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Case Study

Laboratory Medicine

Heparin resistance in a patient with severe acute pancreatitis: a case report

Dai Rongqin, MMed[1]; Bai Zhexin, MD[2]; Liu Yuzhi, MMed[1]; Guo Zhenbin, MMed[3]; Zhang Jinbiao, MMed[3,*]

[1]Department of Medical Technology, Cangzhou Medical College, Cangzhou, China;
[2]Department of Thoracic Surgery, Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing Chest Hospital, Capital Medical University, Beijing, China;
[3]Department of Laboratory Diagnosis, Cangzhou Hospital of Integrated Chinese and Western Medicine, Cangzhou, China

[*]Corresponding author: Jinbiao Zhang (zjb7829325@163.com).

Abstract

Introduction: Severe acute pancreatitis is a life-threatening condition characterized by systemic inflammatory response syndrome and an increased risk of complications such as venous thrombosis, all of which contributes to a high mortality rate. Heparin resistance, although rare, can lead to ineffective anticoagulation and thrombus formation during unfractionated heparin therapy, complicating management.

Methods: We report a case of heparin resistance in which, despite increasing the unfractionated heparin dosage, the patient's activated partial thromboplastin time remained subtherapeutic.

Results: Laboratory findings indicated normal antithrombin levels but undetectable anti-Xa activity, confirming non–antithrombin-mediated heparin resistance. A multidisciplinary approach led to the successful management of thrombosis with rivaroxaban, resulting in substantial clinical improvement.

Discussion: This case highlights the importance of early recognition and management of heparin resistance in patients with severe acute pancreatitis. Combined monitoring of activated partial thromboplastin time and anti-Xa activity is crucial for optimizing anticoagulation therapy and preventing complications such as deep vein thrombosis.

Key words: severe acute pancreatitis; heparin resistance; unfractionated heparin; rivaroxaban; thrombosis prevention

Introduction

Acute pancreatitis is a common surgical emergency, and 10% to 20% of patients with the condition may develop complications such as multiple organ failure and systemic inflammatory response syndrome, eventually progressing to severe acute pancreatitis, which carries a mortality rate of 20% to 40%.[1,2] The hypercoagulable state caused by severe acute pancreatitis can lead to secondary venous thrombosis, such as peripherally inserted central catheter–related thrombosis, splanchnic vein thrombosis, or deep vein thrombosis (DVT) in the lower extremities, increasing the mortality rate in these patients. Therefore, preventing venous thrombosis is critical for the prognosis of patients with severe acute pancreatitis. Early prophylactic anticoagulation can effectively prevent thrombosis and reduce the incidence of acute kidney injury, multiple organ failure, and mortality in these patients.[3-5]

Unfractionated heparin is the most commonly used anticoagulant for the prevention and treatment of venous thrombosis, offering the advantages of both rapid onset and reversibility, making it a preferred choice for preventing venous thrombosis in critically ill patients.[6] During the use of unfractionated heparin, some complications may arise, among which heparin-induced thrombocytopenia is relatively common, with an incidence of 1% to 3% following cardiovascular surgery. This condition has garnered substantial clinical attention, and with proper assessment and management, good clinical outcomes can be achieved.[6] Heparin resistance, another complication of unfractionated heparin, is relatively rare and often overlooked. If not promptly recognized and managed, it can increase the risk of thrombosis or thrombus expansion, potentially leading to serious outcomes such as bleeding. This article reports a case of heparin resistance in a patient with severe acute pancreatitis during unfractionated heparin anticoagulation therapy, with a focus on early identification and management.

Case report

Patient history

A 26-year-old man presented to the emergency department of our hospital with left upper abdominal distension and pain that had persisted for 8 hours. He had had 6 episodes of vomiting

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during which he had expelled all gastric contents but with no relief of pain. Since the onset of symptoms, he had passed no gas or stool, had experienced no chest pain or tightness, and had had no headache or dizziness.

