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Apixaban Induced Acute Interstitial Nephritis: A Case Report and Literature Review

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ABSTRACT

We report a case of biopsy-proven Acute Interstitial Nephritis (AIN) secondary to apixaban in an 83-year-old female presenting with severe acute kidney injury requiring hemodialysis. Kidney biopsy demonstrated tubulointerstitial nephritis with features of acute tubular necrosis. Cessation of apixaban and oral corticosteroid treatment for nine weeks led to near complete renal recovery. In this case report we discuss the association between apixaban and acute kidney injury and suggest possible mechanisms.

Keywords: Acute kidney injury; acute renal failure apixaban; Histology interstitial nephritis

INTRODUCTION

Acute kidney injury associated with Direct Acting Anticoagulants (DOAC) is an increasingly recognized entity. Injury to the kidney may be idiosyncratic such as acute interstitial nephritis, or a consequence of treatment, as is the case with glomerular hemorrhage causing Anticoagulant Related Nephropathy (ARN).[1,2] We report a biopsy proven case of acute interstitial nephritis, with features of ARN, in a patient receiving chronic apixaban treatment.

CASE REPORT

An 83-year-old non-English speaking Caucasian female, with background stage IIIb Chronic Kidney Disease (CKD) presented to a tertiary teaching hospital in Sydney, Australia with progressive functional decline, delirium and an incidental finding of Coronavirus (COVID-19) positivity. Clinical history from family, revealed a 10-day history of lethargy without nausea, vomiting or diarrhoea. There were no recent changes to regular medications and no history

of non-steroidal anti-inflammatory drug (NSAID), traditional Chinese medicine, herbal or over the counter medication use. Background medical history was significant for stage IIIb chronic kidney disease secondary to hypertension and vascular disease, Hypertrophic Obstructive Cardiomyopathy (HOCM) with septal myomectomy, previous multi-territory embolic cerebrovascular accident, atrial fibrillation, osteoporosis and thalassemia minor. Admission medications included apixaban 2.5 mg twice daily, metoprolol 50 mg twice daily, hydralazine 25 mg twice daily, amlodipine 5 mg daily, venlafaxine 150 mg daily, colecalciferol 25 mcg daily and risendronate 150 mg once weekly.

Clinical examination demonstrated hypertension with blood pressure of 145/78 mmHg and a regular heart rate of 90 beats per minute. Oxygen saturation was 97% without supplemental oxygen and respiratory rate was 18 breaths per minute. There was no fever. Cardio respiratory examinations revealed clear lung fields and euvolaemic fluid state. Abdominal examination was benign.

Initial biochemical investigations demonstrated stage 3 acute kidney injury (AKI)[3] with creatinine 1,272 umol/L and estimated glomerular filtration rate (eGFR) of 2 mL/min/1.73 m^2 from a baseline creatinine of 120 umol/L and eGFR 37 mL/min/1.73 m^2 five months earlier. Elevated anion gap metabolic acidosis (30 MEq/L) was noted, with pH 7.26, bicarbonate 12 mmol/L, sodium 133 mmol/L, potassium 5.6 mmol/L and chloride 91 mmol/L. Urea was elevated to 49.5 mmol/L. Inflammatory markers were elevated with total white cell count of 12.1 × 10^9 with neutrophilia and mild lymphopaenia (lymphocyte count of 0.7 × 10^9). Eosinophil count was 0.0 × 10^9 and C - Reactive Protein (CRP) was elevated at 93 mg/L. Microcytic anaemia was noted with hemoglobin of 114 g/L on and mean cell volume of 70 femtolitres. Platelet count was normal at 263,000. Urine studies demonstrated an elevated protein: creatinine ratio of 128 mg/mmol, microalbumin: creatinine ratio of 56.6 mg/mmol. Urine microscopy and culture showed leukocyturia and pure growth of Escherichia coli. Non-contrast computerized tomography demonstrated a right kidney measuring 6.6 cm and left measuring 8.7 cm with bilateral perinephric fat stranding and bilateral renal cortical cysts measuring up to 5.9 cm in diameter without evidence of nephrolithiasis or hydronephrosis.

Screening tests for glomerulonephritis including, Anti-Nuclear Antibody (ANA), extractable nuclear antibody (ENA), Anti-Neutrophil Cytoplasmic antibodies (ANCA) and anti-glomerular basement membrane antibodies (GBM) were negative. Complement levels were normal with C3 of 1.22 g/L and C4 0.42 g/L. Apixaban was ceased due to acute kidney injury but all other medications continued. Despite 48 hours of intravenous fluid resuscitation, parenteral antibiotics for urinary tract infection, kidney function worsened and kidney biopsy was performed. Histological examination (Figure 1) showed 15 glomeruli, two of which were globally sclerosed and the remainder normal. There were no crescents, endocapillary proliferation or tuft necrosis. There were areas of tubular dilatation, tubular epithelial dropout and attenuation with prominent casts including hyaline, red blood cell and granular eosinophilic casts as well as background mild tubular atrophy. The tubulointerstitial inflammation comprised predominantly of lymphocytes and scattered neutrophils. Arteries showed fibrointimal thickening with arteriolar hyalinosis. Immunofluorescence was negative for IgG, IgA, IgM, C3 C1q, fibrinogen, kappa and lambda. Electron microscopy showed no electron dense deposits or abnormal fibrils (Figure 2). There was approximately 80%

podocyte foot process effacement. Overall, the features were of tubulointerstitial nephritis with features of acute tubular necrosis and background changes of hypertensive disease.

