Renal Microvascular Ischemia Secondary to Nonsteroidal Anti-inflammatory Drugs

Abstract
Nonsteroidal anti-inflammatory drugs (NSAIDs), widely prescribed for pain, can affect kidneys in various ways. We present a case of a 37-year-old woman with multiple NSAIDs intake over a short period for dysmenorrhea followed by the development of new-onset bilateral flank pain. Computed tomography revealed bilateral multiple renal infarcts. Renal function was normal. Investigations showed no cardiac or renal artery lesion and vasculitis work-up was negative. She was treated conservatively and further NSAID intake was avoided. Follow-up scan showed complete restoration of the blood flow in previously affected areas. Thus, microvascular ischemia secondary to NSAIDs was thought to be responsible.

Keywords: Microvascular ischemia, NSAIDs, renal infarct

Introduction
Nonsteroidal anti-inflammatory drugs (NSAIDs), widely prescribed for pain, can affect kidneys in various ways. Common lesions involve local hemodynamic alterations leading to acute kidney injury (AKI) that is readily reversible on stopping the drugs. Occasionally, this may culminate in acute tubular injury. Other lesions include interstitial nephritis, nephrotic syndrome with minimal change disease, and papillary necrosis. We present an uncommon manifestation of renal disease associated with NSAID use.

Case Report
A 37-year-old woman, diagnosed with diabetes mellitus since 8 months on metformin and a past history of renal calculus disease came to emergency department with complaints of acute severe colicky pain in both flanks, not radiating and not associated with hematuria, fever, chills, or dysuria. However, she had a history of dysmenorrhea for which she used to take multiple NSAIDs including mefenamic acid, diclofenac, and frequently both. Prior to presentation, she took mefenamic acid with ibuprofen-paracetamol combination for dysmenorrhea and had received intramuscular diclofenac 2 days before admission. The pain of dysmenorrhea subsided but was replaced with flank pain. On examination, she was afebrile, had regular pulse of 88/min, and a blood pressure of 136/86 mmHg with normal jugular vein pressure and no edema. She had bilateral lumbar tenderness in with other systemic examination being unremarkable. Other lesions include interstitial nephritis, nephrotic syndrome with minimal change disease, and papillary necrosis. We present an uncommon manifestation of renal disease associated with NSAID use.

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tests (ANCA) (both PR3 and MPO-ANCA) were negative while C-reactive protein and erythrocyte sediment rate were normal.

She was managed conservatively with opioid analgesics, intravenous fluids and advised to avoid NSAIDs in future. Renal function remained within normal limits. Follow-up CECT scan was done at 3 months which showed restoration of blood flow and contrast-enhancement in the previously affected areas [Figure 1c and d]. Thus, it was considered as reversible ischemia (rather than infarct) which appeared after NSAID intake and resolved with withdrawal of the drugs.

Discussion
Renal infarction is a rare disease with an incidence rate estimated to be 0.007% of all emergency department visits. It commonly presents as flank pain with or without hematuria. Nonspecific presentation often leads to delay in diagnosis and a high index of suspicion is necessary to arrive at this diagnosis which is usually made by CECT. Bilateral renal infaracts are less common than unilateral. Renal infarction has multiple causes: Cardioembolic (9% to 55%), renal artery lesion (7%–81%), thrombophilia (6%–16%) and others. It is noted that a significant proportion of patients (4% to 47%) may not have obvious cause and various case reports describe uncommon causes.

In our patient after ruling out cardioembolic and renal artery-related causes, medium-sized vessel ischemia was considered. Microvascular diseases leading to bilateral multiple renal infaracts have been described previously in literature with systemic vasculitis, recreational drug abuse, and polyarteritis nodosa. In our patient, hepatitis B surface antigen (HBsAg) was negative and none of the visceral arteries revealed aneurysm, making polyarteritis nodosa unlikely. ANA and ANCA were negative. In addition, the absence of history or active urine sediment and clinical improvement without a specific treatment argue against the diagnosis of vasculitis. Thus, a diagnosis of microvascular injury secondary to the NSAIDs was made.

Microvascular renal infarcts secondary to NSAIDs were described in two previous reports. Jeon et al. reported a 37-year-old woman with intake of ketorolac and ibuprofen followed by the development of bilateral acute renal infarcts and AKI. Extensive work up did not reveal any particular etiology and the patient improved without any specific treatment. Ultrasound done 14 days later showed improved vascularity in the affected areas, similar to our patient. Another report in Korean language described a 51-year-old man with the intake of multiple NSAIDs leading to bilateral renal infarcts. No other cause could be found. In this case also, follow-up CT showed improvement in the lesions.

NSAIDs can affect kidneys in various ways. However, severe renal microvascular constriction leading to reversible renal cortical ischemia is rarely described in literature. Prostaglandins (PG) are synthesized locally in the kidney using cyclooxygenase (COX) enzyme and they have an important role in maintaining afferent arteriolar vasodilatation in states with elevated renin-angiotensin-aldosterone system activity. Such states, viz., hypovolemia, chronic liver disease, severe nephrotic syndrome, diabetes mellitus, are PG dependent states, owing to the dependency of renal perfusion on local PG production. By inhibiting COX, NSAIDs reduce PG synthesis. This leads to the imbalance of vasodilators and vasoconstrictors favoring the latter. But neither our patient nor the other two reported patients were hypovolemic. Of note is the use of either combinations of NSAIDs or higher doses in all the three cases. Compared to previously described cases, our patient was normotensive and had normal serum creatinine.

In our patient, no cardioembolic and renal artery lesion could be found and ANA and ANCA were negative. We did not investigate our patient for thrombophilia as the history of NSAIDs intake was strong enough and was considered the likely cause for renal infarction. Though the association between renal ischemia and NSAID intake in our patient remains speculative, it seems the most likely explanation considering the improvement observed in CECT findings in the absence of an active treatment other than withdrawal of the offending drugs; Noranjo score = 4. The withdrawal of NSAIDs probably restores the balance between vasoconstrictors and vasodilators leading to the reversal of microvascular ischemia.

In conclusion, the use of multiple or high doses of NSAIDs appears to be a risk factor for severe ischemia leading to renal infarction.
Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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