

NSAID associated bilateral renal infarctions: a case report

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Abstract: Renal infarctions (RIs) are caused by interruptions in the renal arterial blood flow. RIs are generally considered to be rare, however we present the case of a 37 year old woman whose renal infarction was likely due to the vasoconstrictive effects of non-steroidal anti-inflammatory drugs. Although high-dose non-steroidal anti-inflammatory drugs (NSAIDs) are known to cause a decrease in renal perfusion, they have not been accepted as causative agents in renal infarction. Theoretically, patients in prostaglandin dependent states should be more vulnerable to renovascular vasoconstriction and resulting hypoperfusion in the presence of NSAIDs. Given the high prevalence of NSAID use, we suspect that this mechanism of renal injury may be more prevalent than previously thought.

Keywords: renovascular, acute kidney injury, vasoconstriction, prostaglandins

Introduction

Renal infarctions (RIs) are induced by disruption of arterial flow to the renal parenchyma that could lead to persistent kidney dysfunction or herald underlying cardiovascular or hematological pathology. RI is relatively rare, as an emergency department (ED) study reported RI in 0.004% of visits.¹ In retrospective analyses, RI was defined as the result of an “acute disruption of renal blood flow in the renal arteries or their branches ...”, and diagnosed by radiological findings of wedge-shaped parenchymal deficits. From 438 patients diagnosed with RIs, 55.7% had a cardiogenic cause, 7.5% had renal artery injury, 6.6% were hypercoagulable, and 30.1% were idiopathic.² We argue that NSAIDs should be added as a potential cause of RI.

NSAIDs are commonly used drugs that are also associated with a wide range of adverse effects.³ Pharmacologically, NSAIDs inhibit cyclooxygenases necessary for the synthesis of prostaglandins (PGs). Human and animal studies suggest that NSAIDs can induce renal vasoconstriction in clinical states where vasodilatory renal PGs maintain renal blood flow.^{4,5} However, the role for NSAIDs in RI has not been widely reported. We present a case of a patient with bilateral renal segmental hypoperfusion and acute kidney injury (AKI) in the setting of significant NSAID use.

Case presentation

A 37-year-old Hispanic woman with a history of cholestasis during pregnancy presented with acute on chronic abdominal pain. She had been previously evaluated for chronic right upper quadrant (RUQ) pain and chronically mildly elevated liver

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function tests (LFTs) but had no sonographic evidence of cholelithiasis or choledocolithiasis. She experienced an acute worsening of her right-sided abdominal pain, prompting a visit to the ED. She was given a diagnosis of pelvic congestion syndrome after prominent variceal veins were noted within the pelvis on transvaginal ultrasound. She was given 60 mg of intravenous ketorolac tromethamine and discharged with ibuprofen 600 mg every 6 hrs as needed. She took ibuprofen three times per day for six days, but developed epigastric pain that diminished her appetite. She decreased her ibuprofen intake to 2 doses per day with acetaminophen. She was taking no other medications and denied herbal supplements. Her right-sided abdominal pain worsened and she developed new left-sided abdominal pain, prompting a second ED visit 7 days after the first.

She denied urinary symptoms, fevers, joint pains, rashes, history of miscarriages, or smoking history. Her blood pressure was 141/90, heart rate 76, and temperature 99.6°F. She had right costovertebral angle tenderness, diffuse abdominal tenderness (mostly RUQ) with voluntary guarding, but no rebound tenderness. ED lab work included urinalysis (UA), LFTs, basic metabolic panel, and complete blood count (CBC). UA was normal (specific gravity 1.003, negative protein, blood, leukocytes, and nitrite). LFTs showed stably elevated alkaline phosphatase

