Case Report

Enoxaparin related spontaneous fatal retroperitoneal hemorrhage in a patient with atrial fibrillation

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Spontaneous retroperitoneal hemorrhage (SRH) is a potentially lethal complication of anticoagulation therapy. The signs and symptoms vary from clinical silence to abdominal pain or hemorrhagic shock. The diagnosis of SRH may be difficult, especially in its early clinical course, due to its varied symptoms. Physicians need to have a high degree of suspicion for its early diagnosis. Delayed diagnosis of SRH can lead to serious complications or death. Bleeding complications in anticoagulated patients are well known; however, reports about SRH with fatal outcomes are sporadic. Here, we describe a case of massive SRH in a patient receiving enoxaparin. In our case, the patient died due to delayed diagnosis and treatment. We, therefore, emphasize that physicians should always consider SRH in any patient receiving anticoagulants who presents with abdominal pain.

Keywords

Anticoagulant agents; enoxaparin; hemorrhage; perioperative period; retroperitoneal space

1. Introduction

Spontaneous retroperitoneal hemorrhage (SRH) is a rare complication in patients undergoing anticoagulant therapy. However, it can cause life-threatening complications (Salemis et al., 2014). Symptoms at initial presentation are nonspecific, and therefore diagnosis in such cases is often delayed. For patients with anticoagulant prescriptions, the possibility of SRH should always be considered when complaints of pain in the abdomen, groin, hip, leg, or back are reported. Here, we present a case of massive fatal SRH in a patient taking enoxaparin.

2. Case

A 74-year-old woman (height, 151 cm, and body weight, 48.4 kg) was admitted to our hospital for aggravation of dyspnea. Her medical history included atrial fibrillation, hypothyroidism, iron deficiency anemia, and rheumatic heart disease. She had an anticoagulant (rivaroxaban) prescription since her CHA2DS2-VACs score was 4 points. She had also received diuretics, digoxin, and thyroid hormone replacement for an extended period at local hospitals.

Her chest radiography report showed severe cardiomegaly with a cardiothoracic ratio of 82%. Laboratory investigations performed the day after admission revealed a white blood count of $4950 \times 10^3/mm^3$ (reference range, $4800\text{-}10800 \times 10^3/mm^3$), a hemoglobin level of 9.6 g/dl (reference range, 12.0-16.0 g/dl), hematocrit level of 30.4% (reference range, 38.0-47.0%), and platelet count of $148 \times 10^3/mm^3$ (reference range $130\text{-}400 \times 10^3/mm^3$). Renal and hepatic function tests were within normal ranges, and the creatinine clearance was 0.74 mg/dl. The prothrombin and activated partial thromboplastin times were also normal. Upper and lower gastrointestinal endoscopies could not help identify the possible causes of iron deficiency anemia. Transthoracic echocardiography demonstrated severe mitral and tricuspid regurgitation; the ejection fraction of the left ventricle was 70%, and the right ventricular systolic pressure was 63 mmHg. The patient was scheduled for mitral valve replacement surgery and switched to bridging anticoagulation from rivaroxaban (Xarelto® 20 mg, oral administration) once daily to enoxaparin sodium 1 mg/kg (Clexane® 50 mg, subcutaneous injection) twice daily, six days before the surgery.

Approximately five days after starting enoxaparin, she complained of sudden lower abdominal pain. No tenderness or rebound tenderness was observed on physical examination. Her vital signs were as follows: blood pressure, 118/62 mmHg; heart rate, 80 beats/min; respiration rate, 19 breaths/min; temperature, 36.3 °C; and oxygen saturation, 98% on room air. Laboratory investigations revealed a hemoglobin level of 8.5 g/dl, hematocrit level of 27.2%, and platelet count of $157 \times 10^3/mm^3$. Abdominal radiography showed both psoas muscle shadows to be intact. However, her abdominal pain gradually worsened.

Eight hours later, she started losing consciousness and experienced cold sweats accompanied by hypotension and tachycardia. A physical examination revealed a newly developed large tender mass in the pubic area. Laboratory investigations revealed a hemoglobin level of 6.1 g/dl, hematocrit level of 19.7%, and platelet count of $151 \times 10^3/mm^3$. An emergent enhanced computed tomography (CT) was performed; it showed a large retroperitoneal hematoma with active extravasation (Fig. 1).

