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A Case of Rivaroxaban-induced Hematomyelia of Thoracic Spinal Cord in Patient with Acute Renal Failure

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Abstract

Hematomyelia associated with direct oral anticoagulants (DOACs) is rare. In this report, a case of a 78-year-old male with paraplegia due to hematomyelia after medication of rivaroxaban, which is the first case in which acute renal failure is closely associated with the onset and underwent surgical evacuation is presented. The patient was initially misdiagnosed as a spinal cord infarction, and appropriate therapeutic intervention was not provided. One year later, the patient's symptoms did not improve, he is dependent on a wheelchair for daily activities, and cystostomy was performed. During administration of DOACs, hemorrhagic lesion should be strongly suspected in a patient with acute renal failure.

Keywords: hematomyelia, direct oral anticoagulant, acute renal failure

Introduction

Previous reports provide evidence of intramedullary hemorrhage (hematomyelia) in the spinal cord caused by different conditions, a major part of which were associated with spinal arteriovenous malformations or intramedullary tumors. Therefore, hematomyelia associated with anticoagulant drugs were rare in the past literatures. Most of those were due to warfarin, and few reports are related to direct oral anticoagulants (DOACs). We present a case of a 78-year-old male who presented with sudden-onset paraparesis, sensory, and urinary disturbance owing to thoracic-level hematomyelia. He had been prescribed rivaroxaban and had a transient worsening of renal function immediately before the onset.

Case Report

A 78-year-old male presented with bilateral motor weakness, numbness, and edema of the lower extremities. He visited his local hospital, and blood examination revealed elevated white leukocyte count (10700), inflammatory response (CRP 12.5), creatinine (3.86), creatinine clearance (Ccr, 15.17 mL/min), activated partial thromboplastin time (APTT, 38.2 sec), PT-INR 1.26, platelet 19.2 × 10^4/μL, d-dimer 1.7 μg/mL, and fibrinogen 206 mg/dL. Liver function tests presented total bilirubin 1.0 mg/dL, levels of alanine transaminase (ALT; 18 IU/L), aspartate transaminase (AST; 22 IU/L), gamma-glutamyl transferase 30 IU/L, and slightly increased lactate dehydrogenase 407 IU/L. The diagnoses were cellulitis and acute renal failure. There was no generalized bleeding tendency, and blood sampling findings were negative for disseminated intravascular coagulation or liver dysfunction. Moreover, blood pressure was 135/82, which suggested a low probability of hypertension involvement. He had also been diagnosed with pulmonary embolism due to deep venous thrombosis of the common iliac vein 3 months before this event and started to administer the daily 15 mg rivaroxaban and continued thereafter. He was admitted to the medical ward, and his cellulitis (inflammatory response) and renal function were immediately improved (Cre 0.94 and Ccr 62.3 mL/min, 4 days after admission); however, the paraparesis and sensory disturbance did not improve. Magnetic resonance imaging (MRI) of the whole spine revealed the mixed intensity of T2WI high in the core with T2WI low around the core lesion at the T9 level, which resulted in the diagnosis of "spinal cord infarction" by another department. Therefore, conservative treatment was continued; however, his symptoms did not achieve remission; then, he was referred to a neurosurgeon

