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Rivaroxaban-Induced Acute Interstitial Nephritis: A Case Report

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Statistical Analysis C
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Patient: Male, 70
Final Diagnosis: Acute interstitial nephritis
Symptoms: Dark color urine, difficult voiding
Medication: Rivaroxaban
Clinical Procedure: —
Specialty: General and Internal Medicine

Objective: Challenging differential diagnosis

Background: Direct oral anticoagulant agents (DOACs) have become increasingly more popular in recent years and have largely replaced warfarin in the treatment of certain conditions, such as atrial fibrillation, and in the prevention of thromboembolic events. Rivaroxaban is one of the most commonly used direct anticoagulant drugs for conditions such as atrial fibrillation and thromboprophylaxis.

Case Report: We present a case of a 70-year-old male who developed acute interstitial nephritis after starting rivaroxaban, and who responded to medical treatment, which included corticosteroid therapy. A renal biopsy was not performed because the patient was on essential anticoagulation therapy secondary to a high CHADS2VASc score.

Conclusions: Dose adjustments when using rivaroxaban are necessary in patients with underlying renal failure. Acute interstitial nephritis is a rare condition associated with direct anticoagulant drugs. The treatment of acute interstitial nephritis is usually to remove the offending agent and treat the underlying cause.

MeSH Keywords: Anticoagulants • Drug-Related Side Effects and Adverse Reactions • Nephrology

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Background

In 1898, acute interstitial nephritis (AIN) was first described by William Thomas Councilman [1]. The third most common etiology of acute kidney injury during a hospital course is drug-induced AIN [2]. There are various etiologies of drug-induced AIN, but 70% of cases are due to antibiotics [3]. In addition to antibiotics, other drugs which are common causative agents include nonsteroidal anti-inflammatory drugs, sulfonylureas, thiazide and loop diuretics, and especially proton pump inhibitors nowadays [4]. Factor X inhibitors is a new class of drug that is gaining limelight in medicine as an effective alternative to warfarin due to better pharmacokinetic profile. There has been considerable increase in use of these oral anticoagulants including rivaroxaban in the past few years. Most common adverse effect of these drugs is bleeding and the less commonly reported adverse effects include liver and kidney injury, hypersensitivity reactions and leukocytoclastic vasculitis. In this case report, we are presenting a rare case of drug-induced AIN due to rivaroxaban.

Case Report

A 76-year-old Caucasian male with a past medical history of atrial fibrillation, pulmonary embolism (PE) s/p thrombolysis, essential hypertension, benign prostatic hyperplasia (BPH), and chronic kidney disease (CKD) stage-III was seen at his primary care physician (PCP) office and was referred to the emergency department (ED) with the finding of elevated creatinine. The patient had CKD due to hypertensive nephropathy, but his baseline creatinine was 2.5 mg/dL. The patient was originally started on anticoagulation with warfarin 1 year ago, after being diagnosed with atrial fibrillation and subsequently developing an episode of pulmonary embolism s/p thrombolysis. The patient had also developed a deep vein thrombosis (DVT) in the right lower extremity recently, despite being on warfarin, in the setting of a therapeutic INR. Because of this recent DVT, the patient's hematologist switched him to rivaroxaban about 1 week prior to his ED visit. The patient had noticed a decrease in urine output and dark colored urine for the past 4 days. He also reported mild shortness of breath, fatigue, and generalized itching but denied fever, chills, dysuria, hematuria, abdominal/flank pain, recent upper respiratory tract infection, NSAID use, polyuria or polydipsia. Initial vital signs were within normal limits. The physical examination showed a well-appearing elderly male with multiple scratch marks and a fine maculopapular rash on his upper and lower extremities bilaterally, and right lower extremity calf swelling associated with mild tenderness.

The patient was found to have a creatinine of 8.4 mg/dL and a glomerular filtration rate (GFR) of 6.23 L on admission. Potassium level was 5.2 mEq/L with no electrocardiogram (ECG) changes, likely secondary to renal impairment. A renal ultrasound was performed, which showed echogenic lobulated kidneys bilaterally with a benign simple cyst in the left lower pole with no evidence of hydronephrosis, scarring or atrophy.