(126 U/L; normal 9–122 U/L) and alanine aminotransferase (42 U/L; normal 6–34 U/L). Her serum creatinine (Cr) was elevated compared to her baseline (1.73 mg/dL from 0.61 mg/dL). CBC was normal. CT abdominal pelvis with IV contrast (Figure 1) revealed multiple segmental wedge shaped areas of non-enhancement suggesting pyelonephritis or infarction. Patient was admitted for further assessment and monitoring. A kidney ultrasound with Doppler flows revealed patent renal arteries but bilaterally decreased vascular flow in the upper and lower poles of kidneys corresponding with areas of CT hypoperfusion (Figure 2 and Table 1). Urine culture and examination of urine sediment by microscopy were unremarkable, suggesting neither infection nor tubular necrosis. Hepatitis panel was negative and gallbladder ultrasound was normal. Telemetry and echocardiogram were normal. C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR) were elevated at 16.1mg/L (normal <3.0 mg/L) and 22 mm/hr (normal 0–20 mm/hr) respectively. An extensive rheumatologic lab work up was non-revealing. Lactate dehydrogenase (LDH) was normal at 219 U/L (normal 122–241 U/L).

The patient remained clinically stable. She received 2 liters of normal saline in the ED. Cr started to downtrend by the next day and patient's pain improved (Figure 3). The patient was not anti-coagulated and was discharged 3 days

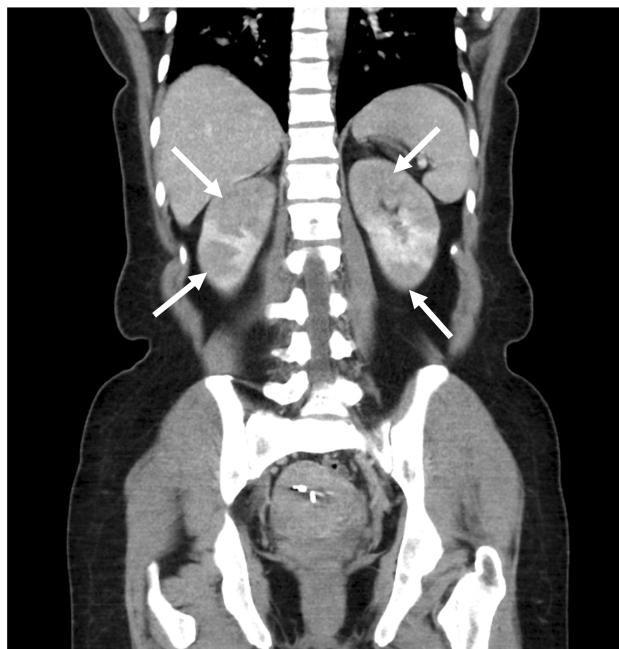


Figure 1 CT Scan of bilateral renal infarctions. CT scan of abdomen and pelvis with intravenous contrast (80cc of Omnipaque 350) showing wedge-shaped infarcts (arrows) of the bilateral kidneys.