On the first day of admission (November 25, 2020), the patient had a temperature of 36.4 °C, a heart rate of 98/min, a respiratory rate of 22/min, and a blood pressure of 117/70 mm Hg. He appeared lethargic but without jaundice. His lung sounds were clear bilaterally. His heart rhythm was regular. He had tenderness in the upper abdomen with mild muscle tension but no rebound tenderness. Bowel sounds were absent. Murphy sign was negative. The McBurney point was nontender. There was no percussion pain in the kidney area. Limb movements were intact. Initial laboratory tests revealed a white blood cell count of 16.48×10^9/L (range, 3.50-9.50×10^9/L), a neutrophil percentage of 87.50% (reference range, 40.00%-75.00%), a lymphocyte percentage of 8.50% (reference range, 20.00%-50.00%), a dimerized plasmin fragment D (D-dimer) level of 620 μg/L (cutoff <0.5 mg/L), thrombin-antithrombin complex was not detected, high-sensitivity C-reactive protein (CRP) was 16.5 mg/L (reference range, 0-6.0 mg/L), a procalcitonin level of 1.03 ng/mL (cutoff <0.5 ng/mL), an amylase level of 873 U/L (reference range, 36-135 U/L), a lipase level of 1129 U/L (cutoff <60 U/L), a glucose level of 12.79 mmol/L (reference range, 3.89-6.11 mmol/L), total cholesterol of 12.0 mmol/L (reference range, 3.10-5.18 mmol/L), a triglycerides level of 19.96 mmol/L (cutoff <1.70 mmol/L), and a potassium level of 5.44 mmol/L (reference range, 3.50-5.30 mmol/L). His arterial blood gas analysis showed a pH of 7.280 (reference range, 7.35-7.45), a PO_2 of 86.7 mmHg (reference range, 83.0-108.0 mmHg), a PCO_2 of 41.1 mmHg (reference range, 35.0-48.0 mmHg), and a lactate level of 3.18 mmol/L (reference range, 0.7-2.5 mmol/L). Abdominal ultrasound revealed an enlarged pancreas with heterogeneous, reduced parenchymal echogenicity; multiple fluid echoes around the liver; and clinically significant bowel distension. No abnormalities were detected in the gallbladder or bile ducts (Figure 1). Axial computed tomography (CT) scans of the abdomen showed no dilation of the intrahepatic or extrahepatic bile ducts. The gallbladder was of normal size, with no thickened walls. The pancreatic structure was blurred, with irregular, patchy, exudative fluid density around it and thickening with edema of the adjacent descending duodenum wall (Figure 2).

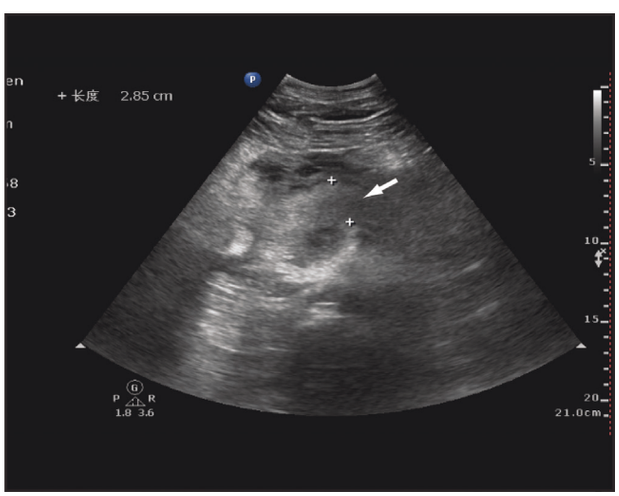

Figure 1. Ultrasound image shows pancreatic enlargement (arrow).

Initial diagnosis: acute pancreatitis, metabolic acidosis, and hyperlipidemia

The patient was started on omeprazole for acid suppression, somatostatin to inhibit enzyme secretion, ulinastatin to inhibit protease hydrolysis, parenteral nutrition with 18a amino acids and alanyl-glutamine, high-glucose support therapy, and active fluid resuscitation. Blood purification therapy was used as needed. The patient was kept nothing by mouth for oral intake.

