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Paraplegia Caused by Spontaneous Spinal Hemorrhage in a Patient Undergoing Rivaroxaban Therapy

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Conflict of interest: None declared

Patient: Female, 82-year-old
Final Diagnosis: Spinal hemorrhage
Symptoms: Back pain • paraplegia • stool retention
Medication: —
Clinical Procedure: —
Specialty: General and Internal Medicine

Objective: Unusual clinical course

Background: Spinal hematomas can be post-traumatic, iatrogenic, or spontaneous. A spontaneous spinal hematoma is a rare finding, but one with very serious clinical implications. There are some risk factors linked to its occurrence, e.g. arteriovenous malformations, lumbar puncture, coagulopathy, neoplasms, or therapeutic anticoagulation. At present, only a few cases of spontaneous spinal hematoma (SSH) associated with new oral anticoagulants (NOACs) have been described, three of which were linked with rivaroxaban.

Case Report: We report the case of an 82-year-old Caucasian woman with persistent atrial fibrillation treated with rivaroxaban, who presented to the Urology Department with acute-onset back pain which was thought to be due to urolithiasis. No kidney stones were found, but her creatinine serum level was elevated, so she was transferred to our clinic for further treatment. During hospitalization she quickly developed paraplegia with urine and stool retention. MRI was performed, and demonstrated an acute epidural hemorrhage in her thoracic and lumbar spine. The neurosurgeons disqualified this patient from surgical intervention due to the extent of the hematoma and its location. The patient was referred to the Neurology Department for treatment and rehabilitation, but, to the best of our knowledge, she did not recover her motor function.

Conclusions: Although rivaroxaban has been shown to be more effective than warfarin in stroke prevention in patients with atrial fibrillation, physicians must remember that its use also carries the risk of major bleeding. SSH occurrence should be taken into account in a patient taking NOACs who develops paraplegia, even if there is no history of trauma prior to admission.

MeSH Keywords: Anticoagulants • Hematoma, Subdural, Spinal • Paraplegia

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Background

Spinal hematomas are quite an uncommon finding. In most cases, they are associated with trauma or medical intervention such as lumbar puncture [1]. Sometimes, however, no identifiable reason for occurrence of a hematoma can be seen, and that is when we classify it as spontaneous. Certain risk factors may contribute to developing a spinal hematoma, such as: coagulopathies, vascular malformations, therapeutic anticoagulation, or neoplasms [2]. Spontaneous spinal bleeding may occur in the subarachnoid, epidural, or subdural space, or in the spinal cord itself. Spontaneous spinal epidural hematoma (SSEH) occurs with an incidence of 0.1/100 000/year, which is still estimated to be four times more common than spontaneous spinal subdural hematoma (SSSH) [2,3]. To the best of our knowledge, there have been about 150 cases of SSSH described in the literature, most of them linked to warfarin use. Our case seems to be the fourth SSSH linked to rivaroxaban, a direct factor Xa inhibitor, since its initial approval for stroke prevention in patients with atrial fibrillation in November 2011 [3–5].

Case Report

An 82-year-old Polish woman was redirected to our department from the urology admission room, where she primarily presented with acute-onset back pain that was thought to be due to urolithiasis. No obstruction in the urinary tract was found in the abdominal ultrasonography performed there, but the laboratory tests showed elevated creatinine serum level [2.33 mg/dl with a glomerular filtration rate (GFR) of 19 ml/min], so she was admitted to our department, the Department of Nephrology. She had a history of diabetes mellitus type 2, stage 4 chronic kidney disease according to KDIGO guidelines, persistent atrial fibrillation, ischemic stroke, and myocardial infarction followed by coronary artery bypass graft. Her daily medication included i.a. rivaroxaban in a dose of 20 mg for stroke prevention. No other anticoagulant was in use, as her other medications were: nebivolol 5 mg 1-0-1/2, digoxin 100 mg 1×1 Monday-Friday, furosemide 40 mg 1×1, and insulin (Humalog Mix50/50) with a total daily dose of 18 units. She denied taking any other medications that are not listed above, including NSAIDs or over-the-counter supplements.

