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【 CASE REPORT 】

Acute Anorectal Thrombophlebitis Caused by a Protein C Deficiency

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Abstract:
A 46-year-old man visited the emergency department of our hospital with a 3-day history of anal pain, hemorrhaging, and a slight fever. He had previously been diagnosed with protein C deficiency and was prescribed dabigatran, a direct oral anticoagulant. Contrast-enhanced computed tomography showed severe rectal wall thickening with partial defect of enhancement. In addition, sigmoidoscopy revealed a dusky purplish swollen anorectal mucosa just above the dentate line. He was diagnosed with acute anorectal thrombophlebitis, and anticoagulant therapy with heparin was initiated. To our knowledge, this is the first case report of acute anorectal thrombophlebitis caused by protein C deficiency.

Key words: acute thrombophlebitis, protein C deficiency, venous thromboembolism, direct oral anticoagulants

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Introduction

Protein C (PC) deficiency results in an impaired ability to control coagulation and an increased risk of venous thromboembolism (VTE), mainly when thrombosis occurs in the pulmonary veins, deep veins of the extremities, and mesenteric veins (1-4). However, ischemic anorectal injury is rare because of the area's rich collateral vascular supply, and acute anorectal thrombophlebitis due to VTE has not been reported. We herein report a rare case of acute anorectal thrombophlebitis caused by PC deficiency.

Case Report

A 46-year-old man was admitted to our hospital with a 3-day history of anal pain, hemorrhaging, and a slight fever. He had had an episode of loss of consciousness due to pulmonary embolism four years earlier and had been diagnosed with PC deficiency (30%; normal range, 64-146%). He was initially treated with warfarin. However, left popliteal artery thrombosis occurred three months later. He subsequently began taking dabigatran (150 mg twice daily) and experienced no further episodes of thrombosis.

On admission, his vital signs were as follows: blood pressure: 110/82 mmHg, pulse rate: 98 beats/min, respiratory rate: 20/min, and body temperature (measured in the axilla): 37.3°C. On a physical examination, only anal pain was remarkable. Laboratory data showed increased levels of C-reactive protein (14.1 mg/dL; normal range, <0.1 mg/dL), white blood cell count (13,770/μL; normal range, 3,900-9,800/μL), activated partial thromboplastin time (aPTT) (62.0 s; normal range, 24.3-36.0 s), and D-dimer (6.8 μg/mL; normal range, <1.0 μg/mL). Prothrombin time with international normalized ratio (PT-INR) was normal (0.93; normal range, 0.85-1.15).

Contrast-enhanced computed tomography (CECT) demonstrated severe rectal wall thickening with partial defect of enhancement (Fig. 1). No arterial or venous thrombus was identified by CECT. Sigmoidoscopy revealed a dusky purplish swollen anorectal mucosa just above the dentate line (Fig. 2a). In addition, the rectal mucosa had a reddish snakeskin appearance and edematous changes with an indistinct vascular pattern, suggesting thrombophlebitis (Fig. 2b-d).

Based on these findings, the patient was diagnosed with

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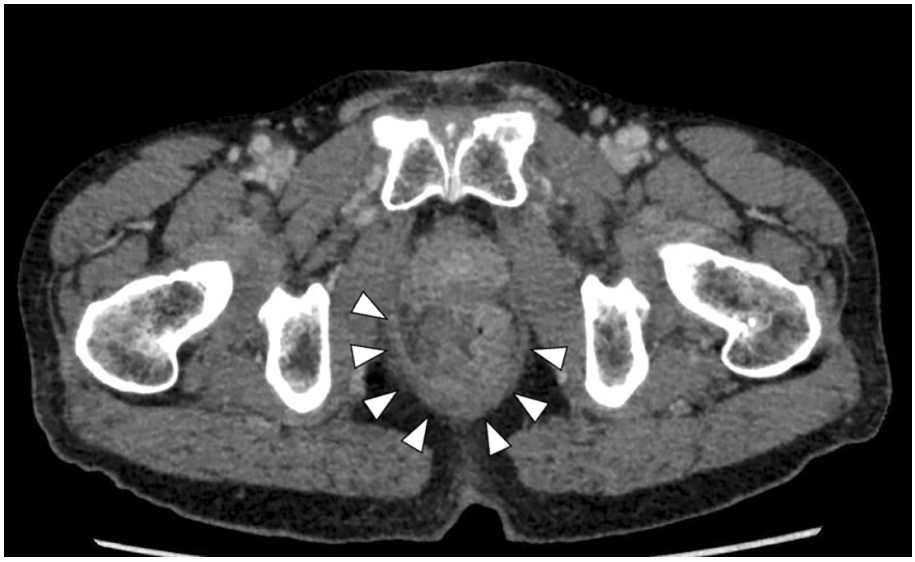