On the third day of admission, the patient was lethargic, with no improvement in upper abdominal pain, a temperature of 36.5 °C, a heart rate of 125/min, a respiratory rate of 25/min, and a blood pressure of 70/50 mmHg. Laboratory results were an albumin level of 27.6 g/L, an amylase level of 2019 U/L, a lipase level of 1811 U/L, a CRP level of 166.4 mg/L, a procalcitonin level of 1.65 ng/mL, a potassium level of 6.9 mmol/L, a creatinine level of 678 μmol/L, a D-dimer level of 11160 μg/L, and thrombin-antithrombin was not detected. Based on the diagnostic criteria for acute pancreatitis and the modified Marshall score (5 points), the patient's further diagnosis was severe acute pancreatitis with hypovolemic shock and high risk of thrombosis.[7,8]

Because of the patient's prolonged bed rest and systemic inflammatory response, thrombosis markers were clinically significantly elevated, indicating a high risk for venous thrombosis. In addition to the existing treatment, unfractionated heparin (Trade name: Ausida; Specification: 2mL:12500 units; Approval number: State Drug License H20045512; Manufacturer: Hebei Changshan Biochemical Pharmaceuticals; Batch number: F201230707; Expiry date: 2020.07.21~2025.07.20) 2 mL (12 500 units) was administered at a dosage of 5000 units in an intravenous bolus followed by 20 u/kg/h (approximately 38 000 units/day) continuous intravenous infusion, with activated partial thromboplastin time (aPTT) monitoring.

On the seventh day of admission, after 4 consecutive days of this treatment, the patient's condition gradually improved, and

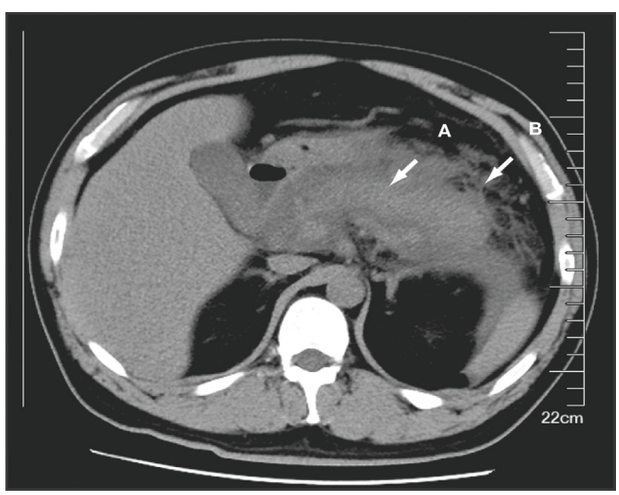

Figure 2. Axial computed tomographic image of the abdomen shows pancreatic enlargement (**A**) and peripancreatic exudative fluid (**B**).

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the symptoms of abdominal pain were substantially relieved. His temperature ranged from 36.5 °C to 37.3 °C, his heart rate went from 71/min to 85/min, his blood pressure went from 119/59 mm Hg to 132/75 mmHg, his respiratory rate went from 18/min to 27/min, and his oxygen saturation was 99% to 100% with 3 L/min oxygen flow. The patient was alert, his pupils were equal and reactive to light, and there was no neck stiffness. Laboratory tests showed an amylase level of 36 U/L; a lipase level of 80 U/L; a potassium level of 3.65 mmol/L; and a creatinine level of 80 μmol/L, with persistently elevated inflammatory markers, including a CRP level of 257.2 mg/L and a procalcitonin level of 2.65 ng/mL. Axial CT scans of the abdomen showed a clearer pancreatic structure than before, with the irregular, patchy, exudative fluid around the pancreas radiographically significantly reduced compared with the previous scan (Figure 3). Ultrasound examination after 4 days of heparin anticoagulation revealed thrombus in both superficial and deep femoral veins of the bilateral lower extremities, with hypoechoic filling and no clinically significant blood flow detected under compression (Figure 4). Following a multidisciplinary consultation with acute DVT experts, the vascular surgery team recommended vascular angiography and filter insertion. The patient refused angiography but agreed to filter insertion.