On admission, her main complaint was the back pain. Her other complaints were transient left lower extremity paresthesia, abdominal discomfort, and an episode of vomiting a few hours before admission. We decided to repeat the abdominal ultrasonography in our unit. It showed some small gallstones in the gallbladder and a 7-mm cyst in the right kidney cortex. The liver, spleen, pancreas, left kidney, and urinary bladder were normal. As no clinically important deviations were found by abdominal ultrasonography, we decided to perform a lumbar spine X-ray even though she denied trauma history. It showed advanced osteoarthritis of the spine, but there was no sign of injury. A chest X-ray also showed no abnormalities, besides osteoarthritis and changes secondary to coronary artery bypass graft surgery.

The physical examination at admission showed features of moderate dehydration and completely irregular heart rate. There were no obvious neurological deficits.

Among the laboratory tests conducted on admission, only elevated plasma creatinine and urea levels (2.33 mg/dl and 152.3 mg/dl, respectively) were notable. Other laboratory parameters were: WBC=6.73 g/l, RBC=3.43 T/l, HGB=6.6 mmol/l, HCT=0.328, MCV=95.6 fl, PLT=187 g/l, CRP=1.23 mg/dl, APTT=38.3 s, PT=21.6 s, INR=1.92, ALT=32 U/l, AST=40 U/l. The patient was admitted to the hospital with a diagnosis of exacerbation of chronic kidney disease (CKD), most likely caused by dehydration. The patient was given tramadol as a painkiller and i.v. fluids for proper hydration, as well as her regular daily medication as stated above.

On the second day of hospitalization, the patient reported muscle weakness in both lower limbs. The physical examination at that time found muscular strength of the right lower limb to be 0/5 and left lower limb 1/5; there was no reaction in the indicator muscles. Sensitivity to the touch was preserved, with mild hyperalgesia (the patient felt the touch as a burning pain stimulus). In laboratory tests, a transient increase in CRP to 45 mg/dL appeared. After a neurological consultation, an MRI of the thoracolumbar spine (C5–S3) was performed, which showed multilevel hemorrhage. At the Th9 level, the spinal canal had narrowed to 8 mm (Figure 1A–1C). At the L5–S2 level, an intraspinal pathological mass measuring 49×12×9 mm was seen (Figure 2A–2C). MRI of the thoracic and lumbosacral region was performed with a GE SIGNA 1.5T device. T1-dependent, T2-dependent, and STIR images were obtained, as well as FSE T1-dependent images after 14 ml of Clariscan™ administration. The differential diagnosis the neurologist took into account before the MRI was Guillain-Barre Syndrome, but, with the MRI result described above, there was no need for further assessment with electromyography. The patient was brought to our neurosurgeons for urgent consultation. Unfortunately, she was disqualified from surgical drainage, as the size and abdominal location of the hemorrhagic lesions made their safe removal unlikely. There was a concern that surgical intervention would not bring the expected improvement, and could only aggravate neurological deficits. The patient was referred for further treatment and rehabilitation to the neurology department of the local hospital. Following the information acquired from the family, no improvement in the patient's motor function has been achieved so far.

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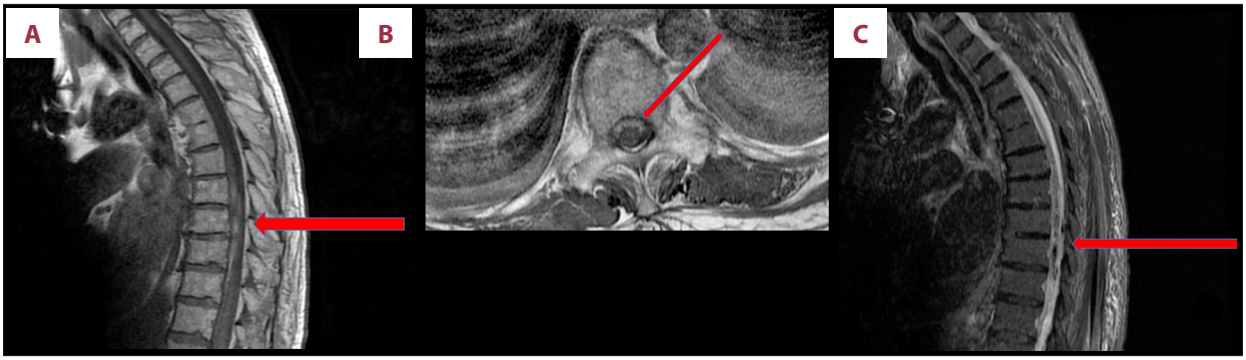

