Letter to the Editor

Contrast-enhanced ultrasonography in the emergency evaluation of a thigh muscle hematoma accompanied by active bleeding in a hemophilia A patient

Ying Liu[1]^, Yang Zhou[1]^, Bisi Wang[2], Jia Liu[3]

[1]Ultrasound Department, The Third People's Hospital of Chengdu, Chengdu, China; [2]Department of Vascular Surgery, The Third People's Hospital of Chengdu, The Affiliated Hospital of Southwest Jiaotong University, Chengdu, China; [3]Department of Hematology, The Third People's Hospital of Chengdu, The Affiliated Hospital of Southwest Jiaotong University, Chengdu, China

Correspondence to: Yang Zhou. Ultrasound Department, The Third People's Hospital of Chengdu, The Affiliated Hospital of Southwest Jiaotong University, Chengdu 610031, China. Email: 45907055@qq.com.

Submitted Mar 24, 2022. Accepted for publication Sep 05, 2022. Published online Sep 23, 2022.
doi: 10.21037/qims-22-261
View this article at: https://dx.doi.org/10.21037/qims-22-261

Hemophiliacs are at the highest risk of bleeding complications. The muscular hematomas (MH) comprise 6.8% of visits to the emergency department by hemophilia A (HA) patients (1). Magnetic resonance imaging (MRI), computed tomography (CT) scanning, and ultrasonography (US) are all used in detecting MHs. In addition, computed tomographic angiography (CTA) can be used to confirm the presence of contrast extravasation following traumatic injuries. However, CTA has limitations because it exposes patients to iodinated contrast material and radiation. Due to availability and cost, CT scans and US are more commonly used than MRIs (2). US imaging has emerged as one of the most useful modalities in evaluating traumatic muscle injuries. At the acute stage, the hematoma may be compressible and appear hyperechoic because of extravasated fresh blood. At the chronic stage, it may appear less compressible and a mix of anechoic/hypoechoic because of the growth of endothelial cells, smooth muscle cells, and fibroblasts (3). However, although active bleeding is seldom visible sonographically, a contrast-enhanced ultrasonography (CEUS) can detect acute emergent hemorrhage (4). The ultrasound contrast agent (UCA) used in this study was SonoVue (Bracco Imaging S.p.A., Milan, Italy), a second-generation contrast medium for diagnostic imaging which was approved in China in 2003. The UCAs consist of stabilized microbubbles containing an inert gas (sulfur hexafluoride, 8 μL/mL of solution) and are covered by a phospholipid membrane. SonoVue is small enough to traverse the pulmonary capillary beds (i.e., <8 μm in size) but stable enough to reflect US signals, which results in improved detection of blood flow signals from vessels that are difficult to assess (e.g., the intracranial vessels, renal arteries, and small capillaries). Further, the filling time of arteries and venous and capillary beds is distinctly different; real-time dynamic CEUS is a dependable modality for emergency physicians to identify the type of bleeding and make treatment decisions immediately.

When HA patients who develop exogenous factor VIII concentrate (FVIII) inhibitors have active bleeding, more aggressive treatment is necessary. Moreover, delays that prolong hemostasis may mean the difference between life and death. Therefore, an accurate diagnosis is critical for ensuring patient triage is conducted appropriately.

This paper reports the case of a 24-year-old man who was diagnosed with HA 22 years ago. He had commenced prophylactic FVIII replacement therapy 3 years ago, and during those 3 years, bleeding had not occurred. The patient felt a sudden pain in his right thigh after going to the toilet 4 days prior admission. Subsequently, he felt a gradual swelling and dyskinesia, with ecchymosis appearing

^ ORCID: Ying Liu, 0000-0002-7666-8459; Yang Zhou, 0000-0001-5031-0347.