After 4 days of unfractionated heparin anticoagulation, multiple DVTs formed in the lower limbs, and thrombosis markers continued to rise. A filter was inserted, but the increased dosage of unfractionated heparin, adjusted from 20 u/kg/h to 25 u/kg/h (as of November 29, 2020), was ineffective, and the aPTT remained subtherapeutic. To assess the thrombotic risk and refine the anticoagulation strategy, further laboratory tests were ordered, and the laboratory department was consulted regarding recommendations for improving thrombosis prevention.

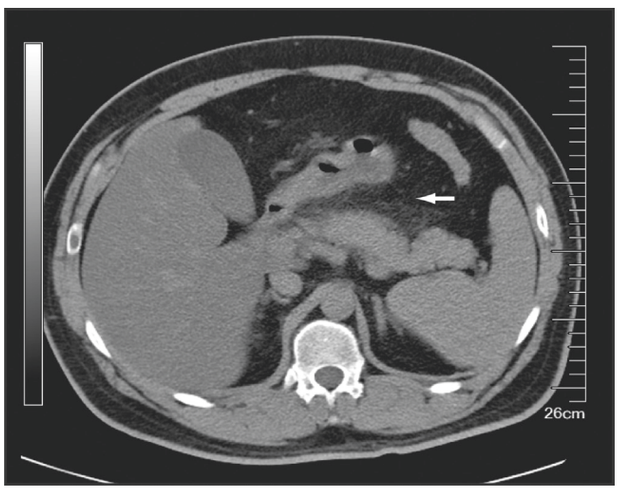

Figure 3. Computed tomographic image of the abdomen after treatment shows a clinically significant reduction in peripancreatic fluid (arrow).

Identification and management

Laboratory consultation analysis

A review of the patient's aPTT monitoring results revealed the following values (Table 1): At baseline, his aPTT was 31.6 seconds; on day 1 of treatment, it fell to 26.2 seconds. On day 2, it was 26.8 seconds; on day 3, 27.8 seconds; and on day 4, 30.5 seconds. The aPTT was subtherapeutic, and thrombin-antithrombin was 41.6 ng/mL (reference range, 0-4.0 ng/mL), suggesting possible heparin resistance.

The patient's antithrombin was 78.0% (reference range, 70%-120%), suggesting non–antithrombin-related heparin resistance. Anti-Xa activity was undetectable (0 U/mL [therapeutic range, 0.6-1.0 U/mL]), indicating no heparin present. Elevated CRP and procalcitonin levels suggested heparin resistance due to acute systemic inflammation. The supplementary diagnosis was non–antithrombin-mediated heparin resistance caused by the systemic inflammatory response.