Figure 1. (**A–C**) Features of acute bleeding in the thoracic spine, visible at the Th7-Th11 level. The changes were the most widespread at the Th9 level, where they narrow the spinal canal to 8 mm, which corresponds to absolute narrowing of the spinal canal. (**A**) T1-dependent sagittal image; arrow denotes weakly textured pathological masses in the ventral part of the spinal canal, probably intrathecal. Their signal and lack of contrast suggest acute hemorrhagic changes. (**B**) T1-dependent transverse image, at level Th8. Notice the lighter color in the ventral spinal canal, indicating the presence of blood (arrow). (**C**) STIR sagittal image showing dark signal intensity indicating hemorrhage (arrow).

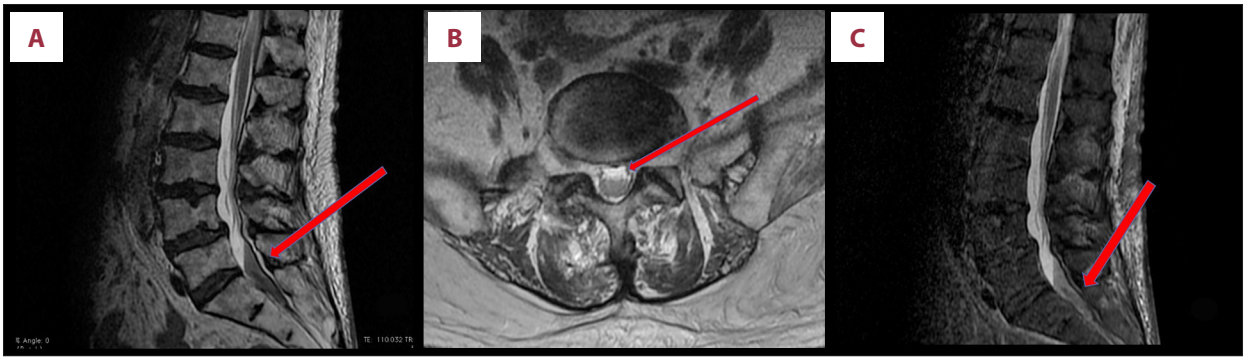

Figure 2. (**A–C**) Notice features of acute bleeding in the lumbosacral spine at the L5–S2 segment. (**A**) T2-dependent sagittal image; arrow denotes an intrathecal pathological mass measuring 49×12×9 mm (hypointense in the image). (**B**) T2-dependent transverse image, at level L5/S1. Notice the hyperintense signal of blood (arrow). (**C**) STIR sagittal image showing an intrathecal pathological mass at the L5–S2 segment of the spinal cord (arrow).

Discussion

According to all available literature, the most common manifestation of spinal hemorrhage is sudden, severe back pain and progressive muscle weakness. SSSH mostly occurs in the thoracic spine. Other locations are the lumbar and, rarely, cervical spine [6]. In the presented case, the occurrence of severe, stabbing pain in the lumbar region was initially taken as a sign of urolithiasis, and this delayed the implementation of further treatment.

There are two treatment options for SSH. The first is laminectomy and hematoma drainage, and the second is conservative management, which may be successful in patients with minor neurological deficits. Based on the available literature, the success of interventional treatment largely depends on the time elapsed from the onset of neurological symptoms to neurosurgical intervention, clinical manifestation at admission, and excess of bleeding [7,8].

New oral anticoagulants (NOACs), unlike warfarin, do not have as many interactions with food and other medications and do not require routine monitoring of international normalized ratio (INR). Their mechanism of action is centered on inhibition of specific points in the

coagulation cascade, for example factor Xa, of which rivaroxaban is a direct inhibitor. Factor Xa is a catalyst for the conversion of prothrombin into thrombin. Thrombin, in turn, converts water-soluble fibrinogen into insoluble fibrin, which leads to the formation of a clot.