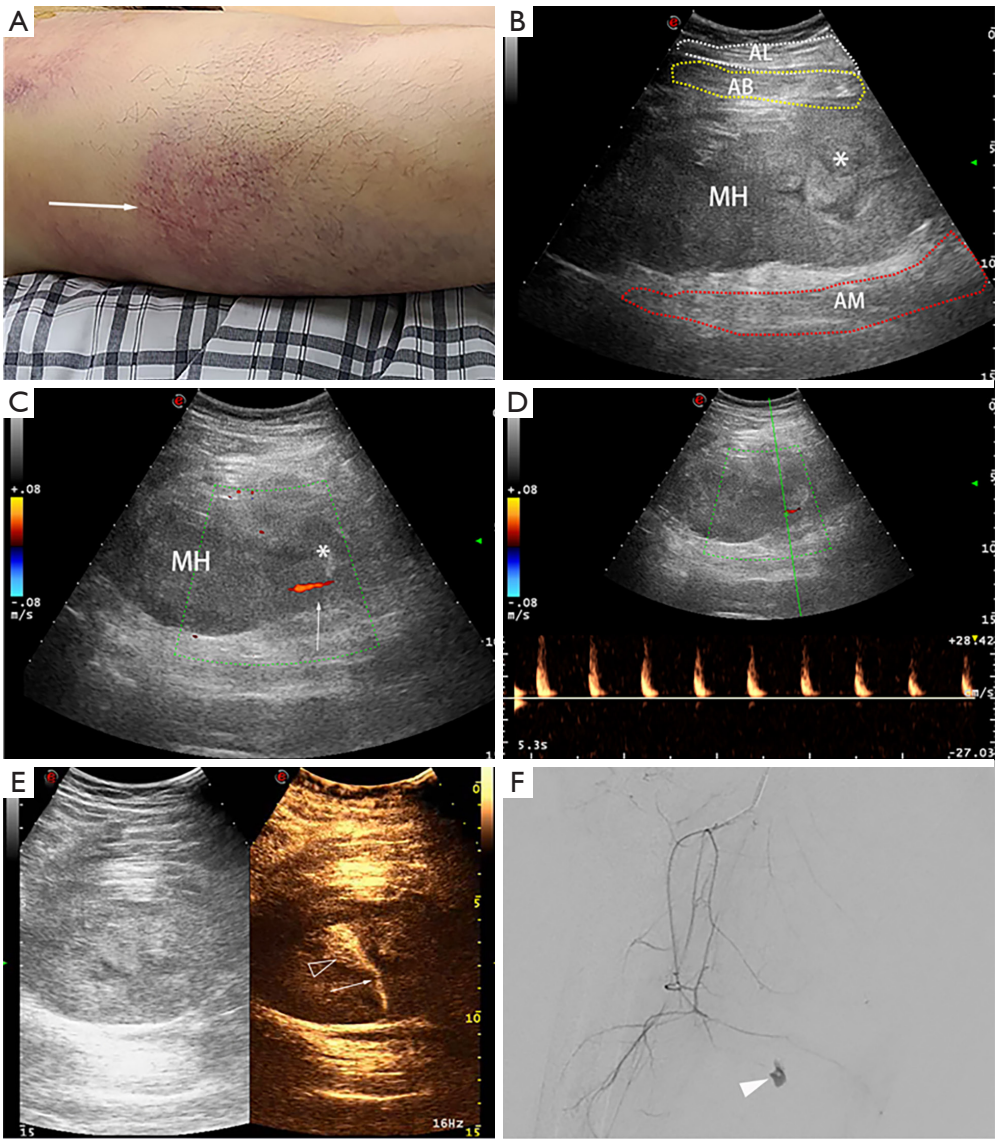

Figure 1 The appearance of the patient's right thigh with ultrasonography and angiography findings at admission. (A) The thigh was enlarged, and the skin had turned purple (arrow). (B) An MH in the right thigh infiltrated the adductor group of muscles, which was detected as a heterogeneous mass by ultrasonography. The MH was isoechoic compared with adjacent muscular structures and had a patchy hyperechoic echo structure in the middle (*). The AL (white dashed area), the AB (yellow dashed area), and the AM (red dashed area) showed decreased thickness and hyperechoic tissue. (C) A striped blood signal (arrow) appeared near the hyperechoic echo structure (*). (D) Pulsed Doppler waveforms showed a single-phase, low-velocity arterial flow. (E) In the hematoma, CEUS enhanced visualization showed that the low-velocity artery that was approximately 40 mm in length (arrow) with a rupture to the arterial branch, which was evidenced by microbubble extravasation (white arrowhead). This was interpreted as a sign of active bleeding. (F) Subsequent angiography confirmed these findings and showed contrast extravasation (white arrowhead). AL, adductor longus muscle; AB, adductor brevis muscle; MH, muscular hematoma; AM, adductor magnus muscle; CEUS, contrast-enhanced ultrasonography.

on the skin of his right thigh (*Figure 1A*). He quickly visited a local hospital and was diagnosed with MH. He received a maintenance dose of FVIII (4,000 IU/day) for 3 days, and subsequently felt sluggish, sleepy, and confused without delirium, indicating that he was in a compensatory stage of shock. Therefore, he was immediately transported to

the emergency room of The Third People's Hospital of Chengdu, The Affiliated Hospital of Southwest Jiaotong University.