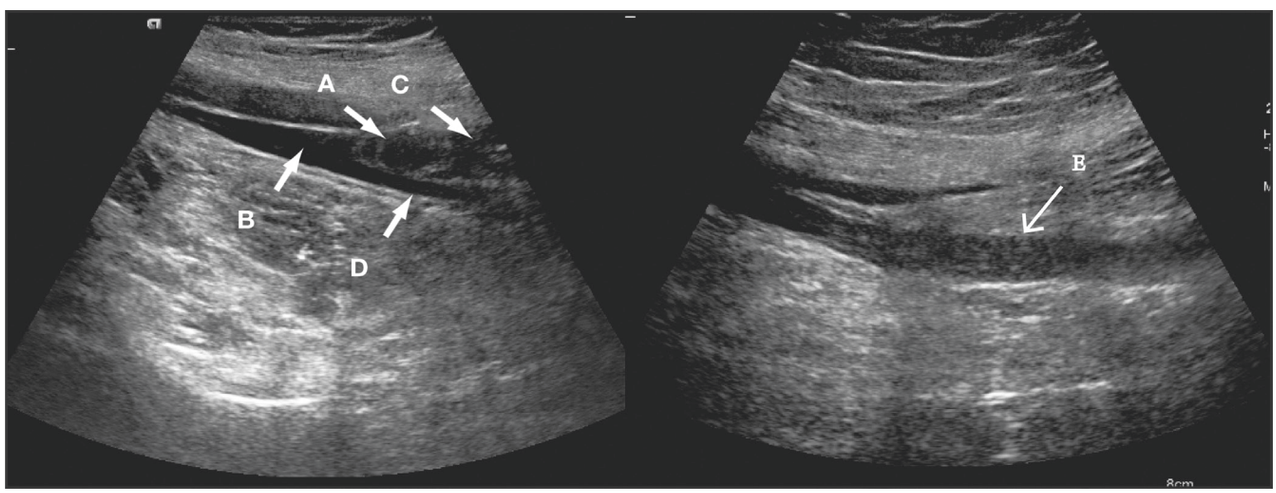

Figure 4. Ultrasound images show formation of DVT in the left lower extremities. (**A**) Head of the DVT (left). (**B**) Common femoral vein (left). (**C**) Superficial femoral vein (left). (**D**) Deep femoral vein (left). (**E**) Middle and lower segments of the superficial femoral vein (left). Abbreviation: DVT, deep vein thrombosis.

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Table 1. Changes in objective indicators before and after anticoagulation in a hospitalized patient after admission

				Unfractionated heparin (10 U/kg/h)					Rivaroxaban (15 mg/12 h)					Rivaroxaban (10 mg/12 h)			
	1 d	2 d	3 d	4 d	5 d	6 d	7 d	8 d	9 d	10 d	11 d	12 d	13 d	14 d	15 d	16 d	17 d
aPTT, *s*	27.60	28.80	28.00	31.60	26.20	26.80	27.80	30.50	—	—	—	—	—	—	—	—	—
D-dimer, μg/L	620	11060	111	0011070	43440	65420	81090	81180	97960	83640	73040	45460	34810	28880	15200	10200	6450
Thrombin-antithrombin, ng/mL	—	—	—	—	—	—	—	—	41.60	23.30	21.10	18.70	11.20	9.50	8.10	6.20	6.70

Abbreviations: aPTT, activated partial thromboplastin time; D-dimer, dimerized plasmin fragment D.

Laboratory consultation recommendations

The laboratory recommending continuation of anti-inflammatory treatment, with a switch from unfractionated heparin to rivaroxaban. The recommended dose is 15 mg every 12 hours. Anticoagulation efficacy using D-dimer and thrombin-antithrombin levels should be monitored, and the care team should check daily for signs of bleeding from the patient's gums or gastrointestinal tract. As thrombin-antithrombin levels decrease and thrombotic risk is controlled, the rivaroxaban dose should be reduced to 10 mg every 12 hours. This plan was clinically implemented.

Outcome

On the 17th day of admission (December 11, 2020), the patient was alert; in good spirits; and had no abdominal pain or distension, no nausea or vomiting, and normal bowel movements. His vital signs were temperature, 36.4 °C; heart rate, 70/min; respiratory rate, 15/minute; and blood pressure, 120/65 mmHg. Laboratory results were as follows: amylase, 32 U/L; lipase, 51 U/L; CRP, 5.7 mg/L; procalcitonin, 0.46 ng/mL; potassium, 3.65 mmol/L; creatinine, 62 μmol/L; D-dimer, 650 μg/L; and thrombin-antithrombin, 6.7 ng/mL. After anticoagulation treatment with rivaroxaban, both thrombosis (Table 1) and inflammatory markers showed clinically significant decreases approaching normal levels (Figure 5). A follow-up ultrasound showed reduced DVT in the lower extremities, with no new thrombi in other veins. On the 29th day of hospitalization (December 23, 2020), the patient gradually recovered and met discharge criteria. The filter was removed on the day of discharge. The patient was informed of the risk of thrombosis recurrence and advised to follow a light, easily digestible diet; avoid fatty foods and alcohol; and maintain regular bowel movements. He was instructed to continue taking rivaroxaban 10 mg/d and return for a follow-up abdominal CT scan, lower extremity venous ultrasound, and coagulation tests in 2 weeks. Follow-up visits at 3, 6, and 12 months showed no recurrence of acute pancreatitis or DVT in the lower extremities.