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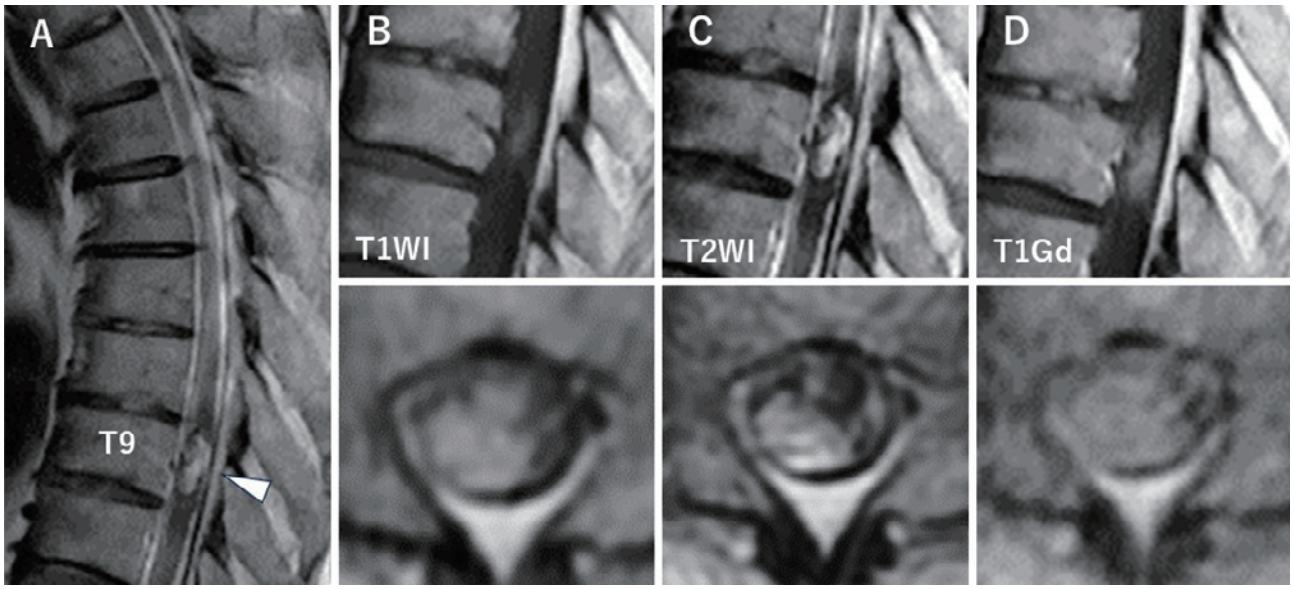

Fig. 1 Preoperative MRI findings. A, Sagittal T2WI view presents an intramedullary lesion (arrowhead) at the T9 spinal level. B-D, Sagittal and axial views of T1WI, T2WI, and T1Gd enhancement MRI show heterogenic intensity and partial enhancement of the lesion.

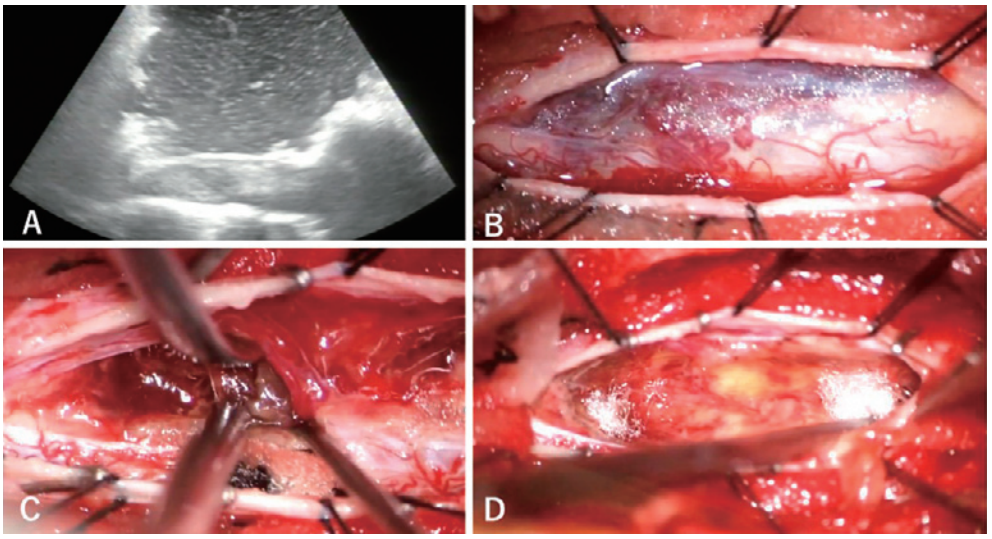

Fig. 2 Intraoperative findings. A, Intraoperative ultrasound following laminectomy shows a hyperechoic lesion inside the spinal cord. B, Dural opening revealed the dark-reddish dorsal aspects of the spinal cord, and dilated pial veins were observed. C, Midline myelotomy revealed hematoma and no evident tumor-like lesion. Note that dilated vessels around the hematoma were mimicking hemangioma. D, Evacuation of hematoma was achieved.