Rivaroxaban is eliminated as follows: 2/3 is metabolized by the liver and 1/3 is excreted in its active, unchanged form by the kidneys [9]. It is important to note that patients with severe renal dysfunction (with eGFR lower than 30 ml/min) were excluded from all phase III clinical trials of rivaroxaban. Our patient presented with an eGFR of 20 ml/min. We suggest that, in patients with renal insufficiency, rivaroxaban should be used

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with high caution due to delayed drug elimination [10]. Our patient also had an INR of 1.92, but it is worth noting that INR is not useful in patients taking NOACs, as this ratio is only standardized for coumarins. Clinicians should only expect longer prothrombin time (PT) and activated partial thromboplastin time (APTT), as these are both dose-dependent. Although we did not determine factor Xa activity in this case, it could be presumed that the reason for spontaneous bleeding into the meninges was exacerbation of kidney disease, and thus an increase in blood anticoagulant levels. According to rivaroxaban's Summary of Product Characteristics for Xarelto, no interactions between rivaroxaban and any of the drugs taken by the patient (listed above) are known. Also, none of the patient's chronic diseases are known to affect coagulation. The drugs that are known to interfere with rivaroxaban metabolism, thus affecting hemostasis, are azole antifungals and HIV-protease inhibitors. Other drugs, like NSAIDs or antiplatelet agents, should be used with caution and avoided when possible.

Although there is no clear contraindication for using rivaroxaban in older patients, most of the available literature assessing its safety profile, including final clinical trials of the drug, includes patients up to 76 years of age. The drug's half-life can be up to 50% longer in elderly subjects than in younger subjects [9,10]. Our patient was 82, and this factor might also alter the pharmacodynamics. As no other clear reason for hematoma occurrence can be seen in this case – no history of trauma or lumbar puncture, no drug interactions, no neoplasms, no liver insufficiency – we concluded that the case was directly linked to rivaroxaban use. Each patient should be assessed for the risk of ischemic complications using the CHA2DS2-VASc scale and the results should be correlated with the sum of points obtained on the HAS-BLED scale, assessing the risk of serious bleeding in patients with non-valvular atrial fibrillation [11]. Our patient's score of 7 points on the CHA2D2S2-VASc scale (age >75 years, diabetes, history of stroke, history of myocardial infarction, female sex) is associated with a bleeding risk of about 9.6% per year. On the HAS-BLED scale, her score was 3 points (episode of stroke, chronic kidney disease with creatinine level above 2.2 mg/dL and age >65 years), which is associated with a high risk of bleeding (about 5.6% per year). In this case, statistically, the benefit of anticoagulant treatment outweighs the risk associated with it. However, the use of the maximum possible dose of 20 mg (the recommended dose for stroke prevention in patients with persistent atrial fibrillation) in a patient over age 80 with stage 4 chronic kidney disease raises doubts about the real safety of this scheme. In such patients, it seems reasonable to use lower doses of rivaroxaban, in light of how easily glomerular filtration rate deteriorates as a result of dehydration. In the elderly, the activity of the thirst center in the brain decreases, which leads to intravascular volume decrease and impaired renal flow. With deteriorating renal function, rivaroxaban clearance slows, and the AUC can be over 1.6-fold higher in subjects with eGFR of less than 30 ml/min. [9]

Conclusions

Clinicians should be aware of the possibility of SSH occurrence in patients treated with NOACs [12,13], despite widespread opinions about their safety. In this group of patients, if sudden, severe pain and paraplegia appears, major spinal bleeding should be urgently ruled out, as outcome depends on the patient's neurological status and time from onset of symptoms to surgical intervention. In addition, the increased risk of major bleeding in older patients with severely impaired renal function should be borne in mind. In our opinion, practitioners should consider lowering rivaroxaban dose for preventing stroke in non-valvular atrial fibrillation from 20 mg to 15 mg in patients with severe renal impairment, when possible [9].

Conflict of interest

None.

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