Discussion

Severe acute pancreatitis is primarily characterized by systemic inflammatory response syndrome and multiple system organ failure. Its pathogenesis is based on 3 main theories: the autodigestion theory of pancreatic enzymes, the microcirculatory dysfunction theory, and the leukocyte-endothelial cell interaction theory. The latter 2 theories are central to the development and progression of severe acute pancreatitis. Microcirculatory dysfunction and endothelial cell injury are key factors in the increased risk of thrombosis.[9] The interaction between inflammation and coagulation plays an active role in the onset and progression of severe acute pancreatitis. Therefore, controlling inflammation and preventing thrombosis remain critical aspects of severe acute pancreatitis treatment. Unfractionated heparin is the most commonly used drug for the prevention of venous thrombosis because of its rapid onset and reversibility. The risk of heparin-induced thrombocytopenia induced by unfractionated heparin is well known and can easily be identified and managed.[10] However, in certain cases, unfractionated

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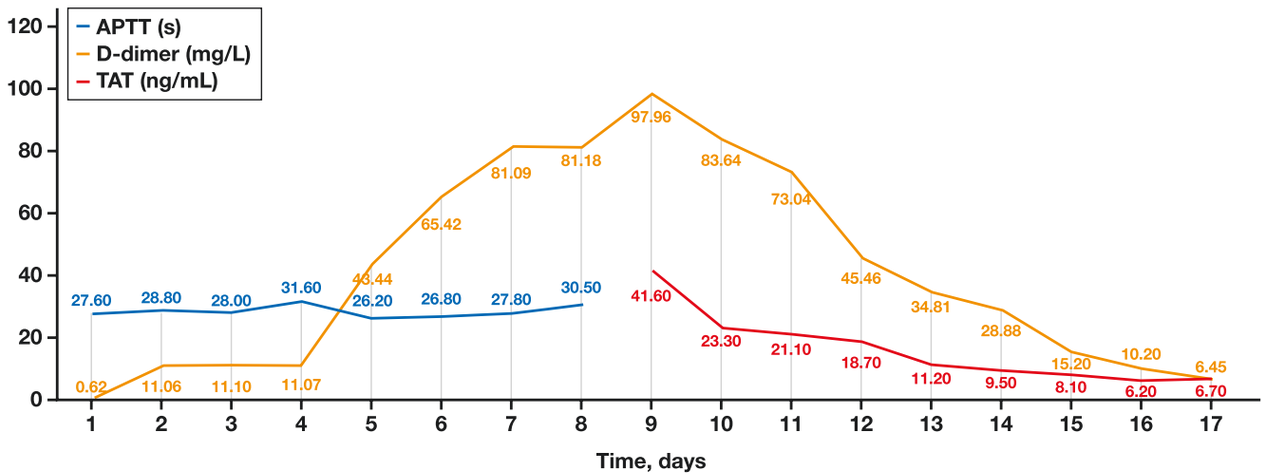

Figure 5. Change curve chart of aPTT, D-dimer, and thrombin-antithrombin. aPTT, activated partial thromboplastin time; D-dimer, dimerized plasmin fragment D; TAT, thrombin-antithrombin.

heparin–induced heparin resistance can be subtle; in fact, it often goes unnoticed until the optimal window for thrombus prevention has passed, resulting in venous thrombosis formation.[11] This case involved severe acute pancreatitis–induced heparin resistance, and by the time of clinical diagnosis, the patient had already developed multiple DVTs in his lower extremities. Following the adjustment of the treatment regimen, the patient exhibited no signs of gingival or gastrointestinal bleeding. In addition, the patient's levels of aPTT, D-dimer, and thrombin-antithrombin decreased, indicating a reduced risk of thrombosis. No thrombus progression or embolization was observed during the remainder of the patient's hospitalization. This outcome underscores the critical importance of timely treatment modification upon identification of heparin resistance.

Concept of heparin resistance

Because of the subtle and rare nature of heparin resistance, there is no clear consensus on its definition. Some reports define heparin resistance in patients undergoing cardiopulmonary bypass as an activated clotting time less than 480 seconds, despite a heparin dose of 500 U/kg. Given that activated clotting time testing is not widely available, in clinical practice with unfractionated heparin, heparin resistance is typically defined as a failure to reach the target aPTT, despite adequate heparin dosing.