When the patient arrived at the emergency department, his vital signs were as follows: blood pressure, 102/60 mmHg; heart rate, 78 beats per min; respiratory rate, 19 breaths/min; and body temperature, 36.3 ℃. The patient's right thigh was enlarged (the girth was approximately 50% greater than that of the left thigh) and had an elevated skin temperature accompanied by purple ecchymosis. Laboratory tests showed the following results: FVIII:C, 0.03 IU/mL (normal range, >0.4 IU/mL); FVIII activity, 4.6% (normal range, 78% to 128%); the factor percentage of FVIII activity inhibitors titer, 0.7 Bethesda units/mL (normal range, <0.6 Bethesda units/mL); hemoglobin, 7.9 mg/dL (normal range, 13 to 17.5 mg/dL); international normalized ratio, 0.99 (normal range, 0.8 to 1.2); and activated partial thromboplastin time, 72 s (normal range, 25 to 36 s).

An US was performed on the MH using a Mylab90 CA541 transducer (Esaote, Genoa, Italy) at 2–4 MHz, which revealed a heterogeneous mass of approximately 190×80×90 mm within the right bicep femoris muscle. The mass was isoechoic with a patchy hyperechoic echo structure (*Figure 1B*) that was near a striped blood signal (*Figure 1C*). Waveforms observed from the striped blood signal showed single-phase, low-velocity arterial flow (*Figure 1D*). As MHs are usually avascular, we performed CEUS to verify whether there was active bleeding. The dynamic CEUS video was recorded after intravenous administration of 2.4 mL SonoVue (Bracco Imaging S.p.A.) using a Mylab90 CA541 transducer (Esaote) at 2–4 MHz and a mechanical index of 0.08. This low mechanical index was a safe potential cavitation-related bio-effects indicator, which could prevent microbubble bursting and improve the image quality of CEUS. Dynamic CEUS improved the visualization of the blood signal mentioned above and revealed a blood flow beam of approximately 40 mm long and 4 mm wide. The CEUS also demonstrated that the blood flow was an arterial-phase flow originating from a perforated branch of the right deep femoral artery. Meanwhile, contrast agent extravasation was found at the end of the blood flow beam (*Figure 1E*). Thus, a diagnosis of arteriole rupture with active hemorrhage was made. The patient was transferred to the interventional radiology suite, where angiography confirmed contrast extravasation (*Figure 1F*). Arterial embolization was performed with successful resolution of active bleeding.

Figure 2 outlines the clinical course of this patient, showing the rapid development of high-titer inhibitors during the first 14 exposure days, which necessitated discontinuing FVIII and switching to prothrombin complex concentrates.

As expected, the patient experienced a fast recovery of both the purple ecchymosis and the swelling in his thigh (*Figure 3A*). The patient underwent subsequent CEUS on postoperative day 3, and no acoustic microbubble extravasation was found (*Figure 3B*). Finally, the area of the MH was reduced with partial liquefaction on postoperative day 10 (*Figure 3C*), and US found no blood flow signals in the whole MH (*Figure 3D*).

This clinical research process was approved by the Ethics Committee of The Third People's Hospital of Chengdu. All procedures performed in this study were in accordance with the ethical standards of the research committee of The Third People's Hospital of Chengdu, and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

According to previous findings, MHs associated with HA often result in capillary rupture and infiltrative bleeding (5). However, the life-threatening active arterial hemorrhage in acute MH has not been reported. The case described here is peculiar because the patient's MH had formed and enlarged due to a rupture of a thigh perforator artery. Arterial rupture in HA with active massive bleeding can cause hemorrhagic shock and death (6). Hence, imaging tests must be performed immediately to confirm the bleeding.

