP (<47.62 nmol/L)	300.86
BUN (2.86–8.21 mmol/L)	10.36
Creatinine (0.06–0.15 mmol/L)	0.14
eGFR (mL/s)	0.73
Total protein (1.09–1.25 mmol/L)	0.80
Albumin (0.53–0.80 mmol/L)	0.51
ALP (750–2150 nkat/L)	1066.67
ALT (83.33–583.33 nkat/L)	750
AST (200–550 nkat/L)	933.33

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; aPTT, activated partial thromboplastin time; BUN, blood urea nitrogen; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; INR, international normalized ratio; MCV, mean corpuscular volume; PT, prothrombin time; RBC, red blood cell; WBC, white blood cell.

Arterial ultrasonography revealed a biphasic flow pattern bilaterally from the superficial femoral artery to the popliteal artery and decreased flow from the left anterior tibial artery. Computed tomography (CT) was also performed to evaluate the lower extremity vessels and revealed flow limitation in both legs, with multifocal calcification, which was more dominant on the right side. The ankle–brachial index was 0.75 for the right side and 1.02 for the left side, suggesting peripheral artery occlusive disease in the right leg. To evaluate neuropathic pain, an electrodiagnostic study was performed, which revealed bilateral

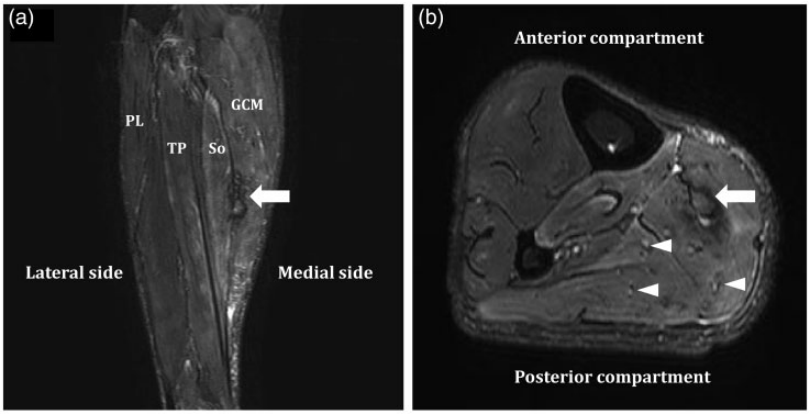

Figure 1. Musculoskeletal ultrasonography showing decreased fibrillary pattern with heterogeneous echogenicity in the soleus muscles: (a) transverse view, (b) longitudinal view.
So, soleus; GCM, gastrocnemius.

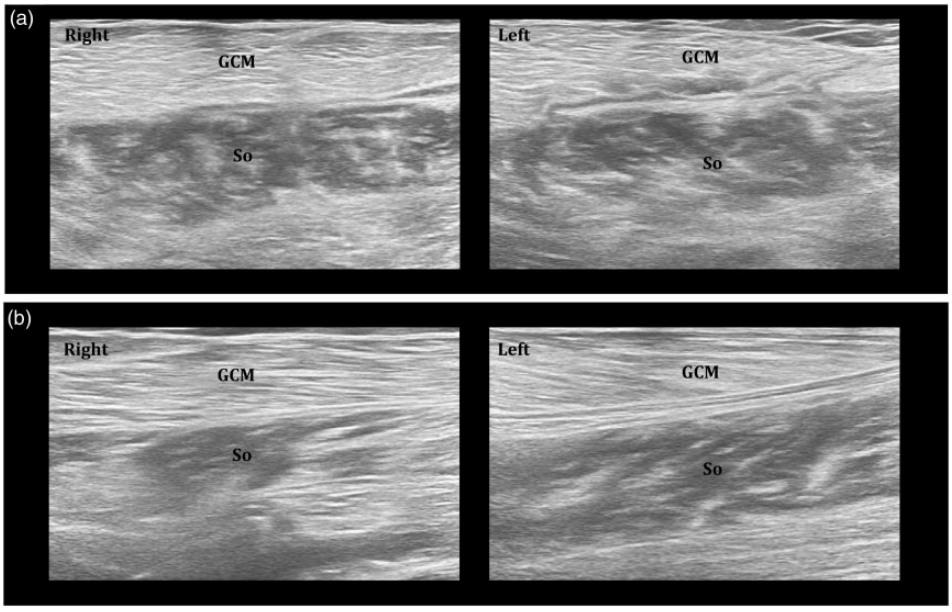

Figure 2. (a) Coronal T2-weighted magnetic resonance image showing a small hematoma at the myotendinous junction of the soleus muscle (arrow). (b) Axial T2-weighted magnetic resonance image showing multifocal hemorrhages in the gastrocnemius and soleus muscles with high signal intensity (arrowhead) and a small hematoma at the myotendinous junction of the soleus muscle (arrow).
PL, peroneus longus; TP, tibialis posterior; So, soleus; GCM, gastrocnemius.

lumbosacral radiculopathy involving mainly the right L3/4 and left L3/4/5/S1 nerve roots. However, these findings did not correlate exactly with the patient's clinical symptoms.

The multifocal muscular hemorrhage in bilateral calf muscles was considered a complication of antiplatelet therapy as the patient denied a history of trauma to the

affected areas. The patient received a cardiac consultation to evaluate the DAPT medications. Considering the risks of further bleeding and stent re-occlusion or peripheral arterial occlusive disease, the cardiologist changed the medication from ticagrelor to clopidogrel.

Using a compression sleeve around both calves was recommended as rehabilitative therapy to decrease the hemorrhage, with ice packs for symptomatic relief. He was also instructed regarding how to elevate both lower limbs slightly above the level of his heart to reduce swelling. Gentle mobilization and active range of motion exercises for bilateral hips, knees, and ankles were also recommended. Gait training was performed in conjunction with transcutaneous electrical nerve stimulation (TENS).[18,19] The patient was also prescribed a medication containing acetaminophen (162.5 mg) and tramadol hydrochloride (18.75 mg) twice daily.

