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Macrohematuria in the Course of Rivaroxaban Therapy: A Case of Bladder Tumor

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Abstract

Background: Rivaroxaban is a directly acting, oral anti-coagulant (factor Xa inhibitor) which is used to treat and prevent the formation of blood clots. A common side effect of this drug is an increase in bleeding tendencies, which can potentially lead to macroscopic hematuria. However, it is important to note that macroscopic hematuria can appear in several other conditions including urological malignancies. The Case: We report a case of a 69-year-old male patient with a history of myocardial infarction undergoing long term Rivaroxaban therapy, presenting with macroscopic hematuria and frequent urination. The clinical history and presenting symptoms were consistent with the side effects of prolonged use of Rivaroxaban, but further investigations revealed the presence of a tumor in the bladder which was instead found to be the cause of macroscopic hematuria. The conclusion: Although macroscopic hematuria is a very common side effect of Rivaroxaban therapy, it is important to consider other conditions which can present with the same symptoms.

Keywords

Macroscopic Hematuria, Rivaroxaban, Urological Malignancies (Source: MeSH, NLM)

1. Introduction

Rivaroxaban is an oral anti-coagulant that has been approved by the U.S. Food and Drug Administration (FDA) for secondary prevention after acute coronary syndrome [1]. It's a non-vitamin K antagonist that selectively inhibits factor Xa. As it does not require routine check-ups to adjust dosage according to coagulogram monitoring and checking of the International Normalized Ratio (INR), it

can be more convenient for the patient [2]. Anti-Xa agent rivaroxaban doesn't require laboratory testing for dose adjustment [3].

One of the most common side effects of using this drug is macroscopic hematuria [1] [4]. But there are several other conditions that can present with macroscopic hematuria, such as urological malignancies including Bladder Cancer. Recurrent macroscopic hematuria presents with a multitude of differentials. One of the most common causes is urinary tract infection and urinary tract stones, but these typically present with pain. It also may be the only sign of an underlying urological malignancy. It isn't rare for patients on anticoagulant therapy to have visible hematuria [5]. Macroscopic hematuria may be present in benign causes such as benign prostatic hyperplasia, urinary tract calculi and urinary tract infections [6].

Bladder cancer is the tenth most common cancer worldwide and the most common cancer of the urinary tract [7]. The most predominant presenting symptom in 80% of patients is hematuria, which is usually gross, painless and intermittent in nature [7]. Some of the independent risk factors for the presence of bladder cancer include male sex, advanced age or age over 60 years and macrohematuria. Bladder cancer is the most frequent urological cancer to be diagnosed in patients presenting with visible hematuria [8].

Although hematuria is a frequent presentation in patients undergoing anti-coagulant therapy, especially in patients taking Rivaroxaban [2], it is usually considered to be less severe than other life-threatening complications following the utilization of these drugs such as intracranial hemorrhages, gastrointestinal bleeding etc [9]. As such, the population of patients on anti-coagulants who present with hematuria as their only complaint are usually considered to be medication induced and further diagnostic evaluations are not always performed. Due to the less severe nature of this complication, there is little existing literature solely focused on hematuria in patients taking anti-coagulants.

This report outlines the case of a patient on long term rivaroxaban therapy who developed macroscopic hematuria, not as a consequence of the medication but rather due to bladder cancer. Even though anti-coagulation therapy induced hematuria is common, this report serves to highlight the importance of considering other urological conditions that may present similarly.

Written informed consent was obtained from the patient and the CARE framework was followed in the drafting of this case report.

2. The Case

A 69-year-old man presented to the nephrological department with fluctuations in blood pressure, frequent urination and brown urine. Deterioration of health had started three days ago. The patient has a past medical history of type 2 Diabetes Mellitus, Arterial Hypertension, Coronary Artery Disease complicated by Myocardial Infarction (in 2018) for which he has undergone coronary artery bypass grafting as well as stenting of the coronary artery. A family history of oncological diseases is absent. The patient has no relevant psychosocial history.

On a daily basis, he takes Valsartan 80/12.5mg two times a day and Bisoprolol 2.5 mg once a day as an antihypertensive medication. Metformin 1500mg per day for control of diabetes, Rosuvastatin 20mg per day as a lipid lowering agent and Molsidomine 2mg a day for stenocardia is also taken. Rivaroxaban 20mg per day was taken for anti-coagulation purposes for about 7 months at the time of admission.

Upon examination of the patient, he was conscious and alert, with a rhythmic pulse of 78 beats per minute. The respiratory rate was 17 breaths per minute, blood pressure was measured as 130/80 mmHg, and oxygen saturation of 97% in room air. He has a hypersthenic body constitution with a BMI of 38.7 (Obese class II). No lymphadenopathy was noted. Lung sounds were clear, and heart sounds were muted and rhythmic upon auscultation. Renal angle tenderness was absent. The rest of the examination yielded no significant findings.