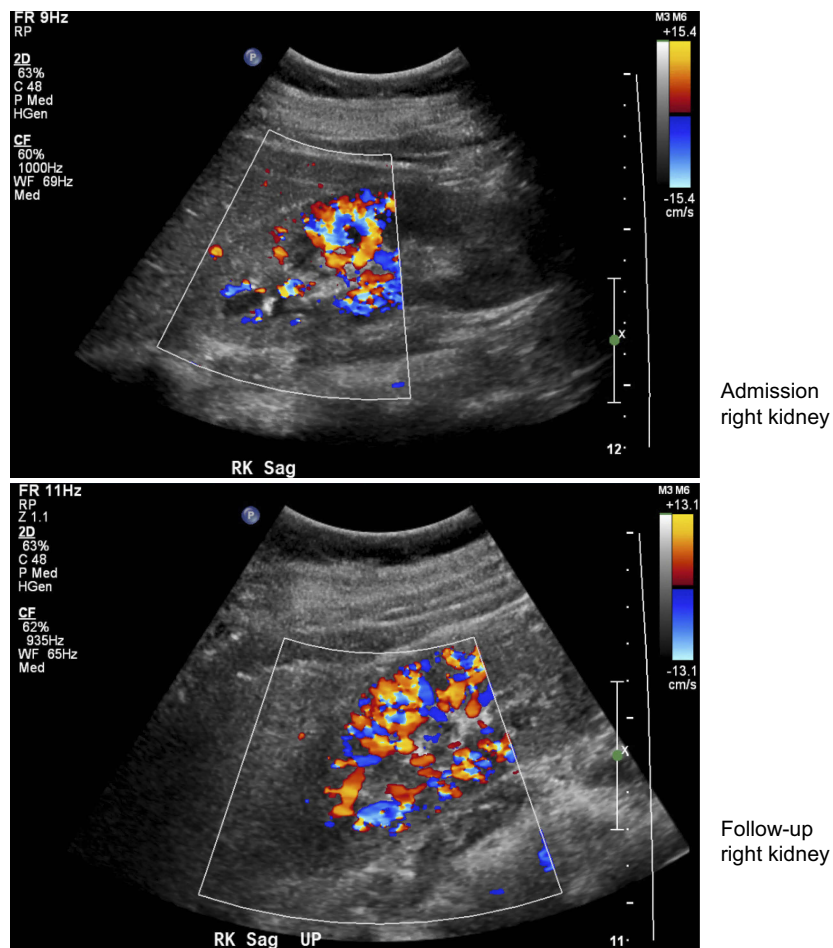


Figure 2 Kidney ultrasounds with doppler flow on admission and on follow-up.

after admission. Follow-up 14 days after discharge showed normalization of Cr, and a renal ultrasound with improved vascularity (Figure 2 and Table 1). Patient has been advised to avoid future NSAID use.

Discussion

This clinical case raises interesting questions about RI. Radiologically, pyelonephritis could present similarly. However, the patient showed no signs of infection, and this alternative diagnosis was dismissed early in her hospitalization. Like most RI patients, our patient had abdominal/flank pain, but our patient was significantly younger than the 60-year-old mean age reported. In the largest study of RI patients, only 20.9% had AKI, and laboratory abnormalities typically consisted of elevated LDH and CRP.² Although our patient had an elevated CRP, her LDH was normal. In our opinion, LDH is an important test in the evaluation of RI. LDH, which is present within all cells, is used as a marker for cell death. The lack of increased LDH and the lack of any signs of renal tubular damage in the

urine sediment suggested that there was minimal renal damage associated with the hypoperfusion seen by CT. In addition, her Cr rapidly improved with some volume resuscitation and holding of NSAIDs. Workup failed to identify any cardiogenic, autoimmune, renovascular, or hypercoagulability etiology. It is our opinion that her prominent radiological findings were due to a vasoconstrictive effect of her NSAID use prior to admission. This is supported by the rapid improvement in her Cr after NSAIDs were discontinued. We propose that NSAIDs should be recognized as a distinct non-thromboembolic cause of RI.

There has been one similar case reported in which a previously healthy Korean man presented with hypertension, bilateral flank pain, AKI, and CT showing bilateral wedge shaped hypoattenuation days after taking high dose NSAIDs.⁶ His work-up was also negative for other etiologies. He was treated conservatively, and his kidney function returned to baseline. Follow-up CT demonstrated improved perfusion. It was concluded that his clinical syndrome was due to NSAID related renal ischemia.

Table 1 Renal ultrasound measurements

	Admission	Follow-up
Right Kidney		
Resistive indices		
Upper pole	0.51	0.52
Middle pole	0.67	0.45
Lower pole	0.64	0.54
Peak systolic velocities (cm/s)		
Aorta Junction	78	121
Mid artery	83	123
Hilum	87	140
Left Kidney		
Resistive indices		
Upper pole	0.63	0.57
Middle pole	0.62	0.54
Lower pole	0.77	0.49
Peak systolic velocities (cm/s)		
Aorta Junction	64	107
Mid artery	96	111
Hilum	106	89

Transient renal hypoperfusion has been described in other clinical scenarios as well. Acute renal failure with loin pain after anaerobic exercise (ALPE) has been reported.^{7,8} CT in these cases demonstrate bilateral patchy wedge shaped hypo-attenuation with delayed persistence of enhancement in these same areas from the gradual resolution of vasoconstriction.^{7,8} It has been suggested that vasospasm of intrarenal vessels is secondary to non-myoglobin nephrotoxins or reactive oxygen species secondary to muscle injury, leading to ischemia, acute tubular necrosis, and loin pain.^{7,8} Our patient denied any strenuous exercise prior to admission.