Twelve hours after symptom onset, emergency angiography indicated diffuse pelvic hemorrhage (Fig. 2A). Angiographic embolization was performed on both internal iliac, left circumflex
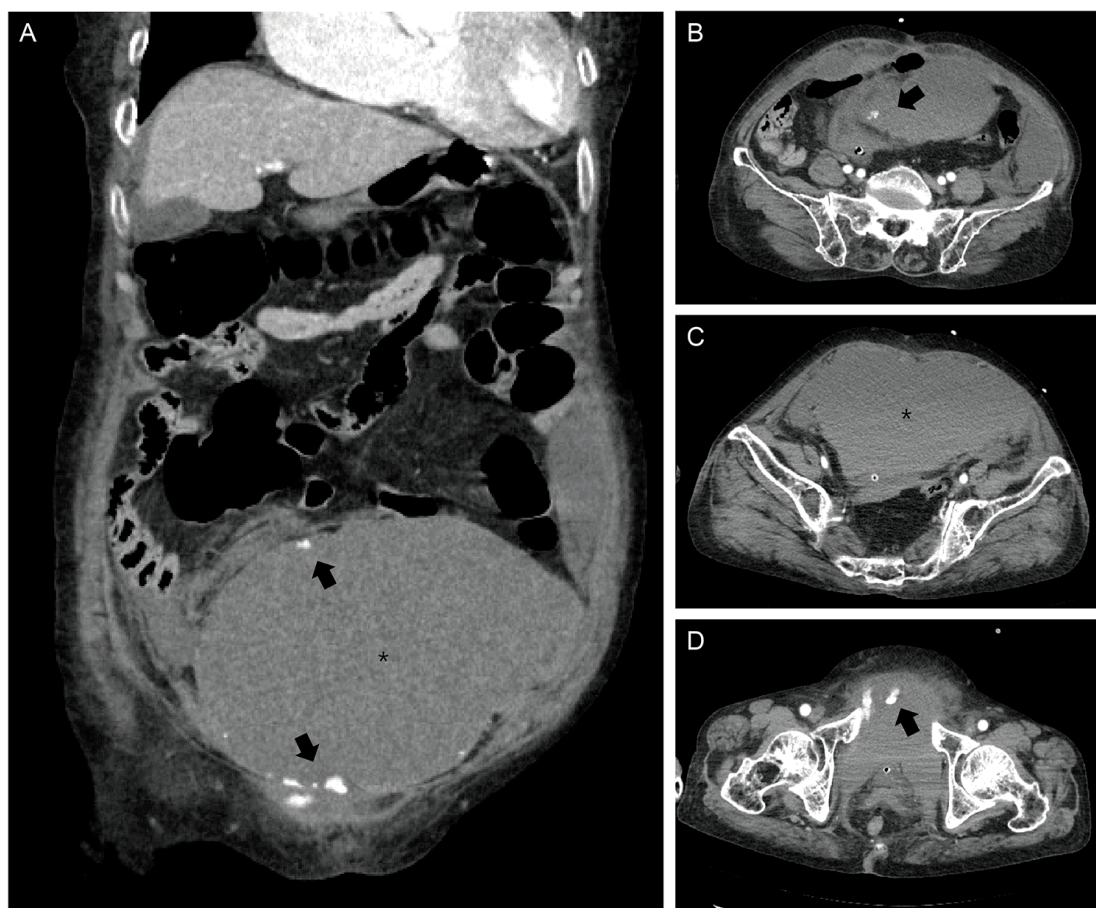
Fig. 1. Eight hours later after symptom onset, physical examination revealed a newly developed large tender mass in the pubic area. An emergent abdominal contrast-enhanced computed tomography was performed; it showed a large retroperitoneal hematoma (black strat in A and C) measuring 197 mm × 127 mm × 104 mm with contrast media extravasation (black arrow in A, B, and D).

iliac, and inferior epigastric arteries (Fig. 2B). However, this intervention failed to control the bleeding. Despite vigorous resuscitation, she remained hemodynamically unstable, and her clinical status deteriorated rapidly. She died of hypovolemic shock 36 hours after symptom onset.

3. Discussion

SRH is defined as a retroperitoneal hemorrhage that is unrelated to surgery, invasive procedures, trauma, or any underlying pathology (Salemis et al., 2014). Its common manifestations include abdominal or groin pain, back pain, leg pain, hip pain, leg paresis, palpable mass, hypotension, and hemorrhagic shock (González et al., 2003; Lissoway and Booth, 2010; Sunga et al., 2012).

SRH is a clinical entity associated with fatal outcomes and accounts for 5% of enoxaparin-induced complications. Reports indicate that it may occur within five days of therapy. The major risk factors for SRH are advanced age ($\geq$ 65 years), renal insufficiency, doses of enoxaparin approaching 1 mg/kg, and concomitant anticoagulant medications (González et al., 2003; Lissoway and Booth, 2010). Our patient was a 74-year-old female who developed SRH five days after starting enoxaparin.