Upon admission, Rivaroxaban was discontinued due to the suspicion that the patient's hematuria was a result of this drug. It was subsequently replaced by Aspirin. Aspirin, an antiplatelet agent, was recommended as studies show lesser complication-related hematuria [9]. Based on the patient's age and probability of having another life-threatening cardiac event in the future, Aspirin was considered to be the suitable drug to treat the patient until a proper diagnosis was made, and Rivaroxaban-induced hematuria was either confirmed or disregarded. The patient was catheterized using a Foley catheter and urine output was monitored. Haemorrhagic admixture was still noted in the urine with no improvement despite the change in medication.

Hematological investigations were performed, revealing increased Erythrocyte Sedimentation Rate (ESR) and Normocytic Normochromic Anemia. Biochemical Analysis showed a markedly elevated C-Reactive Protein and increased Uric acid. Urinalysis revealed a dark yellow colored urine, decreased pH and the presence of epithelial cells. Coagulogram results were within normal limits (**Table 1**). Although the patient complained of frequent urination, his diuresis was within normal limits.

Table 1. Relevant laboratory findings of the patient.

Category	Laboratory Test	Results
Complete Blood Count	Red Blood Cells	8.4 × 109/l (4 - 9 × 10^9/l)
	Hemoglobin	110 g/l (130 – 170 g/l)
	Hematocrit	34.5% (35% - 50%)
	Mean Corpuscular Volume	86.9 fl (82 - 92 fl)
	Mean Corpuscular Hemoglobin Concentration	319 g/l (320 – 360 g/l)
	White Blood Cells	8.4 × 10^9/l (4 - 9 × 10^9/l)
	Platelets	185 × 10^9/l (150 - 450 × 10^9/l)
	Erythrocyte Sedimentation Rate	18 (2 - 10)

Continued

Biochemical Analysis	Total Protein	64 g/l (65 - 85 g/l)
	Uric Acid	0.53 mmol/l (0.2 - 0.42 mmol/l)
	Low Density Lipoprotein	0.91 mmol/l (>1.42 mmol/l)
	C-Reactive Protein	21.2 mg/l (0 - 6 mg/l)
	Blood Glucose	6.9 mmol/l (3.5 - 6.2 mmol/l)
Urinalysis	Colour	Dark Yellow (Yellow)
	pH	5 (5.5 - 7)
	Epithelial Cells	3/hpf (<3/hpf)
Coagulogram	Activated Partial Thromboplastin Time	25.9 seconds (20.9 - 30.3 seconds)
	Prothrombin Time	11.4 seconds (9.7 - 11.8 seconds)
	International Normalised Ratio	1.05 (0.8 - 1.2)

Relevant instrumental investigations included ultrasound which showed the presence of a hypoechoic formation (41 × 37 × 40 mm) with clear, uneven contours along the posterior wall of the bladder. Slight prostate enlargement was also noted and was confirmed to be Benign Prostatic Hyperplasia (BPH) Grade II.

Other differential diagnoses considered were macroscopic hematuria caused by BPH but as Prostate Specific Antigen was within normal levels (1.1 ng/ml; normal levels should be 4.0 ng/ml and lower), this diagnosis was excluded.

Echocardiography of the heart as well as ultrasound of pleura, pleural cavity and brachiocephalic arteries was also performed and revealed no abnormalities.

Further investigation using Multi-Slice Computer Tomography (MSCT) was performed to further visualize the formation discovered in the bladder in the Ultrasound imaging. MSCT revealed a hyperdense structure with uneven contours in the lumen of the bladder along the posterior wall that did not accumulate a contrast agent (Figure 1).

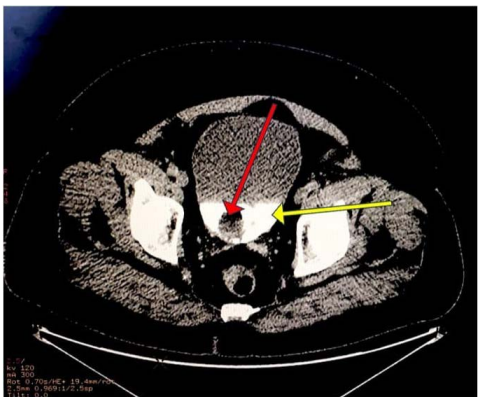

Figure 1. MSCT image showing a hyperdense structure (red arrow) along the posterior wall of the bladder. Yellow arrow points to surrounding urine.

The patient was recommended to undergo Transurethral resection (TUR) of the bladder as both a diagnostic and therapeutic intervention. The procedure involved the use of a cystoscope to visualize the bladder and remove visible tumors. Since a singular procedure could treat and diagnose without additional procedures, in a patient suspected of having a tumor, this procedure has the additional benefit of reducing the risk of spreading cancer cells while investigations are being conducted, thus containing the disease.

The formation confirmed by imaging studies was resected and sent for histopathological analysis and the result revealed the presence of a papillary urothelial carcinoma with low malignant potential (T1N0M0) (**Figure 2**).

