

## CASE REPORT

## A rare case of lamotrigine-induced acute interstitial nephritis

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Medications, especially non-steroidal anti-inflammatory drugs and antimicrobials, have been most commonly associated with acute interstitial nephritis (AIN); antiepileptic drugs (AEDs) are rarely known to cause AIN. This is a case of a 27-year-old male who was recently started on treatment with lamotrigine for bipolar disorder and was found to have rapidly progressive renal failure. Renal biopsy features were suggestive of AIN. Lamotrigine-induced AIN was suspected to be the most likely cause. Discontinuation of the drug and treatment with steroids resulted in complete renal recovery. Lamotrigine use has been recently gaining popularity, not only as an AED but also as a mood stabilizer. With the use of this drug becoming more popular, it is important to emphasize that – although rare – AIN is one of its potential complications.

Keywords: *acute interstitial nephritis; antiepileptic drugs; lamotrigine; renal failure; bipolar disorder; steroids*

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Acute interstitial nephritis (AIN) is an acute inflammation of the renal interstitium accounting for 2% of inpatient acute kidney injury cases. The most common cause of AIN is usually medications (70–75%) (1). Non-steroidal anti-inflammatory drugs (NSAIDs) and antimicrobials are thought to be the most common culprits. There are several other causes of AIN, including infections and autoimmune systemic diseases (1, 2). Rare etiologies of AIN have also been reported, including antiepileptic drugs (AEDs).

Lamotrigine, an AED commonly used for mood disorders, can result in some serious reactions such as Stevens–Johnson syndrome and aseptic meningitis; however, it is not commonly known to cause AIN. Here, we present a case of biopsy-proven AIN induced by lamotrigine. To our knowledge, there are only three case reports in the literature about this rare complication of lamotrigine use (3–5).

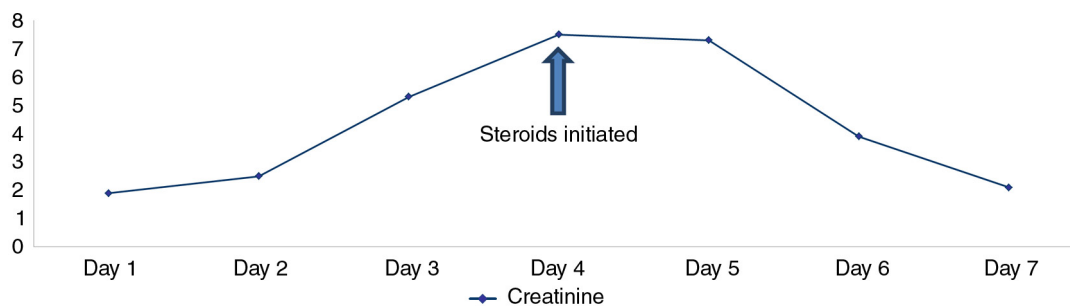
### Case presentation

A 27-year-old Hispanic male presented to our hospital complaining of headache, rash, and fever. The rash started a week before presentation and was followed by a generalized headache 4 days later. He visited an outside emergency room where he was diagnosed with a non-specific viral illness and was discharged with a prescription of ketorolac.

Two days later, he presented to this hospital with persistent rash and headache. His home medications included fluoxetine and lamotrigine for bipolar disorder. The dose of lamotrigine had been increased recently from 50 to 100 mg daily. Physical examination was positive for a fever (103°F) and a fine, erythematous, maculopapular rash on the hands, legs, and back. Laboratory studies included normal complete blood cell count, normal cerebral spinal fluid analysis, and elevated creatinine (1.9 mg/dl); creatinine had been 1.16 mg/dl 2 days before admission. Urinalysis was significant for 3+ protein, 2–5 red blood cells/hpf, 10–20 white blood cells/hpf, and 1–5 eosinophils/hpf. Urinalysis 2 days before admission was significant for 1+ protein. Head computed tomography was unremarkable.

In spite of adequate hydration, the patient's renal function continued to deteriorate, and serum creatinine peaked at 7.5 mg/dl on day 4 (Fig. 1). His urine protein/creatinine ratio was 3.3 mg/mg.

Autoimmune serology including complement levels, antinuclear antibodies, antinuclear cytoplasmic antibodies, and glomerular basement membrane antibodies was negative. Common viral infections including Epstein–Barr virus, cytomegalovirus, and human immunodeficiency virus serologies were all negative. A drug-induced systemic reaction was then suspected; fluoxetine and lamotrigine



**Fig. 1.** Graph depicting creatinine trend. The arrow points to the day when high-dose steroid therapy was initiated.

were discontinued. The patient underwent a kidney biopsy which was compatible with AIN (Fig. 2a and b). A skin biopsy of the rash was compatible with perifolliculitis and superficial perivascular dermatitis. Lamotrigine-induced AIN was the most likely diagnosis given the recent increase in dose.

High-dose methylprednisolone was initiated at the time of the kidney biopsy. His rash started to resolve, and his renal function improved over 3 days to a creatinine of 2 mg/dl. A repeat urinalysis was negative for proteinuria. Fluoxetine was resumed without any complications, and he was discharged on a taper of prednisone over 2 weeks. He was followed up a week later, and his rash had resolved and his renal function returned to baseline.