After 8 days of treatment, the calf pain improved from 5 to 3 on a visual analog scale. Gait function improved from a functional independence measure level of minimal assist to supervision. No adverse effects were observed during the treatment period, and the patient was lost to follow-up after discharge.

Discussion

Spontaneous bleeding in patients receiving DAPT typically occurs in the rectus sheath or the iliopsoas muscle.[15,16] Few patients have developed spontaneous intramuscular hemorrhage in the calf muscle, particularly bilaterally. We report an unusual case of a patient with multifocal muscular hemorrhage in bilateral triceps surae muscles, which led to bilateral lower extremity pain and gait disturbance.

Antiplatelet therapy, including with aspirin or ticagrelor, is widely recommended for patients with heart disease and ischemic stroke.[20,21] Previous reports have shown that DAPT with aspirin and ticagrelor is associated with a higher risk of bleeding than DAPT with aspirin and clopidogrel.[22] Ticagrelor is a reversible and direct-acting antagonist of the adenosine diphosphate receptor P2Y12. Compared with clopidogrel, ticagrelor induces faster and stronger inhibition of platelet aggregation.[6,23] The European Society of Cardiology (ECS) DAPT guidelines define mild bleeding as requiring medical attention without hospitalization or non-significant blood loss (hemoglobin: <2 mmol/L). If mild bleeding occurs, the guidelines advise that DAPT be continued and that changing from ticagrelor to clopidogrel be considered.[5] With moderate bleeding, in which the patient is hemodynamically stable but has significant blood loss (hemoglobin: ≥ 2 mmol/) or requires hospitalization, the guidelines recommend shortening the duration of DAPT and changing from ticagrelor to clopidogrel.[5]

In our case, the patient was hemodynamically stable, and the reduction in hemoglobin was within 0.7 mmol/L; however, he was considered to be at a high risk for bleeding owing to severe chronic kidney disease (eGFR: <30 mL/min/1.73 m^2), hemoglobin <110 g/L, and moderate to severe baseline thrombocytopenia (platelet count: $<100 \times 10^9$/L).[24] He complained of severe pain in both calves; therefore, hospitalization was required.

Importantly, the patient had multiple comorbidities, namely hypertension, diabetes mellitus, peripheral arterial obstructive disease, and lumbosacral radiculopathies. His bilateral calf pain may have been caused by a combination of these factors. However his pain developed acutely, and considering that the comorbid diseases may have been present for a long time, they may not have been the main cause of his pain. In addition, his physical examination findings inferred a possible diagnosis

different from the above diseases. To determine the exact cause of the pain, a quick screening test using MSK US was performed, then MRI of the right lower leg was performed immediately after bilateral muscular hemorrhage was suspected. The MRI results revealed multifocal hemorrhagic lesions in the soleus and GCM muscles.

It is uncertain why the bleeding occurred simultaneously in both legs. The patient was almost bedridden after the PCI procedure, and trauma was less likely. On lower extremity CT, vascular calcification was observed in bilateral peroneal arteries; however, no sign of large vessel bleeding was observed. We considered that the hemorrhagic lesions were a complication of DAPT as the patient had neither a trauma history nor suspicions of other causes. As his symptoms gradually improved while receiving conservative treatment after hemorrhage was diagnosed, further evaluation of coagulopathy was not performed.

Acute stage intramuscular hematomas may appear on MSK US as a hypoechoic cyst-like fluid collection with internal echoes, debris, septations, and fluid–fluid level. In our patient, we observed muscle fiber disruption at the pain site and a mixed edematous pattern of hyper- and hypoechogenicity with unclear boundaries. These findings were clearly distinguishable from typical intramuscular hematomas.[18,25,26] Acute intramuscular hemorrhages typically appear on MRI as high signal intensity signals on T2-weighted images and low signal intensity signals on T1-weighted images. Similarly, in our patient, high signal intensity lesions were multifocal and widespread in the GCM and soleus muscles.[26,27]

Acute treatment in cases such as ours aims to manage hemorrhage and pain. Limiting excessive stretching and applying cryotherapy, compression, and affected leg elevation are recommended for 3 to 5 days after the onset of treatment. The use of non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided or limited for 2 to 3 days after symptom onset owing to their antiplatelet effects. Other anti-inflammatory drugs, such as celecoxib and other cyclooxygenase-2 (COX-2) inhibitors with less antiplatelet effects, and pain relief medication, such as acetaminophen or narcotics, are acceptable options during this period. After the initial intervention, isometric or isotonic exercises, such as passive stretching and dynamic strength training, respectively, are recommended to prevent muscle atrophy. These exercises should be performed under the following conditions: 1) the patient's pain has decreased by one-third since beginning treatment, and 2) an absence of pain during joint movement within two-thirds of the normal range. Additional pain therapies, such as transcutaneous electrical nerve stimulation (TENS), electrical stimulation therapy (EST), and ultrasonography can be applied.[18,19] Surgical intervention, including drainage, should be considered if a large hematoma impairs clinical progress. In cases of compartment syndrome where conservative treatment was ineffective, fasciotomy is required to relieve pressure.[19,27]

Spontaneous bilateral multifocal muscular hemorrhage is rare in STEMI patients undergoing PCI and receiving DAPT. Clinical symptoms, including bilateral calf pain or swelling, are characteristically vague and poorly localized. For these reasons, the condition is difficult to diagnose precisely. If a patient complains of sudden pain in the calf muscles during DAPT, we can promptly detect muscular hemorrhage using MSK US and establish an appropriate treatment plan.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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