CT is excellent for identifying fractures and soft-tissue mineralization but plays a limited role in imaging acute muscle injury. MRI, with its high spatial and contrast resolution, is ideally suited for imaging muscle trauma and hematomas (7). CTA is widely applied and is safe for use in clinical practice of vascular injury. CTA has superior diagnostic accuracy in many urgent and emergent conditions and is valuable even for patients with minor trauma. However, it has the same drawbacks as CT: it needs highly trained staff, patients must be transported from the emergency department, and it is difficult to follow long vessels in the extremities because of the contrast amount that can be injected. Similarly, conventional US has inherently limited imaging capability and lower sensitivity to slow blood extravasation. Advanced imaging modalities are urgently required. Catheter angiography remains the gold standard examination method for definitive diagnosis

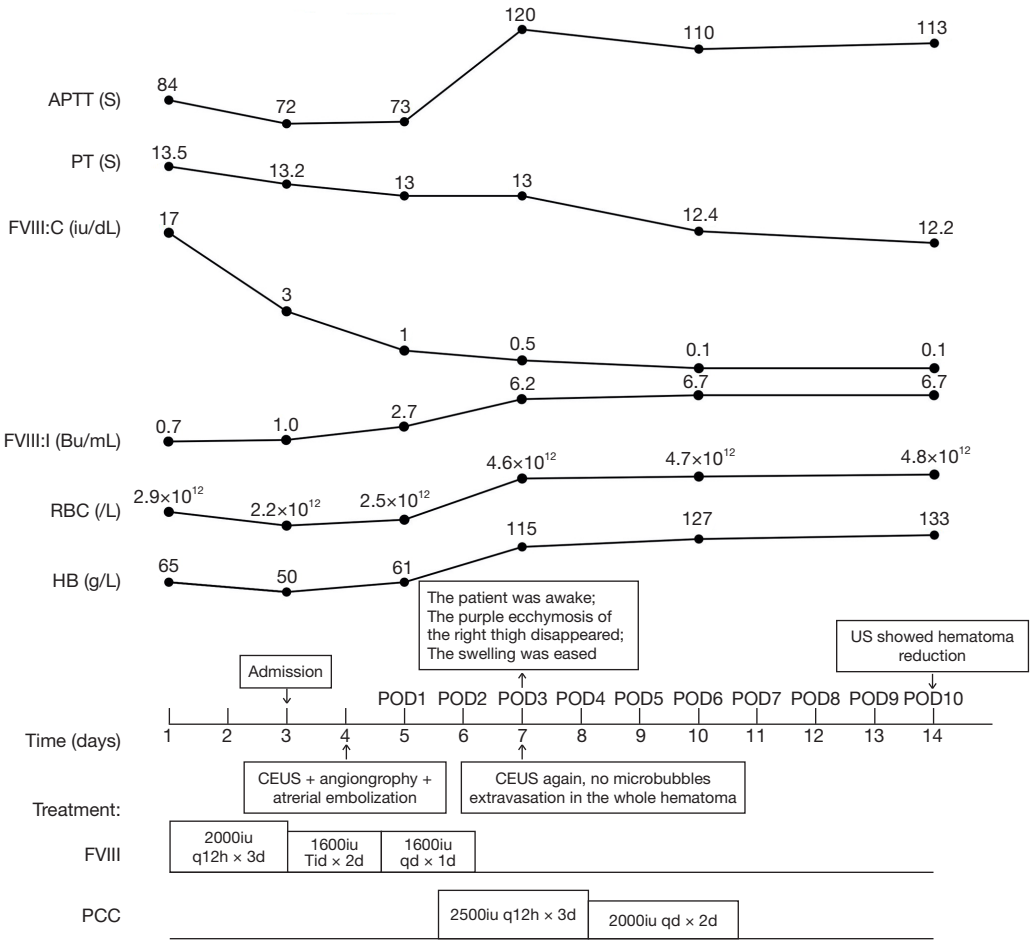

Figure 2 The clinical course of this case. The timeline begins with the patient's first hospitalization on 3 April 2021, and ends after his short-term follow-up on 17 April 2021. The major laboratory tests, symptoms, treatments, and acoustic changes of both US and CEUS during the course of the patient's illness are indicated. aPTT, activated partial thromboplastin time; S, second; PT, partial thromboplastin time; FVIII:C, FVIII coagulant activity; FVIII:I, FVIII inhibitor; RBC, red blood cell; HB, hemoglobin; POD, postoperative day; CEUS, contrast-enhanced ultrasonography; US, ultrasonography; PCC, prothrombin complex concentrates.