Initially, there was suspicion for prerenal azotemia versus obstructive uropathy, so the patient was started on intravenous (IV) normal saline and a Foley catheter was placed. Despite these measures, the patient's creatinine failed to improve. A nephrology consultation was obtained. As per the nephrologist consultation, it was recommended that, as the patient had progressive acute worsening of renal function associated with a rash, there could be certain possibilities including antineutrophil cytoplasmic antibody/antinuclear antibody (ANCA/ANA) associated vasculitis versus AIN. There was a possibility of rivaroxaban as the culprit agent as the patient's symptoms began soon after initiation of this medication. Rivaroxaban was discontinued and further workup was ordered. ANA, C-ANCA, P-ANCA, C3, and C4 levels were all found to be within normal limits.

On the second day of hospitalization, urine eosinophils were checked, and the patient was found to have 2+ eosinophils in the urine. A diagnosis of acute interstitial nephritis was made, and the patient was started on methylprednisolone IV 125 mg twice a day. The decision to obtain a kidney biopsy for confirmatory diagnosis was discussed with the case consultants. It was ultimately decided not to discontinue the patient's anticoagulation at any point, due to his significant history of atrial fibrillation and venous thromboembolism (VTE). The patient reported improvement in his symptoms in the days following the initiation of methylprednisolone, and progressive improvement was seen in the patient's renal function and urine output. Methylprednisolone was given for approximately 4 days and was then de-escalated to prednisone 60 mg orally daily, and subsequently tapered off over a few weeks. The trend of renal function is described in Figure 1.

Although rivaroxaban was stopped, the patient required anticoagulation because of his history of atrial fibrillation and VTE. Heparin drip was started on the day of admission. Hematology was consulted, during the hospital admission, to provide a better recommendation regarding anticoagulation. Hematology recommended that anticoagulation be provided with warfarin and aspirin, or warfarin with a higher INR goal. The patient was eventually discharged in stable condition on warfarin with a higher INR goal of 2.5 to 3.5 as per hematology. The patient's INR on day of admission was 1.6 and on day of discharge was 2.6.

Discussion

Warfarin, in addition to other vitamin K antagonists (VKA), has long been a mainstay in the prevention of thromboembolic

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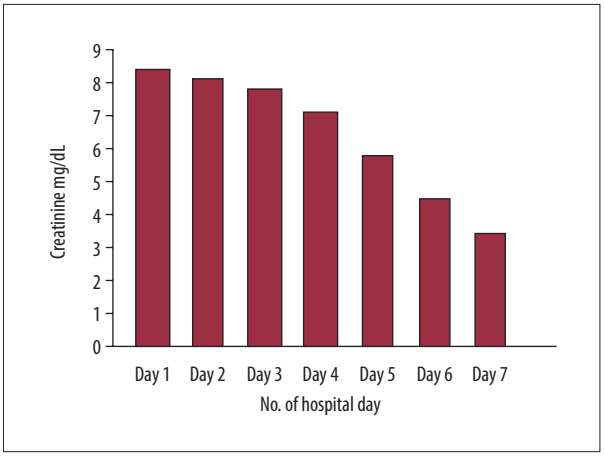

Figure 1. Trend of creatinine during hospitalization for acute interstitial nephritis secondary to rivaroxaban with subsequent improvement upon initiation of steroids.

events for over 50 years [5]. Various drug and nutritional interactions can occur while using VKAs, and frequent monitoring is often required, which subsequently leads to decreased patient compliance, predominantly in the elderly population [6]. These and other limitations have given rise to the alternative drugs in anticoagulation, resulting in direct oral anticoagulant (DOAC) drugs [7]. DOACs include certain medications which specifically inhibit thrombin, such as dabigatran, as well as those which directly inhibit coagulation factor X, such as rivaroxaban, apixaban, and edoxaban [7–10].

Approximately 10% to 15% of all cases of acute renal failure have been attributed to acute interstitial nephritis (AIN). Subsequently, more than half of those cases are drug-induced [11]. The effect of drugs causing acute interstitial nephritis is dose-independent, in which a single dose of a drug is enough to cause AIN [12]. The most common drugs associated with AIN are non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics, such as penicillin and sulfa drugs [3]. Other drugs, such as anticoagulants, have also been implicated in inducing AIN. VKAs, such as warfarin, have been associated with AIN regardless of the therapeutic levels of the drug. To date, there have been very few cases reported of AIN induced by other anticoagulant medications [13].

