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Case Report:

Spontaneous retroperitoneal hemorrhage after hemodialysis involving anticoagulant agents

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Abstract: In this paper, we described the symptoms and treatment of a patient with diabetic nephropathy accompanied by spontaneous retroperitoneal hemorrhage after hemodialysis. An elderly female patient with diabetic nephropathy presented with severe pain, numbness, and an increasing swelling in the left hip and left thigh after six sessions of hemodialysis involving the use of an antiplatelet drug and an anticoagulant agent. Her hemoglobin decreased to 46 g/L. An abdominal ultrasound showed a hematoma in the left retroperitoneal space, and computed tomography (CT) findings revealed a 6 cm×8 cm×10 cm hematoma in the left psoas muscle. After aggressive supportive therapy [the administration of packed red blood cell transfusion, carbazochrome sodium sulfonate injection, and continuous venovenous hemofiltration (CVVH)], the patient's vital signs stabilized and her hemoglobin increased to 86 g/L. Repeat CT showed that the hematoma had been partially absorbed after two weeks. Eventually, the patient was discharged with stable vital signs. Physicians should be aware of the possibility of spontaneous retroperitoneal hemorrhage, particularly in patients with diabetic nephropathy undergoing hemodialysis involving the use of anticoagulant agents.

Key words: Spontaneous retroperitoneal hemorrhage, Diabetic nephropathy, Hemodialysis, Nadroparin calcium
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1 Introduction

Falling, crush injury, road traffic accidents, injury to the retroperitoneal organs, fracture of the pelvis or lower spine, and retroperitoneal vascular injury are all potential causes of retroperitoneal hemorrhage or hematoma. A detailed physical examination and thorough history rarely lead to misdiagnosis of the condition (Peters *et al.*, 2007). However, spontaneous retroperitoneal hemorrhage is a much less common distinct clinical entity that can be life-threatening. Local or systemic conditions impacting the retroperitoneal organs or blood vessels can result in spontaneous retroperitoneal hemorrhage. Examples of such conditions include benign or malignant tumors of the kidney or adrenal gland (Brodey *et al.*, 1982; Tappe *et al.*, 1997), hemangioma (González-Valverde *et al.*, 2007), vascular malformation, thrombosis, pancreatitis or pancreatic cancer, the use of anticoagulants and antiplatelet drugs (Melde, 2003; Otrock *et al.*, 2006; Daliakopoulos *et al.*, 2008), hemophilia, and leukemia (Vayá *et al.*, 2003).

Spontaneous hemorrhage occurs only infrequently, particularly in patients with diabetic nephropathy, yet it is a significant cause of morbidity and is challenging to diagnose precisely and treat. In this paper, we describe an elderly patient with diabetic nephropathy who suffered from spontaneous retroperitoneal hemorrhage after six sessions of hemodialysis involving the use of an antiplatelet drug and the anticoagulant nadroparin calcium. A review of the literature identifying possible risk factors for spontaneous retroperitoneal hemorrhage and management strategies is also included.

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2 Subjects and methods

2.1 Medical history and physical examination

A 67-year-old woman, diagnosed with type 2 diabetes mellitus six years previously and diabetic retinopathy one year previously, presented with severe body edema. The patient had no history of coagulopathy, renal tumors, liver disease, or abdominal aortic aneurysm. The patient did not use tobacco or consume alcohol, and had no known allergies. On admission, a physical examination revealed a heart rate of 84 beats/min, a blood pressure of 180/100 mmHg, and a body temperature of 36.7 °C. Severe pitting edema was evident in the lateral aspect of the lower abdominal and pelvic regions and lower extremities. The patient also had signs of shifting dullness. The study was approved by the ethics committee of West China Hospital of Sichuan University, and written informed consent was obtained from the patient in this study.

2.2 Laboratory examination

Laboratory findings revealed a hemoglobin (Hb) level of 108 g/L, a white blood cell count of 6.42×10^9 L^{-1}, neutrophils of 81.0%, blood urea nitrogen (BUN) at 8.68 mmol/L, creatinine (CREA) at 184.5 μmol/L, fasting blood glucose at 8.8 mmol/L, an estimated glomerular filtration rate (eGFR) of 20 ml/min, albumin (Alb) at 22.5 g/L, 24-h proteinuria at 12.94 g, a prothrombin time (PT) of 9.5 s, and an international normalized ratio (INR) of 0.83. Antinuclear antibody, anti-double stranded deoxyribonucleic acid (anti-dsDNA) antibody, and anti-neutrophil cytoplasmic antibody tests were negative. An ultrasound examination of the arteries of the heart showed atherosclerosis and intimal thickening of the carotid arteries.