Following kidney biopsy, intravenous methylprednisolone 250 mg was administered for three consecutive days. Following initial therapy, oral prednisolone 30 mg daily (0.5 mg/kg) was administered for 1 month and weaned by 5 mg every 7 days to cessation. Serum creatinine improved to 940 umol/L after 4 days of corticosteroid treatment however urea was elevated at 55 mmol/L and hemodialysis *via* tunneled vascular catheter was commenced for symptomatic uraemia. Haemodialysis treatment was initially required three times weekly, but this was progressively reduced with complete cessation 51 days after admission to hospital. Serum creatinine stabilized at 137 umol/L and eGFR 31 mL/min/1.73 m^2 following cessation of hemodialysis (Figure 2). Apixaban, which was commenced nearly 18 months earlier was suspected to be the culprit drug causing AIN and was permanently discontinued. Vitamin K antagonist warfarin was used for ongoing anticoagulation and all other medications were continued unchanged.

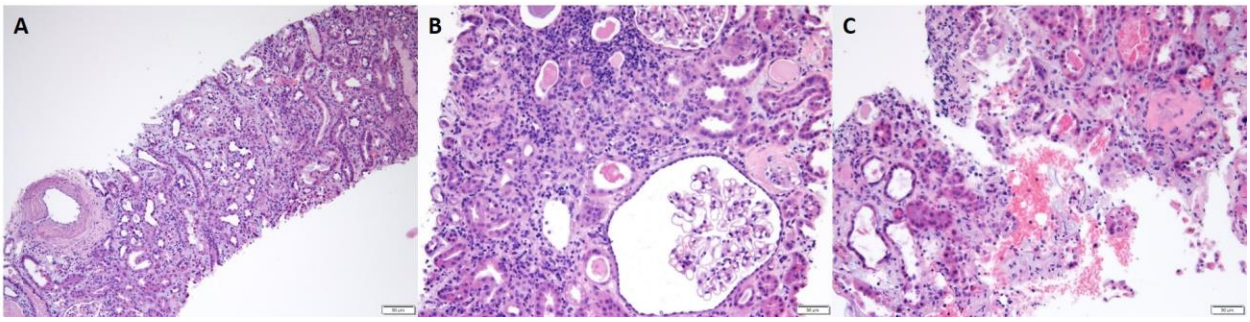

Figure 1: A). Low power view of kidney biopsy demonstrating fibrointimal thickening of artery and tubular changes including dilatation and attenuation of tubular epithelium. This is seen in higher power in Figure 1C. There is also interstitial inflammation. B). Higher power view of kidney biopsy. Casts (hyaline and granular eosinophilic) are prominent in the tubules as well as background interstitial inflammation composed of lymphocytes and scattered neutrophils. The glomeruli are normal. C). High power view demonstrating acute tubular necrosis, tubular changes including dilatation, epithelial attenuation and nuclear changes as well as prominent casts. Some tubules contain sloughed epithelium.

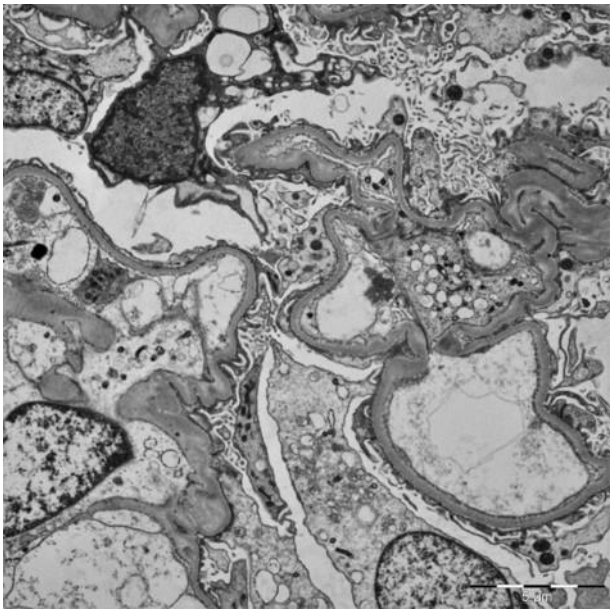

Figure 2: Electron microscopy showed capillary loops with no evidence of electron dense deposits or abnormal fibrils. There was approximately 80% podocyte foot process effacement.