of acute arterial trauma, yet this invasive procedure in HA patients poses a challenge of uncontrolled bleeding at venipuncture sites. Further, the use of angiography for screening HA patients with suspected arterial active bleeding is associated with an unacceptable delay in ongoing resuscitation and immediate treatment. On the other hand, a few reports have shown that the interventional therapy of HA cardiovascular emergency is feasible and safe with close cooperation between all disciplines (8). If the location of the bleeding site can be accurately determined through fast pre-imaging, angiography and therapeutic embolization could be conducted quickly and efficiently, and these are the preferred procedures for treating hemorrhagic complications in HA (9). Many recent publications (10) have focused on applying CEUS after trauma because it can be performed quicker than angiography with no nephrotoxic or cardiotoxic effects (11). The incidence of severe adverse reactions to CEUS has been evaluated in large clinical studies (remained unchanged at 0.01%) (12), which is much lower than that of either contrast-enhanced CT or MRI. In the United States, UCAs are Food and Drug Authority (FDA)-approved only for cardiac and liver imaging and for evaluation of pediatric vesicoureteral reflux. However, several off-label applications have also been described, such as those used in evaluating abdominal aortic aneurysm rupture, deep venous thrombosis, and testicular

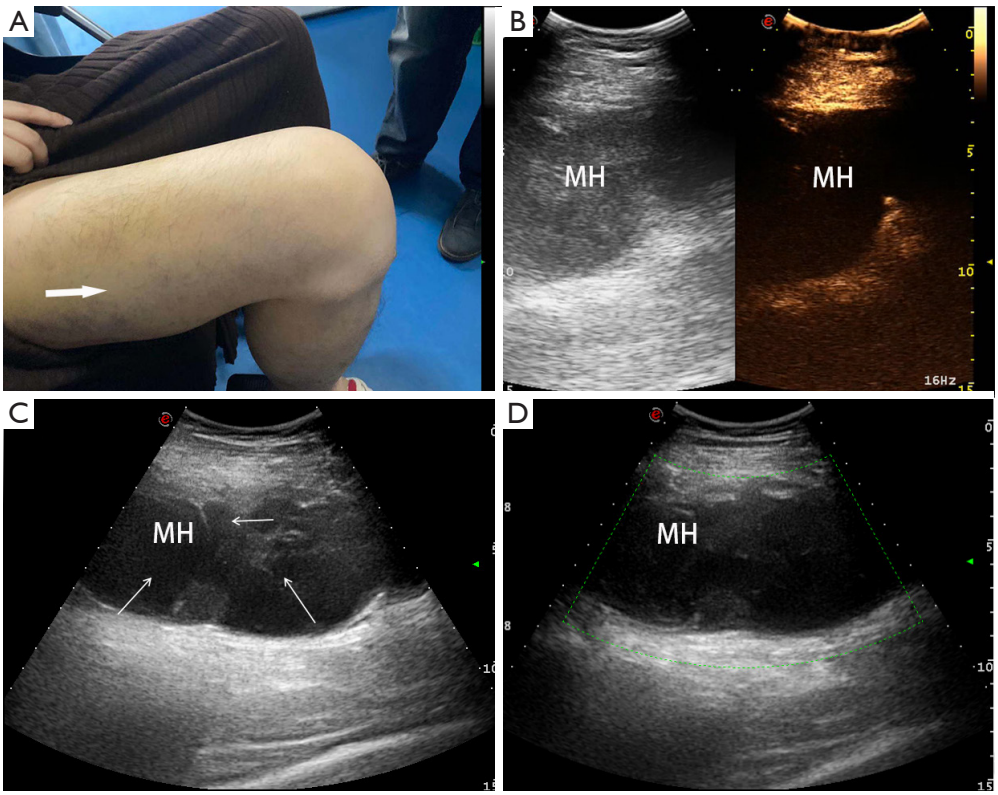

Figure 3 The appearance of the patient's right thigh with ultrasound images after arterial embolization. (A) On postoperative day 3, the purple ecchymosis of the right thigh had disappeared, and the swelling had eased (arrow). (B) CEUS displayed no enhancement in the whole MH. (C) On postoperative day 10, the area of hematoma was reduced (approximately 140×50×70 mm in size), and the lesion was demonstrated to be a complex cyst in the right thigh with multiple liquefied lesions (arrows). (D) Color Doppler demonstrated no blood flow signals in the hematoma, which again proved the therapeutic effect of the embolization. MH, muscular hematoma; CEUS, contrast-enhanced ultrasonography.

or ovarian torsion. For these reasons, we successfully performed immediate bedside CEUS on this patient. However, caution should be exercised when performing CEUS in patients with severe coronary artery disease and pulmonary hypertension as relative contradictions in the emergency room. Further, UCAs are not licensed for use during pregnancy, and there are limited data about their effects during breastfeeding.