The pathophysiological mechanism behind drug-induced AIN is most likely due to either a type I or type IV hypersensitivity reaction (HSR) [14]. Type I is an IgE-mediated HSR which occurs after re-exposure to a specific drug. Type IV HSR also called delayed HSR, occurs 24 to 72 hours after exposure to the offending agent [4]. The most common organ involved in type IV HSR is skin, which manifests as urticaria and a maculopapular rash [15]. The second most affected organ is the kidney because of a predominance of lymphocytes in the renal interstitium [3]. Two essential mechanisms are involved in kidney damage. Because of high blood flow present in the kidneys, the kidneys are susceptible to this delayed hypersensitivity reaction where the antigen is processed and then secreted. The excretory function of the kidneys also plays a vital role in the development of the antigen-antibody response in the kidneys. The filtered antigens are endocytosed by interstitial cells, which function as antigen presenters to the dendritic cells. These dendritic cells then become activated and express the compound on their surface MHC-II molecule. These cells then migrate through the kidney lymphatic vessels, where the antigen is then presented to naive T cells. The recruited macrophages and fibroblasts initiate the inflammatory response, which is further increased by surrounding neutrophils and eosinophils [14].

The classical clinical presentation of drug-induced AIN is acute renal failure that begins shortly after initiation of the offending drug [12]. The initial appearance of clinical symptoms varies from days to weeks and depends on the patient's previous exposure to the offending agent. Symptoms typically begin 3 to 5 days after re-exposure [12]. The classic triad of fever, eosinophilia, and rash, which is usually associated with AIN, does not typically appear in drug-induced AIN [12].

As previously mentioned, rivaroxaban is one of the oral Factor Xa inhibitors which are frequently used in the prevention and treatment of thromboembolic events. The onset of action of this drug is rapid and usually does not require routine laboratory monitoring [7]. The most common side effect associated with rivaroxaban use is bleeding [7]. However, there have been only a few cases reported in which rivaroxaban was associated with rash [16] and drug-induced AIN [11]. In our case, the patient was started on rivaroxaban, and after the fifth day of initiating the offending agent, the patient was found to have increased creatinine levels, which led to the diagnosis of drug-induced interstitial nephritis. After discontinuing the offending medication, and starting steroids, the patient's creatinine improved to baseline.

Drug-induced interstitial nephritis should be suspected when there is an unexplained rise in serum creatinine after few days of initiating the offending drug [12]. Eosinophilia can also occur but has a low predictive value; therefore, its absence does not eliminate the possibility of drug-induced interstitial nephritis [12]. Renal biopsy is the gold standard in diagnosing drug-induced AIN; however, if the clinical suspicion is high, then it is not required [3]. In AIN, the kidneys are usually enlarged, pale and soft on gross examination [17]. Microscopically, an interstitial infiltrate can be observed, which is composed of inflammatory cells and lymphocytes causing edema, leading to the expansion of the interstitium [17].

The diagnosis of drug-induced AIN usually requires a renal biopsy in cases where there is no increased risk of bleeding from

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discontinuing the medication, unlike in our case. Anticoagulation with warfarin was continued, in our patient, because of active pulmonary embolism and atrial fibrillation. Therefore, a renal biopsy was not possible in our reported case.

The management of drug-induced AIN typically involves discontinuation of the offending agent [18]. The role of steroid treatment in drug-induced AIN remains controversial, and its efficacy has not been tested in randomized trials [19]. Early treatment within 5 days of diagnosis has been shown to reduce the development of interstitial fibrosis and to avoid incomplete recovery of renal function [20,21]. Chowdry et al. reported no difference in outcome between the use of IV versus oral steroids, as both are equally effective when used early. More severe complications, however, such as an increase in blood pressure was more apparent in the IV steroid group [18]. There is no definitive guideline regarding the duration of steroid therapy in the treatment of drug-induced AIN. However, 4 to 6 weeks of a tapered dose of steroids has been widely used [21]. Our case also demonstrated improvement in renal function after stopping the offending agent and initiating prednisone. Repeat renal function tests demonstrated complete recovery of the patient's renal function weeks after the initiation of steroid therapy.

Conclusions

Rivaroxaban was most likely the causative agent in our case based on the clinical and laboratory findings. A renal biopsy could have aided in providing a more definitive diagnosis, however, was considered high risk due to an increased risk of bleeding, as anticoagulation could not be stopped due to the patient's history of atrial fibrillation and DVT. Since rivaroxaban is now frequently being used, it is imperative to keep in mind this rare, albeit important, adverse effect of this DOAC. This case demonstrates the necessity of further research into this particular association, and will hopefully aid in better identifying at-risk patients, as well as developing a more favorable approach to managing these types of patients.

Disclaimer

The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

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