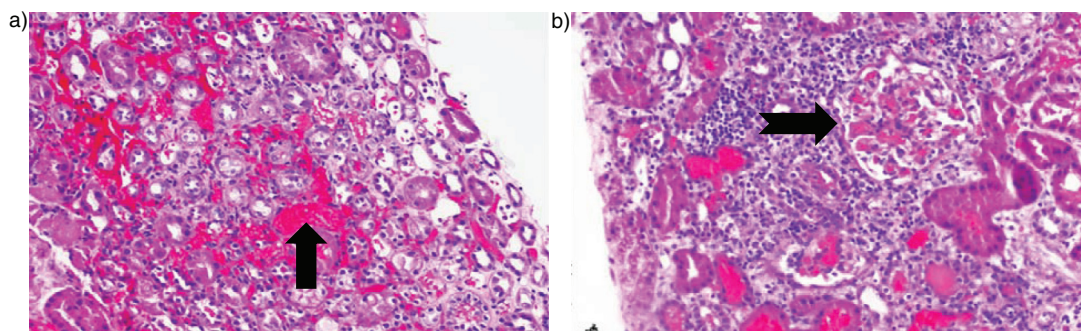
## Discussion

AIN accounts for 15–27% of renal biopsy findings in cases of acute renal failure (2). Interstitial inflammation with edema and tubulitis are the characteristic lesions of AIN. Cell-mediated immunity plays a major role in pathogenesis of AIN. A type-B idiosyncratic non-immunoglobulin-E-mediated immune reaction is suspected, especially in drug-induced AIN (6). The latent period between introduction of the offending agent and renal dysfunction onset ranges from 1 day to several months, with a mean of 10 days. Some non-renal manifestations such as fever, rash, and eosinophilia are seen in a small percentage of patients (2).

Lamotrigine is a novel antiepileptic agent with an incompletely understood mechanism of action. It most likely affects voltage-activated sodium channels, resulting in inhibition of the presynaptic release of the excitatory neurotransmitter glutamate (7). It is also widely used to treat bipolar disorder. Common side effects include nausea, dizziness, headache, and non-serious skin rash (8). Some uncommon yet life-threatening adverse effects of lamotrigine include Stevens–Johnson syndrome, toxic epidermal necrolysis, and aseptic meningitis (9, 10).

AIN is not a commonly encountered complication of lamotrigine use. To our knowledge, there have been only three reported cases of lamotrigine-induced AIN (3–5). This patient had been recently started on lamotrigine, and the dose was increased 2 weeks before the onset of renal failure. Once lamotrigine was discontinued and intravenous methylprednisolone was started, his renal function improved and was back to baseline within a week of discharge.

One might argue that ketorolac could have contributed to the patient's renal failure given that NSAIDs are one of the most common causes of drug-induced AIN (1). However, in NSAID-induced AIN, the latency period for development of renal impairment is usually several months (2, 11); furthermore, associated eosinophilia and/or eosinophiluria are less commonly seen (2). Finally, the patient developed proteinuria before his exposure to ketorolac,



**Fig. 2.** (a) H&E stain  $\times 100$ : Core biopsy showing a small focus of interstitial hemorrhage in the corticomedullary junction (pointed by the arrow). (b) H&E stain  $\times 200$ : Core biopsy showing renal cortex with diffuse interstitial inflammation consisting of mainly lymphocytes, plasma cells, and sparse eosinophils. A congested but otherwise unremarkable glomerulus (pointed by the arrow) and a cluster of proximal tubules, few of which contain red cell casts, can be seen in the background.

and his symptoms started a week before his exposure to ketorolac, which makes a reaction to NSAIDs less likely.

It is also interesting to note the similarities between this case and the previously reported cases (3–5). All the patients initially presented with fever, maculopapular rash, and generalized malaise. The onset of symptoms was around 4 weeks from the time of an increase in dose or the initiation of lamotrigine therapy. At the time of admission, they were all found to have elevated creatinine that was promptly followed by a rapid decline in renal function and oliguria; this prompted the renal biopsies which led to the diagnosis of AIN.

The treatment of lamotrigine-induced AIN is no different from any other drug-induced AIN. Identification and discontinuation of the offending agent is the first line of management (6). The use of corticosteroids in drug-induced AIN is controversial due to lack of randomized, prospective trials. Data from the retrospective studies have so far been inconsistent. However, considering the pathophysiology of AIN and its underlying immunological mechanism, one may argue that corticosteroids can be an effective treatment option (6). The timing of initiation of corticosteroid therapy, however, remains crucial. Data from two retrospective studies have shown that early initiation of steroid therapy helps in the recovery of renal function and also helps prevent progression to chronic renal failure (1, 12). In patients resistant or intolerant to steroids, the use of mycophenolate mofetil has shown to be beneficial (2, 6). One case report has also shown the resolution of AIN with the use of cyclosporine after failure of steroid therapy (13).

Despite the inconsistency in the available data, it is a common practice to use corticosteroid therapy in drug-induced AIN. In fact, in all the three reported cases of lamotrigine-induced AIN, corticosteroid therapy was initiated immediately following the biopsy results. However, two of the three cases required renal replacement therapy before complete renal recovery (3, 4). In this case, treatment was started before biopsy results became available but after other etiologies were ruled out. It is highly likely that early initiation of corticosteroid therapy hastened renal recovery and prevented progression of the disease.

## Conclusion

AIN is a rare side effect of lamotrigine. Early recognition of this complication and initiation of corticosteroid

therapy are critical to prevent progression to renal failure requiring renal replacement therapy.

## Conflict of interest and funding

The authors declare that they have no conflicts of interest concerning this case report.

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