Figure 1. **A contrast-enhanced computed tomography scan on admission showing severe rectal wall thickening with partial defect of enhancement (white arrowheads).**

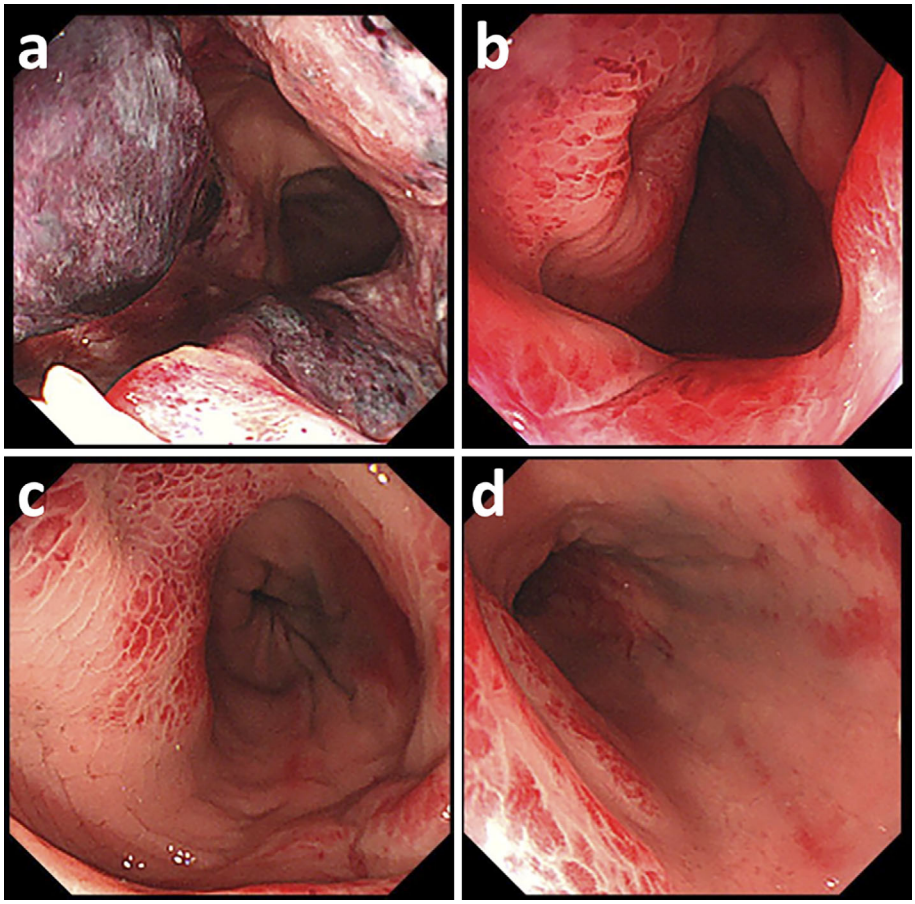

Figure 2. **Findings of sigmoidoscopy on admission. (a) Sigmoidoscopy revealed a dusky purplish swollen anorectal mucosa just above the dentate line. (b-d) The rectal mucosa had a reddish snake-skin appearance and edematous changes with an indistinct vascular pattern.**

acute anorectal thrombophlebitis. Anticoagulant therapy using heparin was immediately initiated. After 6 days of treatment with heparin, the patient's anal pain had nearly disappeared, and the D-dimer level decreased to 3.7 μg/mL. Anticoagulant therapy was switched from heparin to rivaroxaban (15 mg once daily). A follow-up CECT on hospital day 7 revealed marked thinning of the rectal wall with a recovery of homogenous enhancement (Fig. 3a). In addition, sigmoidoscopy showed shallow anorectal ulcers in the area of the previously purplish mucosa (Fig. 3b and c). The D-dimer