DISCUSSION

We report a case of severe, biopsy proven, Acute Interstitial Nephritis (AIN) secondary to apixaban, requiring one month of hemodialysis and nine weeks of corticosteroid treatment. Interstitial nephritis in this case was likely the result of apixaban as no deterioration in kidney function occurred with continuation of all other medications. Apixaban is rarely associated with AIN and has been documented in only two previous reports.[4,5]

Acute kidney injury is well reported with use of other Direct Acting Anticoagulants (DOAC) including dabigatran and rivaroxaban.[1,6] In these cases, acute kidney injury manifested within days to weeks of initiation of treatment, however it is well known that drug induced AIN may be delayed by weeks to months.[7] Additionally, Anticoagulant-Related Nephropathy (ARN) is a known cause of acute kidney injury associated with DOACs with histologic features including intratubular hemorrhage, tubular red blood cell casts and tubular epithelial injury.[2] In addition to features of AIN, we identified red blood cells casts in our case suggesting features of ARN.

Acute interstitial nephritis accounts for approximately 15% to 30% of AKI cases, when kidney biopsy is performed.[7] Drug induced AIN is the most common aetiology, accounting for over 75% of cases.[7] Other causes of AIN include bacterial or viral infections, systemic inflammatory conditions or rarely idiopathic.[7]

Drug induced AIN typically presents with acute or subacute kidney injury. Clinical features are variable with only 5-10% of patients presenting with the classic syndrome of AKI, fever, rash and eosinophilia.[8] Patients may be asymptomatic, however, associated features may include malaise, anorexia, chills, flank pain, rash, myalgias and arthralgias.[8] The presentation is typically of a non-oliguric AKI of varying severity with up to one third of patients requiring dialysis.[9] Drug induced AIN is most commonly secondary to antibiotics including β-lactams,

sulfonamides, fluoroquinolones and rifampicin, other common causative agents include proton pump inhibitors and NSAIDs however numerous medications have been previously reported.[8-10] Acute interstitial nephritis is classically thought to develop 7 days to 10 days after drug exposure, though with repeat exposure it may occur more rapidly and in some cases may develop months after initial exposure to the drug.[8,9]

Drug induced AIN may be associated with mild proteinuria (< 1 g/day) and the presence of white blood cell casts is common.[8] Leukocyturia is common and may be present in over 80% of cases but haematuria occurs in less than 50% of patients.[7,8] Renal tract imaging can demonstrate normal to slightly-enlarged kidneys with increased cortical echogenicity.[8] Recovery from AIN is primarily dependent on the duration of kidney injury prior to cessation of the causative drug as scaring may develop and up to 40% of patients develop CKD.[7,8]

Direct Acting Oral Anticoagulants (DOACs) including apixaban represent an increasingly popular alternative to warfarin in patients with venous thromboembolism and atrial fibrillation.[11,12] These medications are eliminated by the kidneys, however there is growing evidence of safety and efficacy for use in patients with stage IV and V CKD. [13] Direct acting oral anticoagulants have previously been implicated in the development of AKI on their initiation and in the development of ARN.[14,15] Currently, there are two published reports of apixaban induced AIN. Firstly, Abdulhadi et al report a case of AIN secondary to Apixaban in a 76-year- old female with stage IV CKD that resolved with cessation of apixaban and treatment with 1 mg/kg prednisolone tapered over 14 days, though no kidney biopsy was performed.[4] In 2019, Di Maria et al published a case of a 70-year-old male with no history of kidney disease presenting with haematuria who was found to have AIN and features of IgA nephropathy on kidney biopsy. Importantly, AIN manifested after 12 months of treatment with apixaban.[5]

Drug induced AIN typically develops through a type-IV cell mediated immune response.[16] Injury occurs through numerous indirect drug-host interactions and direct damage may occur through parent drug or drug metabolite stimulation of innate immunity. In the case of apixaban causing AKI, the AIN is complicated further by the potential contribution of ARN which can cause tubular damage independent of the immune response. The mechanism of acute kidney injury in ARN is thought to a sequalae of glomerular hemorrhage with tubular obstruction from red cell casts and oxidative stress from degraded heme molecules leading to an inflammatory cascade.[14]

The role of corticosteroids in the management of drug induced AIN remains unclear, with current evidence suggesting it may promote earlier recovery in kidney function if initiated early.[8] There appears to be a stronger indication for steroid therapy in patients with more severe renal impairment. Oral prednisolone at a dose of 40 mg to 60 mg tapered over 1.5 weeks to 12 weeks may be used with consideration of an initial pulse of intravenous methylprednisolone.[17] Factors associated with non-recovery of kidney function include a delay in culprit drug discontinuation and a delay in initiation of corticosteroids. Higher dose or prolonged duration of corticosteroids beyond 8 weeks are not associated with renal recovery.[18] A current trial (PRAISE) comparing prednisolone 60 mg daily, tapered over 8 weeks compared with no treatment is in progress, with the primary outcome of eGFR at 3 months.[19]

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CONCLUSION

With the increasingly widespread use of DOACs, it is important that clinicians recognize the risk of developing impaired kidney function as a consequence. Due to the enduring nature of these treatments, apixaban should be considered alongside other DOACs as a cause AKI, particularly AIN and ARN even when treatment is chronic. Immediate drug cessation is critical to renal recovery. The role of corticosteroid treatment in AIN remains unclear and depends on patient characteristics, severity of kidney injury and perceived tolerability.

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