Mechanisms of heparin resistance

The mechanisms of heparin resistance can be divided into antithrombin-mediated and non–antithrombin-mediated resistance. Antithrombin-mediated heparin resistance occurs because of reduced antithrombin activity leading to decreased heparin efficacy. Clinically, fresh frozen plasma or recombinant antithrombin can be administered to increase antithrombin activity. Clinicians should be reminded to check antithrombin levels before administering heparin anticoagulants.[12] With antithrombin activity at 80%, the anticoagulant effect of heparin is optimal. At 70%, it is reduced to 65% of normal efficacy. At 50%, it is reduced to 20%, and at 30% or below, heparin resistance or complete ineffectiveness occurs.[13]

During acute systemic inflammation, platelets, platelet factor 4 (a heparin-binding protein), histidine-rich glycoproteins, fibronectin, and von Willebrand factor may nonspecifically bind to heparin, with the degree of binding being positively correlated with inflammatory severity.[10,14] This binding reduces the amplifying effect of heparin on antithrombin activity, diminishing its anticoagulant efficacy. The levels of platelet factor 4, histidine-rich glycoproteins, fibronectin, and von Willebrand factor vary among different diseases, thus determining the likelihood and severity of heparin resistance. Failure to identify and address heparin resistance can lead to thrombosis. According to research by Bachler et al,[15] the risk of thrombosis in critically ill patients with heparin resistance can increase to 40% to 80%. This case represents inflammation-induced heparin resistance, classified as the non–antithrombin-mediated form.

Identification and management of heparin resistance

Objective markers often precede clinical symptoms. During the use of unfractionated heparin monitored by aPTT, heparin resistance is not considered if the aPTT meets the standard. However, if the aPTT fails to meet the standard, heparin resistance should be considered, and further evaluation of antithrombin activity and anti-Xa activity is warranted. When antithrombin activity is less than 70% and anti-Xa activity is below 0.2 U/mL, it is considered antithrombin-mediated heparin resistance.[16] In this condition, antithrombin supplementation or switching to an alternative anticoagulant is recommended, with continued monitoring of aPTT. When antithrombin activity is greater than 70% but anti-Xa activity remains below 0.2 U/mL, it is considered non– antithrombin-mediated heparin resistance. In this case, increasing the heparin dosage or switching to an alternative anticoagulant may be required,[17,18] with continued monitoring of aPTT. If antithrombin activity exceeds 70% and anti-Xa activity is greater than 0.2 U/mL, it is considered pseudo-heparin resistance. In such cases, increasing the heparin dose should be avoided because it substantially increases the risk of bleeding.[19,20] Instead, switching to an alternative anticoagulant and monitoring anti-Xa activity is advised. In addition, when antithrombin activity is below 50%, the use of heparin as an anticoagulant is generally not recommended. Therefore, combined monitoring of aPTT, antithrombin, and anti-Xa activity during heparin therapy facilitates the early and accurate identification