For HA patients, even with the regular use of prophylactic FVIII replacement therapy, the risk of active bleeding after a subtle trauma still exists. Consensus on diagnostic, hemostatic pharmaceutical intervention and type/timing of physiotherapy for managing MH in HA patients is limited. Our CEUS findings, in this case, were consistent with the follow-up angiography, demonstrating the strength of CEUS for the identification of an active hemorrhage in acute MH. Further, the use of CEUS as a follow-up monitoring modality in this HA case reduced medical radiation exposure and catheter puncture from repeated angiography.

There is always a risk of active bleeding in HA; therefore, these patients require lifelong treatment and ongoing monitoring. A carefully performed US examination with CEUS might be the fastest, easiest, most accurate, and most inexpensive procedure for the emergency evaluation of an active hemorrhage in HA patients who develop acute MH. Thus, CEUS is a promising imaging technique for the short-term follow-up evaluation of patients with HA and MH.

Acknowledgments

The authors thank Ms. Cai Wen for the language editing.

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-261/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was provided by the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

References

1. García Sánchez P, Martín Sánchez J, Rivas Pollmar MI, Álvarez Román MT, Jiménez Yuste V. Haemophilia: Reasons for visits to the paediatric emergency department. An Pediatr (Engl Ed) 2019;91:394-400.
2. Zhang C, Wang X, Tang J. Correlation between microcirculation and contrast-enhanced ultrasonography after crush injury of limbs. J Med Ultrason (2001) 2018;45:307-13.
3. Chang KV, Wu WT, Özçakar L. Ultrasound Imaging and Rehabilitation of Muscle Disorders: Part 1. Traumatic Injuries. Am J Phys Med Rehabil 2019;98:1133-41.
4. Catalano O, Sandomenico F, Raso MM, Siani A. Real-time, contrast-enhanced sonography: a new tool for detecting active bleeding. J Trauma 2005;59:933-9.
5. Alcalay M, Deplas A. Rheumatological management of patients with hemophilia. Part II: Muscle hematomas and pseudotumors. Joint Bone Spine 2002;69:556-9.
6. Beeton K, Cornwell J, Alltree J. Muscle rehabilitation in haemophilia. Haemophilia 1998;4:532-7.
7. Flores DV, Mejía Gómez C, Estrada-Castrillón M, Smitaman E, Pathria MN. MR Imaging of Muscle Trauma: Anatomy, Biomechanics, Pathophysiology, and Imaging Appearance. Radiographics 2018;38:124-48.
8. Kim DK, Kim DI, Kim MS, Lee EJ, Kim YB, Cho HJ, Han YC, Kim U, Seol SH, Yang TH, Kim DK, Kim DS. Successful percutaneous coronary intervention for acute coronary syndrome in a patient with severe hemophilia a. Korean Circ J 2010;40:527-9.
9. Kim MJ, Oh JY, Park YS. Availability of angiography and therapeutic embolization for the treatment of acute bleeding in patients with hemophilia. Int J Hematol 2017;106:787-93.
10. Valentino M, Serra C, Pavlica P, Barozzi L. Contrast-enhanced ultrasound for blunt abdominal trauma. Semin Ultrasound CT MR 2007;28:130-40.
11. Rübenthaler J, Bogner F, Reiser M, Clevert DA. Contrast-Enhanced Ultrasound (CEUS) of the Kidneys by Using the Bosniak Classification. Ultraschall Med 2016;37:234-51.
12. Senior R, Lindner JR, Edvardsen T, Cosyns B. Ultrasound contrast agent hypersensitivity in patients allergic to polyethylene glycol: position statement by the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2021;22:959-60. Erratum in: Eur Heart J Cardiovasc Imaging 2021;22:960.

Cite this article as: Liu Y, Zhou Y, Wang B, Liu J. Contrast-enhanced ultrasonography in the emergency evaluation of a thigh muscle hematoma accompanied by active bleeding in a hemophilia A patient. Quant Imaging Med Surg 2023;13(1):512-517. doi: 10.21037/qims-22-261