who diagnosed intramedullary hemorrhage associated with a tumor. He was transferred to our hospital 15 days after onset. His paraparesis was worsened to nearly paraplegia accompanied by urinary disturbance. Secondary MRI including a Gd-enhanced one showed a partially enhanced lesion without surrounding flow voids (Fig. 1), which was consistent with intramedullary hematoma. No evident tumor nor arteriovenous malformation was detected. Preoperative blood examination performed 2 days before surgery revealed that APTT was 32.4, prothrombin time international normalized ratio (PT-INR) 1.07, d-dimer 9.7 μg/mL, and fibrinogen 412 mg/dL; then, rivaroxaban was subsequently interrupted until the next day of surgery. Andexanet alfa was not administered.

He underwent emergent surgery for the removal of supposed responsible tumors, for example, small ependymoma, cavernoma, and hemangioblastoma. Laminectomy from T8 to T9 and midline myelotomy were performed, and intramedullary hematoma was evacuated (Fig. 2). Although no evident tumors existed, dilated vessels around

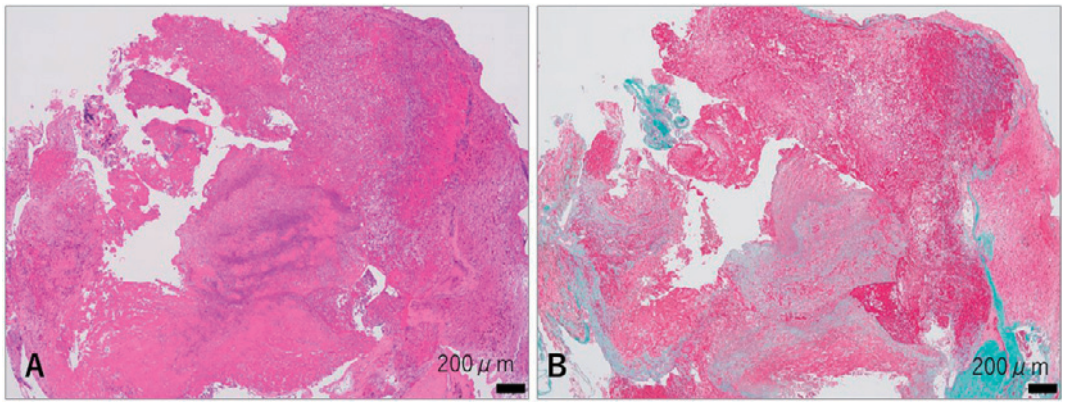

Fig. 3 Pathological findings. A, Hematoxylin-eosin stain shows hematoma. B, Elastic tissue-Masson stain revealed no elastic fiber structures.

Table 1 Hematomyelia during DOAC administration. N/A: not applicable

Author	Age	Sex	DOAC	Spinal level	Renal dysfunction	Treatment
Park, 2023[15]	63	Male	Rivaroxaban	N/A	N/A	Steroid pulse
Verma, 2021[14]	58	Female	Apixaban	T3-T5	–	Blood pressure control
Present case, 2023	78	Male	Rivaroxaban	T9	+	Surgery

the hematoma mimicked hemangioma. Pathological findings include the simple hematoma without elastic fiber structure indicating the presence of hemangioma (Fig. 3), which led to the diagnosis of hematomyelia. His symptoms did not improve after surgery; he was then transferred to another hospital for physical rehabilitation.

The patient provided consent for this case report.