Another syndrome of AKI related to NSAID intake is “syndrome of flank pain and acute renal failure after binge drinking and NSAIDs”.^{9,10} This syndrome has been reported in healthy patients who present with severe back pain and AKI after heavy ethanol consumption and NSAID intake. These patients saw resolution of pain and renal dysfunction with conservative therapy and intravenous fluids. Pathology was attributed to ethanol induced volume depletion creating a PG dependent state and NSAIDs induced loss of renal perfusion. Our patient denied significant alcohol intake.

NSAIDs have long been implicated in several renal pathologies. NSAID related renal dysfunction may be seen in 1–5% of all NSAID users, which given its common use, represents a significant clinical problem.¹¹ NSAIDs have been implicated in fluid and electrolyte imbalances, acute and chronic kidney injury, nephrotic syndrome, interstitial nephritis, and renal papillary necrosis.¹¹ NSAIDs reduce PG synthesis by inhibiting cyclooxygenase 1 and 2. PGs are synthesized locally in the kidney by the glomerulus and medullary interstitial cells.^{11,12} PGI₂, PGE₂, and PGD₂ mediate renal perfusion by decreasing vascular resistance.¹¹ Interestingly, inhibition of PG synthesis has little impact on healthy individuals.¹² However in PG dependent states, a patient may become vulnerable to NSAID related renal injury.⁵ In states of elevated adrenergic and renin-angiotensin-aldosterone stimulation, such as in hypovolemia, low cardiac output states, cirrhosis, or nephrotic syndrome, there is increased renal vasoconstriction which must be modulated by PG driven vasodilation to sustain normal renal blood flow.⁵ In these scenarios, blocking PG could lead to unopposed vasoconstriction and kidney ischemia. We suspect our patient was in a PG dependent state and developed NSAID induced renal vasoconstriction. She

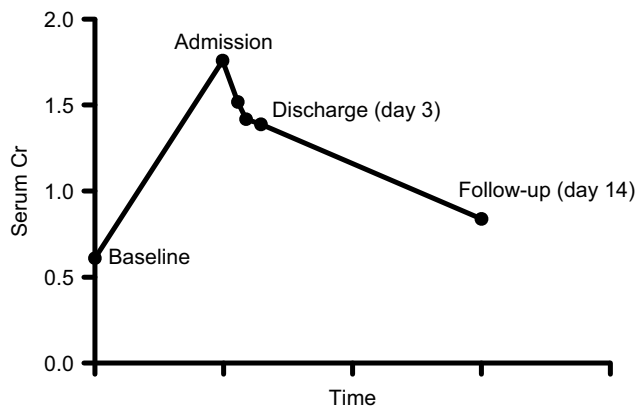


Figure 3 Graph of serum Cr including baseline, admission, hospital, and follow-up.

reported decreased oral intake of food due to epigastric pain that began after taking initiation of NSAIDs. This may have led to mild volume depletion. Alternatively, she may have underlying liver disease manifested as chronically elevated LFTs.

An interesting clinical question is whether such patients should be anticoagulated. In a case series, 81% of patients with RI were anticoagulated with heparin.² Our patient and the case previously reported did not receive anticoagulation when NSAID induced vasoconstriction was suspected. Although anticoagulation would not benefit transient vasoconstriction, it would be reasonable to begin the hypercoagulability work-up and initiate anticoagulation while other etiologies for RI were investigated.

Clearly, more clinical experience is needed to make informed decisions. Given how commonly NSAIDs are used, we suspect that the prevalence of NSAID induced RI is more than we previously appreciated. We therefore invite readers to share their cases of suspected NSAID induced RI (<http://bit.ly/NephNSAID>) so that we may assess them and report the results in a future report. As part of this investigation, we will evaluate whether normal LDH in the setting of radiological signs of RI is a distinguishing characteristic of NSAID induced RI.

Ethics

Written informed consent has been provided by the patient to have case details and accompanying images published. Further institutional approval is not required to publish de-identified case information.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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