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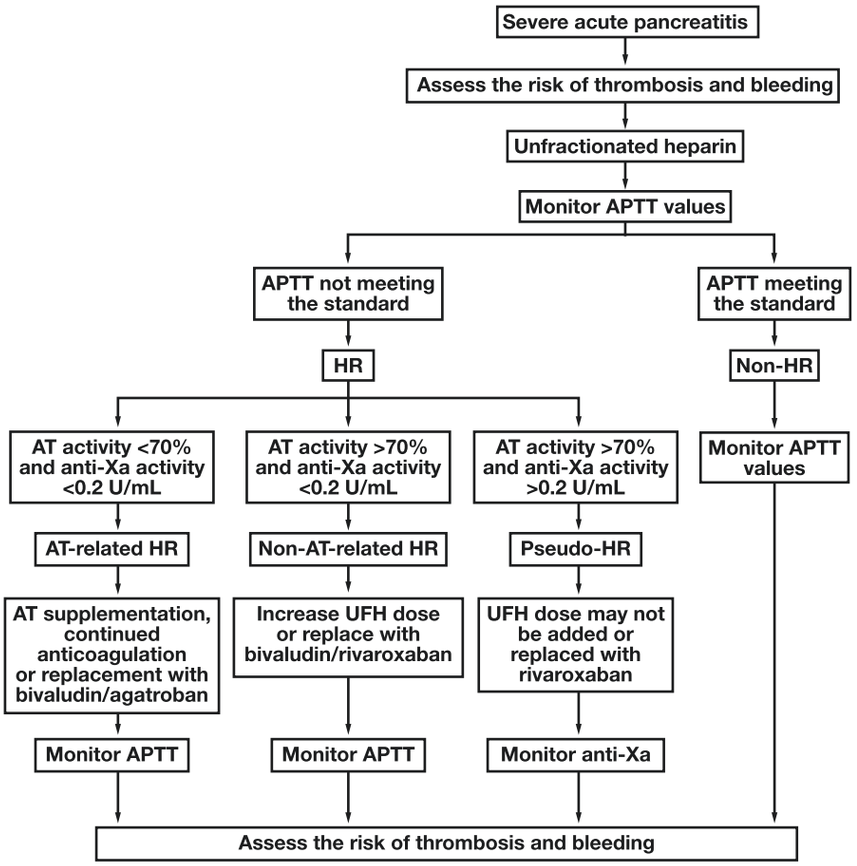

Figure 6. Flowchart for workup of antithrombin-related and non–antithrombin-related heparin resistance. Abbreviations: APTT, activated partial thromboplastin time; AT, antithrombin; HR, heparin resistance; UFH, unfractionated heparin.

of heparin resistance.[21] To provide a clear summary of this process, we created a flowchart (Figure 6). In the present case, the patient's aPTT did not reach the target range. Based on the assessment, antithrombin activity was found to be greater than 70%, while anti-Xa activity was below 0.2 U/mL. This presentation was diagnosed as non–antithrombin-mediated heparin resistance.

After identifying heparin resistance, the patient was immediately switched to rivaroxaban, with good results. Reports of bivalirudin being effective are also seen in cases of heparin resistance.[22] Due to concerns about bleeding risk, increasing the heparin dose was not chosen in this case. If chosen, clinicians should monitor anti-Xa levels instead of aPTT to ensure the efficacy and safety of the drug. The safe range of anti-Xa activity for unfractionated heparin is 0.1 to 0.2 U/mL for prophylaxis and 0.3 to 0.7 U/mL for treatment. For low-molecular-weight heparin, the prophylactic range is 0.2 to 0.4 U/mL, and the therapeutic range is 0.6 to 1.0 u/mL.[23] Therefore, combined monitoring of aPTT and anti-Xa is crucial for early identification and management of heparin resistance, and clinicians should be fully aware of its importance.

Anti-inflammatory effects of anticoagulants

In this case, under active anti-inflammatory treatment, anticoagulation therapy with unfractionated heparin was transitioned to rivaroxaban, which played a clinically significant role in controlling the patient's inflammation and improving his condition. The interaction between inflammation and coagulation is synergistic. Effective anticoagulation can counteract the progression of inflammation.

Pathophysiologically, antithrombin can induce endothelial cells to synthesize prostaglandins under certain conditions, which further interferes with leukocyte activity by exerting an antithrombin effect. In addition, antithrombin can inhibit proinflammatory thrombin pathways, contributing to thrombin's anti-inflammatory properties.[24] Therefore, factor II and factor X inhibitors (such as unfractionated heparin and rivaroxaban) can indirectly reduce inflammation by decreasing overall thrombin production.

Although heparin resistance is rare, it can lead to anticoagulation failure, increasing the risk of recurrent thrombosis and causing bleeding if improperly managed. In the treatment of severe acute pancreatitis, it is essential to recognize and manage heparin resistance early and to use monitoring markers effectively. Combined monitoring of antithrombin, aPTT, and anti-Xa levels is the best method for early identification and timely management of heparin resistance, providing clinicians with the diagnostic basis needed for better patient outcomes.

Conflicts of interest

The authors have nothing to disclose.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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