2.3 Procedure of diagnosis and treatment

In the process of initial treatment, insulin was administered to control the hyperglycemia, amlodipine was prescribed to decrease the blood pressure, and a diuretic was used to increase urine output. Ozagrel and sulodexide were also administered intravenously, and 1400 ml of blood plasma and 50 g of human serum albumin were infused, followed by a diuretic.

Five days later, the urine volume was 700 ml/24 h and no notable improvement in the edema was observed. However, the fasting blood glucose level had decreased to 6.9 mmol/L and the blood pressure was 130/80 mmHg. The patient reported increasing episodes of dyspnea and shortness of breath. Hemodialysis with nadroparin calcium (for anticoagulation) was initiated 6 d after admission, and was administered every other day. After six sessions of hemodialysis, the edema had markedly improved. On Day 15 of hospitalization, the patient complained of severe pain, numbness, and increased swelling in the left hip and left thigh. No local masses or ecchymoses were detected. Her blood pressure had decreased to 106/59 mmHg, her heart rate was 110 beats/min, and her hemoglobin was 46 g/L. On Day 17 of hospitalization, the white blood cell count was 15.25×10^9 L^{-1}, neutrophils were 96.5%, no gross hematuria was noted, and a stool occult blood test was negative. Repeat PT was 10.2 s, INR was 0.89, BUN was 15.21 mmol/L, and CREA was 367.3 μmol/L. An abdominal puncture revealed no abnormal findings but abdominal ultrasonography revealed a 6 cm×8 cm hematoma in the left retroperitoneal space. Computed tomography (CT) findings were consistent with the ultrasonography examination and revealed clearly a 6 cm×8 cm×10 cm hematoma in the left psoas muscle (Fig. 1). No abdominal aneurysms were noted.

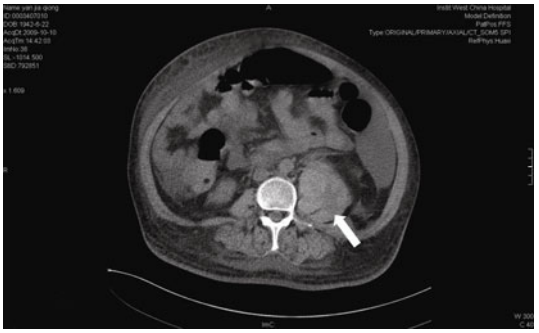

Fig. 1 Computed tomography (CT) scan of the abdomen showing a massive retroperitoneal hematoma, measuring 6 cm×8 cm×10 cm, and an extension of the left psoas muscle

Arrow indicates the hematoma

3 Results

The hematoma developed spontaneously and occurred following administration of the ozagrel, sulodexide, and nadroparin calcium, which was then

immediately discontinued. No protamine was administered because more than 12 h had elapsed since the last nadroparin calcium dose. Surgery was considered but was rejected because the hematoma was relatively small and there was no evidence of active hemorrhage. The patient's vital signs were stable and evacuation of the hematoma was considered risky. Conservative treatment was initiated with a transfusion of 5 units of packed red blood cells and injection of carbazochrome sodium sulfonate, and the patient responded rapidly. Continuous venovenous hemofiltration (CVVH) was initiated with sodium citrate for anticoagulation. On the third day of treatment, the patient's hemoglobin level increased to 86 g/L and her symptoms improved. Two weeks later, repeat CT showed that the hematoma was partially absorbed, measuring 4 cm×5 cm×7 cm (Fig. 2). Prior to discharge, no evidence of platelet or coagulation disorder was evident: fibrinogen 3.8 g/L, C reactive protein 92%, protein C antigen 70.2%, protein S antigen 41.3%, von Willebrand factor activity 232%, factor assay VIII 115%, and factor assay V 96%. The patient was discharged after one month with stable vital signs.

Fig. 2 Repeat computed tomography (CT), two weeks later, at the same level of the abdomen demonstrating the liquefied blood in left retroperitoneal and the hematoma partially absorbed (arrow)

4 Discussion

Spontaneous retroperitoneal hemorrhage characterized by a sudden onset of bleeding into the retroperitoneal space is a significant cause of morbidity and a diagnostic challenge. The hemorrhage can occur in association with bleeding disorders, rupturing of any of the retroperitoneal organs, or through an aneurysm. However, patients with spontaneous retroperitoneal bleeding are rarely reported. Herein, we describe the occurrence of spontaneous retroperitoneal hematoma in a high-risk elderly patient with diabetic nephropathy, a vascular lesion, and renal insufficiency (eGFR was 20 ml/min), and undergoing long-life low molecular weight heparin (LMWH) treatment combined with antiplatelet drugs. Spontaneous retroperitoneal hemorrhage occurred after receiving nadroparin calcium [0.025 mg/(kg·h)] and antiplatelet drugs.