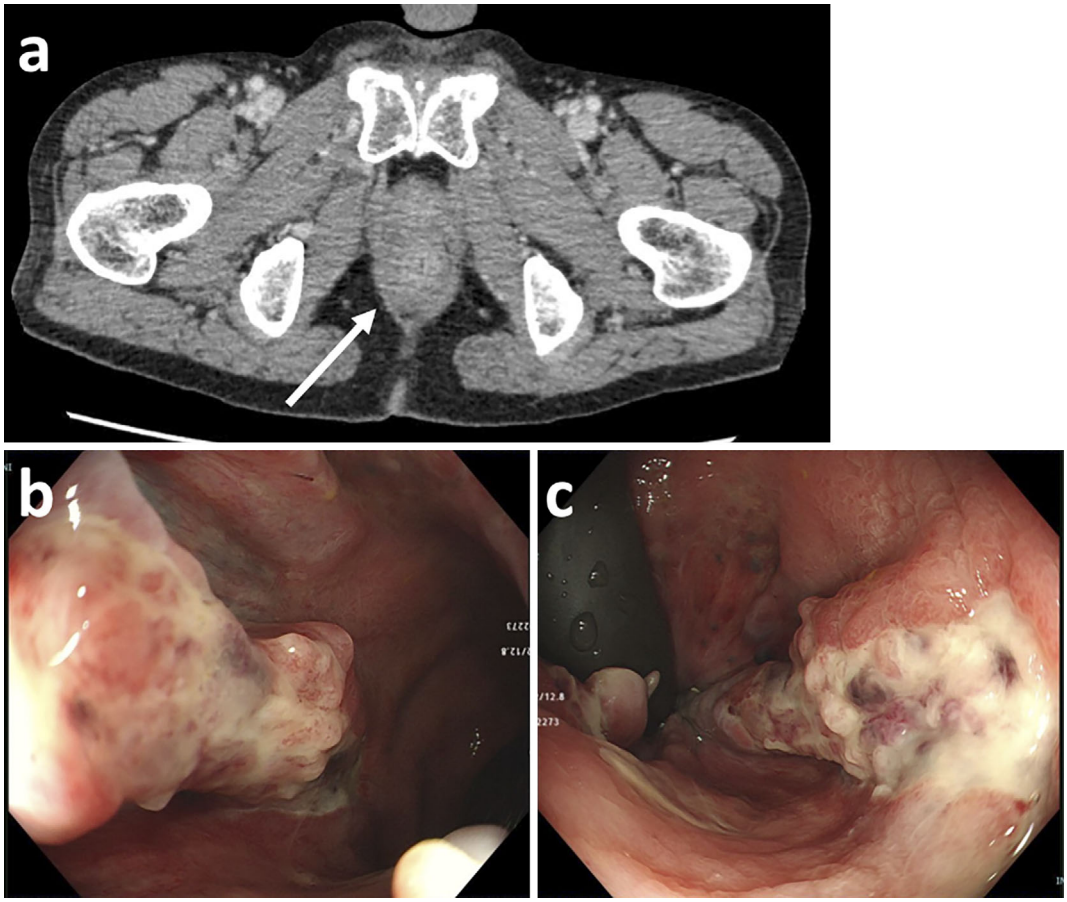

Figure 3. **Findings of contrast-enhanced computed tomography and sigmoidoscopy after 7-day anticoagulant therapy. (a) Contrast-enhanced computed tomography showed marked thinning of the rectal wall with recovery of homogenous enhancement (white arrow). (b, c) Sigmoidoscopy revealed shallow anorectal ulcers at the area of the previously purplish mucosa.**

level dropped to 1.0 μg/mL on hospital day 11. The patient recovered uneventfully and was discharged on hospital day 12.