Discussion

Intramedullary hemorrhage of the spinal cord is a rare but serious condition that is often associated with spinal cord tumors[1,2] arteriovenous shunts,[3] or traumas.[4] Although it is very rare, idiopathic spontaneous hematomyelia have been reported.[5] Hida et al. described a case of intramedullary hemorrhage caused by hemangioblastoma,[6] and Tsujino et al. reported cases of ependymoma and cavernous malformations,[7] whereas Lemmen et al. reported a case of intramedullary malignant teratoma. Iampreechakful et al. presented a case of intramedullary hemorrhage in a lumbosacral epidural arteriovenous fistula.[8] Therefore, based on the majority of the previous reports, intramedullary hemorrhage is usually outlined as a tumor or arteriovenous shunt. However, it was negative in the present case because no obvious tumor components could be noted on preoperative MRI, intraoperative inspection, or pathological examination after surgery.

There have been only a few but multiple previous reports of hematomyelia associated with warfarin.[9-13] The safe therapeutic range of warfarin can be monitored using the INR, and vitamin K is usually administered to reverse to the normal range of INR.

Famularo et al. mentioned that compared with patients with intracranial hemorrhages due to anticoagulants, those with spinal hemorrhages are younger, less frequently have hypertension, receive warfarin alone more frequently, more commonly have a therapeutic anticoagulation level, and undergo surgical treatment more frequently.[11] In this review, four out of seven patients improved their neurological function in the surgically treated group.

This is the third reported case of hematomyelia associated with DOAC according to our review. Rivaroxaban and apixaban were used in the other two cases (Table 1),[14,15] and these cases were treated conservatively, which resulted in improved and left only mild neurofunctional disturbances. Both cases had no evident description of renal disturbance. This is the first case of hematomyelia surgically treated and obviously related to acute renal failure (ARF) with the onset of hemorrhage. After the initial onset of symptoms, the patient was diagnosed with spinal infarction, which caused his paraparesis, sensory disturbance, and bladder dysfunction to be severely affected. (modified McCormick Scale IV, Karnofsky Performance Status 20) At the time of referral to our department, no clear improvement could be achieved because of its severity even after our surgical interval.

In terms of DOAC-related spinal hematoma (SH), including epidural/subdural hematoma, Guerrero-Nino et al. and Ismail et al. reported and reviewed six cases of SH that the most of the causative agents were rivaroxaban (i.e., five of

the six cases, and only one with aspirin).[16,17] No special consideration was mentioned because rivaroxaban was involved in many of the cases but its relation is still unknown. Nonetheless, we may have to consider the DOAC selection for the patients of SH based on the 2019 American Geriatrics Society Beers criteria, which recommend cautious use of Dabigatran and rivaroxaban in patients with atrial fibrillation aged ≥75 years.[16] Moreover, apixaban has been suggested as a reasonable first choice either in older patients or in those with chronic renal failure. In our case, the age of >75 years and ARF (Ccr 15.17 mL/min, which is close to contraindication for the use of rivaroxaban) were considered to be the causative factors.

Moreover, notably, rivaroxaban itself can cause ARF. Marcelino et al. reported a case of an 82-year-old woman who received 20 mg of rivaroxaban once a day due to atrial fibrillation 2 weeks earlier, and she developed bilateral leg pitting edema in the lower limbs associated with weight gain.[18] Immediately after rivaroxaban was stopped, her renal function was improved. Based on their review of the literature, six cases have reported an association between rivaroxaban and ARF. Therefore, immediate discontinuation should be considered when ARF occurs during DOAC administration.

Conclusions

This is the first case of hematomyelia that was associated with DOAC and in which surgery of evacuation was performed. The patient was prescribed rivaroxaban 3 months before the onset and presented with transient ARF simultaneously. Hemorrhagic lesion should be strongly suspected in patients with ARF during DOAC administration.

Author Contributions

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Methodology: n/a
Project Administration: n/a
Writing-Original Draft: Iwasaki
Writing-Review & Editing: n/a

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Conflicts of Interest Disclosure

The authors have nothing to disclose.

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