The clinical features of bleeding are often variable and nonspecific, which can lead to a life-threatening situation. Spontaneous retroperitoneal hemorrhage can be presented as acute abdominal pain, back pain, nausea, vomiting, abdominal distension, intestinal obstruction, unexplained hypovolemia, anemia, unexplained limb swelling, paresthesia, femoral nerve compression causing paralysis of a lower limb, muscle weakness, reduced knee or thigh reflex, and/or increased intra-abdominal pressure-abdominal compartment syndrome (Hodin and Dass, 1969; Milutinovich *et al*., 1977; Lee *et al*., 2003; Jeong *et al*., 2003; Topgül *et al*., 2005; Parmer *et al*., 2006). Physicians are encouraged to be cognizant of these highly variable symptoms and include retroperitoneal hemorrhage on their list of differentials to prevent serious sequelae.

Diagnostic paracentesis is valuable for diagnosing abdominal organ injury, but lacks the sensitivity and specificity for retroperitoneal organ injury. Radiographs typically show a haziness around the psoas muscle, which usually disappears over time. Ultrasonography is an effective screening tool that can identify irregular hazy hyperechoic retroperitoneal masses, ascites, and organ contusions. Similarly, a CT is able to show clearly the location and extent of hemoperitoneum, effusion, abnormalities of the abdominal viscera, changes in the retroperitoneal structures, pressure shifts, or other abnormalities. The symptoms presented herein included unexplained severe pain, numbness, increased swelling in the left hip and left thigh with hypotension and a steadily decreasing hemoglobin concentration. Abdominal ultrasonography and CT examinations were invaluable for confirming the diagnosis.

Spontaneous retroperitoneal hemorrhage is rarely reported in relation to LMWH anticoagulation therapy (Montoya *et al.*, 1999; Chan-Tack, 2003).

Developed in the late 1980s, LMWH differs in its mechanism of action from unfractionated heparin by its inhibitory effect against factor Xa and thrombin. Since its development, LMWH has become an excellent alternative to unfractionated heparin because it offers superior efficacy and safety, has improved pharmacokinetics, and permits once- or twice-daily administration, without the need for laboratory monitoring (Büller, 2002). Unfortunately, LMWH therapy is not without risk. Abdominal wall, thigh, spinal and epidermal hematomas (Wysowski *et al*., 1998; Antonelli *et al*., 2000; Kumar and Solti, 2001; Topgül *et al*., 2005; Kim *et al*., 2009), and retroperitoneal bleeding (Melde, 2003) have all been reported following treatment with LMWH. Nadroparin calcium, a specific LMWH, is widely used in ischemic diseases for the prevention and treatment of venous thromboembolism. Only Schneiter *et al*. (2007) described a patient with temporary anuric kidney failure who developed an extensive retroperitoneal hematoma following nadroparin calcium administration. LMWH should be used cautiously, especially in elderly patients with vascular diseases and in patients with underlying diseases, such as antineutrophil cytoplasmic antibodies (ANCA)-related vasculitis, hypertension, or diabetes (Jeong *et al*., 2003; Kruzel-Davila *et al*., 2005), and in patients with renal insufficiency (i.e., creatinine clearance <30 ml/min) because of the risk of delayed clearance (Schneiter *et al*., 2007). LMWH is mainly excreted by the kidney. Thus, repeated administration of therapeutic doses of LMWH may lead to overdosage and/or an accumulation effect in patients with renal impairment, particularly the elderly, which may cause bleeding complications (Schneiter *et al*., 2007). In these high-risk patients, an initial reduced dosage in elderly patients with or without renal failure is recommended in addition to monitoring anti-Xa activity to detect any overdosage and/or any accumulation effect of LMWH (Siguret *et al*., 2004). Elevated anti-factor Xa values should alert clinicians to the potential of bleeding complications. Treatment of spontaneous retroperitoneal hemorrhage related to LMWH is multi-factorial, including complete bed rest, discontinuation of antiplatelet and anticoagulation drugs, blood transfusion, and supportive therapy, and is best implemented in an intensive care setting (Milutinovich *et al*., 1977).

In conclusion, physicians should be aware of the possibility of spontaneous retroperitoneal hemorrhage, particularly in patients with diabetic nephropathy and undergoing hemodialysis involving the use of anticoagulant agents. Precise diagnosis and timely treatment lead to a better prognosis.

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