Hemorrhagic shock was identified as the main cause of death. The signs of hemorrhagic shock may or may not be present in such

patients, depending on the extent and duration of bleeding. Early diagnosis and aggressive treatment of SRH are of paramount importance for successful management (González et al., 2003; Lissoway and Booth, 2010; Salemis et al., 2014; Sunga et al., 2012). The diagnosis of SRH may be difficult, especially upon initial presentation, due to its varied symptoms. Physicians must, therefore, have a high index suspicion to enable early diagnosis. The possibility of SRH should always be considered when patients receiving anticoagulant medications complain of abdominal, groin, hip, leg, or back pain.

Enhanced CT imaging is the diagnostic tool of choice for the detection of SRH. It can provide detailed information regarding location, the volume of hematoma, and the presence of active bleeding, and can help in decision making for an appropriate treatment strategy. If CT shows active extravasation of the contrast media, emergent angiographic embolization can be a treatment option. Active bleeding that is not rapidly detected and corrected may result in systemic hypoperfusion, which may lead to multi-organ failure. The mainstay of treatment, therefore, includes early identification of patients at risk for hypovolemic shock, temporary interruption of anticoagulants, administration of protamine sulfate, transfusion and volume replacement, as well as invasive procedures, such as angiographic embolization, percutaneous drainage, or surgery, as needed (González et al., 2003; Lissoway and Booth,
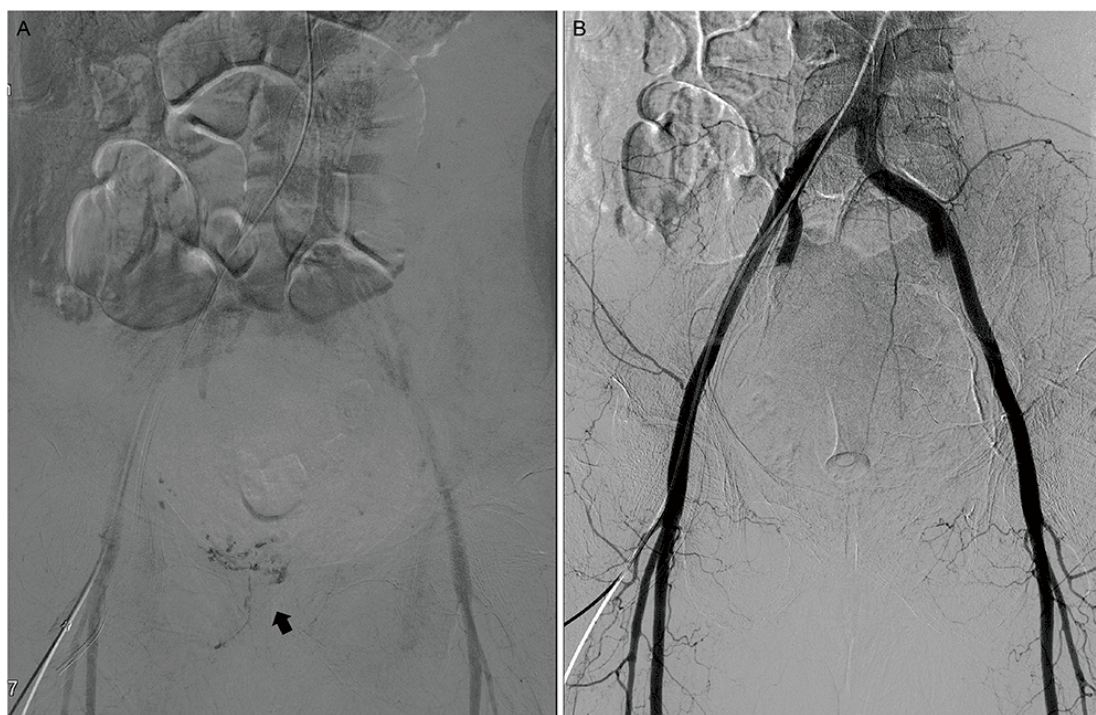
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Fig. 2. Twelve hours after symptom onset, emergency angiography showing (A) diffuse pelvic hemorrhage (black arrow) and (B) embolization was performed on both internal iliac, left circumflex iliac, and inferior epigastric arteries.

2010; Salemis et al., 2014; Sunga et al., 2012). Our patient was treated using angiographic embolization and a massive transfusion. However, delayed detection of SRH gave rise to severe complications leading to her death. The importance of appropriate patient assessment within the first few hours of resuscitation cannot, therefore, be overstated.

4. Conclusions

The diagnosis of SRH requires a high index of suspicion; physicians should always consider the possibility of SRH in the differential diagnosis when a patient presents with abdominal pain while receiving anticoagulants. Since this was our first encounter with a case of SRH, a delayed diagnosis led to the patient's death. An enhanced CT scan is the imaging modality of choice for evaluating SRH. Early diagnosis and aggressive management are essential for saving cases of SRH.

Authors' contributions

All authors have contributed significantly.

Ethics approval and consent to participate

The study was approved by the ethics committee of the Kyungpook National University Hospital, Daegu, Republic of Korea

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