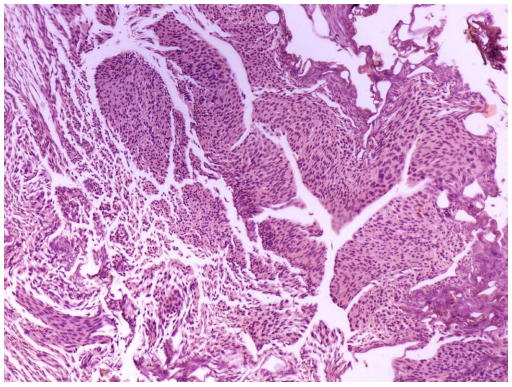

Figure 2. Histopathological analysis of the biopsied material, revealing a papillary urothelial carcinoma with low malignant potential (T1N0M0). (Zoom ×100).

The patient's post-operative condition was satisfactory, and he had no complaints. Some blood in the urine was noted in the catheter collection bag immediately following the procedure. This disappeared and the patient's urine was clear and light yellow by the second day. The patient was prescribed Amikacin as a post-operative antibiotic prophylaxis. The patient was discharged four days after the procedure, with recommendations for a follow-up with oncologist and instrumental testing in a month.

3. Discussion

Anticoagulants are widely being used to treat patients with cardiovascular diseases and macroscopic hematuria is one of the most commonly presenting complications of long-term use [2] [4]. It is also necessary to check for compliance and overdosing of the anticoagulants by the patients because improper use might precipitate complications such as hematuria. However, the fact that bleeding from the urinary tract can present with several other conditions such as bladder cancer [10], differentiating between these conditions can pose a diagnostic challenge.

As presented, there may be possibilities of overdosing. Thus, it requires you to pay attention to INR when a patient presents with hematuria. Boris Seryozhev Mladenov et al. conducted a study in relation to INR and macroscopic hematuria which shows that patient groups with INR > 4 on oral anticoagulants show a lower

incidence of urological etiology of hematuria. In the group of patients with INR < 4, more than 50% of the group was diagnosed with hematuria of urological etiology including urological malignancies, most commonly being bladder cancer.

Due to the prevalence of hematuria in patients undergoing anti-coagulant therapy and the diagnostic investigations specific for bladder cancer being limited and expensive [11], there are some studies suggesting that other conditions need not always be considered as a form of primary investigation for patients on anticoagulants [11]. According to several studies, there is a higher prevalence of urogenital tumors manifesting as hematuria in patients taking anticoagulant therapy in contrast to patients not on such therapy [8]. But there is no definitive knowledge on this, and more precise studies are required to come to an evidence-based conclusion.

The challenge presenting in this patient is the fact that hematuria due to anticoagulants and bladder cancer may both present as intermittent and the fact that this patient lacks specific risk factors for bladder cancer [12] [13]. The patient has no family history indicating cancer and does not smoke or abuse alcohol and, as such, there was no specific reason to suspect cancer, especially as he had no other symptoms suggesting it.

The patient having a T1N0M0 tumor, which is quite difficult to diagnose [13], made the process even more challenging. The need for further investigative techniques to be developed in order to diagnose this condition should be bought into awareness as bladder cancer rate is increasing with time [14] especially as it's a malignancy that, the longer it goes undiscovered and untreated, can invade other tissues and organs, making treatment harder and more complicated with more adverse effects.

There is no specific screening test for bladder cancer even in people with moderate-to-high risk. Therefore, it is important to consider the need for standard screens for early detection of bladder cancer.

There are some limitations with this case report as rivaroxaban is an anti-coagulant that was bought into clinical practice quite recently [1]. Further studies are needed to be able to determine the time taken for the development of hematuria on rivaroxaban therapy and statistics on whether it produces persistent or intermittent hematuria need to be investigated to ease the process of differentiating between rivaroxaban-induced hematuria and hematuria associated with other conditions. Patients on antiplatelet agents, specifically older medications (aspirin and warfarin) showed fewer complications related to hematuria [9].

As discussed before, although it isn't uncommon for patients on anticoagulants to present with hematuria, the incidence of the etiology to be of urological nature is lower than in the general population. Some studies suggest that the use of antithrombotic agents increases the likelihood or shows an increased proportion of diagnosed bladder cancer than those unexposed to these agents [9].

Another significant hurdle in diagnosing bladder cancer in patients undergoing anti-coagulant therapy is that one of the most common symptoms in early stages of this cancer is hematuria. Hematuria (especially when it is macroscopic) in

patients not undergoing anti-coagulant therapy, would be taken as a serious symptom and further investigations would be promptly conducted. However, in patients undergoing this therapy, such a symptom could be easily dismissed, leading to late diagnosis of cancer, which can have a potentially fatal outcome for this patient population.

4. Conclusion

Patients on long-term anticoagulant therapy presenting with bleeding from the urinary system are very common. Regardless, it's always necessary to eliminate other possible, more dangerous causes by performing a proper diagnostic assessment of hematuria before arriving at the conclusion that it is medication-induced. Also, not all patients will have typical risk factors for bladder cancer, much like this patient. It is important to always consider the possibility of such situations and careful evaluation of all patients is necessary.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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