Discussion

We encountered a case of acute anorectal thrombophlebitis caused by PC deficiency. PC is a vitamin K-dependent anticoagulant protein that is synthesized in the liver. PC is activated to activated PC (APC) by the complex of thrombin and thrombomodulin, and APC exerts important anticoagulant effects on the endothelial surface (1). APC, with its cofactor protein S, inhibits the generation of thrombin via inactivating coagulation factors Va and VIIIa. The incidence of PC deficiency in healthy individuals is reported to be approximately 0.2% to 0.5% (5, 6). PC deficiency results in an impairment of the ability to control coagulation through the destruction of factors Va and VIIIa leading to an increased risk of VTE (1-4, 7).

The risk of VTE in patients with PC deficiency varies depending on other modifying factors; the risk in such patients with a positive family history is 30% to 75% (8-10). Regardless of the family history, the risk of VTE is increased to 40% to 68% by additional inherited or acquired VTE risk factors (e.g., hormonal contraceptive use, surgery, factor V Leiden mutation) or a history of VTE (11-14). Therefore, for the treatment or secondary prevention of VTE, many patients with PC deficiency receive anticoagulant therapy, such as a vitamin K antagonist (warfarin) or direct oral anticoagulants (DOACs).

Long-term anticoagulant therapy with warfarin and a PT-INR of 2 to 3 has been reported to be effective in preventing VTE in patients with PC deficiency (15). Recently, positive outcomes have been reported for the use of DOACs in inherited thrombophilia (16). However, PC deficiency is associated with numerous different mutations throughout the protein C gene; furthermore, the efficacy of warfarin or DOACs can be altered based on the mutation profile of each patient (4). In the present case, warfarin was determined to be ineffective due to the early recurrence of VTE. Therefore, warfarin was switched to dabigatran, a direct inhibitor of thrombin. The patient took dabigatran regularly, and aPTT was elevated to 45 to 55 seconds. Although why dabigatran could not prevent anorectal thrombophlebitis was unclear, dabigatran was nevertheless switched to rivaroxaban, a direct factor Xa inhibitor. Careful observation is needed to ensure the effectiveness of anticoagulant therapy with rivaroxaban.

Patients with acute anorectal disorders often present to the

emergency department with a variety of conditions, including infectious, inflammatory, benign, and malignant diseases. However, ischemic anorectal injury is rare because of the area's rich collateral vascular supply (17). Ischemic anorectal injury must be distinguished as thrombosed hemorrhoids, ischemic proctitis, or anorectal thrombophlebitis. Most patients with thrombosed hemorrhoids have a history of other anal symptoms, such as pruritus ani, rectal bleeding, and mucosal descent (18). It is difficult to discriminate between ischemic proctitis and anorectal thrombophlebitis because their symptoms and endoscopic appearances are similar. Ischemic proctitis is mainly encountered in patients with significant atherosclerotic and cardiac risk factors who present with rectal bleeding in the setting of hemodynamic instability (17, 19, 20). In contrast, thrombophlebitis is thought to occur mainly in patients with a background of thrombophilia (21). In the present case, the patient had a history of protein C deficiency; therefore, we diagnosed him with acute anorectal thrombophlebitis due to thrombogenesis in the anorectal vascular plexus.

To our knowledge, acute anorectal thrombophlebitis due to VTE has not been reported. CECT is reported to be useful in the diagnosis of acute anorectal injury caused by thrombosis (22). The most common findings are bowel wall thickening and heterogeneous enhancement of a thickened wall. However, in mild cases where only wall thickening is present on CECT, the differentiation between thrombotic diseases and inflammatory or infectious disorders is often difficult based on CECT alone (22). Sigmoidoscopic findings, such as submucosal hemorrhaging and dusky purple mucosa, are also useful for ensuring an accurate diagnosis. In the present case, the patient had a history of protein C deficiency and was treated with dabigatran. Therefore, rapid anticoagulant therapy using heparin may contribute to the early resolution of anorectal thrombophlebitis.

In conclusion, the possibility of anorectal thrombophlebitis should be considered when encountering patients with acute anal pain, hemorrhaging, and a slight fever, especially in those with a background of thrombophilia.

The authors state that they have no Conflict of Interest (COI).

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