Management of corticosteroid-dependent eosinophilic interstitial nephritis
A case report

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Abstract
Introduction: Drug-induced acute interstitial nephritis (DI-AIN) is an important cause of acute kidney injury. In renal biopsy specimens, tubulitis with eosinophilic infiltration is suggestive of DI-AIN. Although corticosteroid therapy and discontinuation of the offending drug can improve renal dysfunction in most cases of DI-AIN, some patients experience AIN recurrence, leading to corticosteroid dependency. Corticosteroid-dependent eosinophilic interstitial nephritis presents a difficult dilemma in diagnosis and information regarding optimum management is limited.

Patient concerns: A 25-year-old man, who received treatment with carbamazepine, zonisamide, valproate, and lacosamide for temporal lobe epilepsy, showed an increase in serum creatinine level from 0.98 to 1.29 mg/dL over a period of 6 months. Although he exhibited no symptoms, his serum creatinine level increased to 1.74 mg/dL.

Diagnosis: Renal biopsy revealed tubulitis and interstitial inflammatory infiltrates with eosinophils. Immunological and ophthalmological examinations showed no abnormal findings, and thus, his renal dysfunction was presumed to be caused by DI-AIN. Although oral prednisolone (PSL) administration (40 mg/d) and discontinuation of zonisamide immediately improved his renal function, AIN recurred 10 months later. The increase in PSL dose along with discontinuation of valproate and lacosamide improved renal function. However, 10 months later, recurrent AIN with eosinophilic infiltration was confirmed by further biopsy. The patient was therefore diagnosed with corticosteroid-dependent eosinophilic interstitial nephritis.

Interventions: To prevent life-threatening epilepsy, carbamazepine could not be discontinued; hence, he was treated with an increased dose of PSL (60 mg/d) and 1500 mg/d of mycophenolate mofetil (MMF).

Outcomes: MMF was well tolerated and PSL was successfully tapered to 5 mg/d; renal function stabilized over a 20-month period.

Lessons: The presence of underdetermined autoimmune processes and difficulties in discontinuing the putative offending drug are contributing factors to corticosteroid dependency in patients with eosinophilic interstitial nephritis. MMF may be beneficial in the management of corticosteroid-dependent eosinophilic interstitial nephritis by reducing the adverse effects related to high-dose and long-term corticosteroid use.

Abbreviations: AIN = acute interstitial nephritis, DI-AIN = drug-induced acute interstitial nephritis, LST = lymphocyte stimulation test, MMF = mycophenolate mofetil, PSL = prednisolone, TINU = tubulointerstitial nephritis with uveitis.

Keywords: corticosteroid, drug-induced interstitial nephritis, eosinophils, mycophenolate mofetil, polypharmacy

1. Introduction

Acute interstitial nephritis (AIN), an important cause of acute kidney injury, is histologically defined by an interstitial mononuclear cell infiltration with tubulitis characterized by inflammatory cells in the renal tubular wall. Drug-induced AIN (DI-AIN) accounts for approximately two-thirds of AIN cases.[1] DI-AIN abruptly reduces renal function and is often associated with fever and/or eruption, whereas in some cases, renal dysfunction insidiously progresses without symptoms,[2] suggesting the importance of histological diagnosis. Significant eosinophilic infiltration into the kidney is a characteristic finding of AIN, which suggests an underlying allergic mechanism. However, a similar pathology can be observed in rare autoimmune disorders, thus diagnostic dilemmas are common in cases of eosinophilic interstitial nephritis.

The main therapeutic strategy for DI-AIN is to discontinue the offending drug; moreover, corticosteroid therapy is initiated in patients with moderate to severe renal injury. However, despite renal recovery after corticosteroid therapy, some patients experience AIN recurrence, thereby exposing them to repeated...
and long-term corticosteroid administration, which is known as corticosteroid dependency. [1] Unfortunately, there is little information regarding the management of corticosteroid-dependent eosinophilic interstitial nephritis.

Herein, we present a case of corticosteroid-dependent AIN with renal eosinophilic infiltration in a patient with multiple anti-epileptic drug use; further, we discuss the factors contributing to corticosteroid dependency and potential strategies against recurrent eosinophilic interstitial nephritis. Written informed consent was obtained from the patient for publication of this case report.

Table 1

| Laboratory test (unit) | Result     | Reference range |
|------------------------|------------|-----------------|
| Hemoglobin (g/dL)      | 13.1       | 13.7-16.8       |
| White blood cells (μL) | 4,720      | 3,300-8,600     |
| Eosinophils (μL)       | 113        | 0-946           |
| Platelets (×10^5/μL)   | 286        | 158-348         |
| Protein (g/dL)         | 7.5        | 6-8.1           |
| Albumin (g/dL)         | 4.2        | 4.1-5.1         |
| Blood urea nitrogen (mg/dL) | 25.3    | 8-20.0          |
| Creatinine (mg/dL)     | 1.74       | 0.65-1.07       |
| Sodium (mEq/L)         | 139        | 138-145         |
| Potassium (mEq/L)      | 3.8        | 3.6-4.8         |
| Chloride (mEq/L)       | 105        | 101-108         |
| Bicarbonate (mEq/L)    | 21.3       | 22.0-26.0       |
| Calcium (mg/dL)        | 9.3        | 8.8-10.1        |
| C-reactive protein (mg/dL) | 1.77  | <0.15           |
| IgG (mg/dL)            | 1,404.6    | 861.0-1,470.0   |
| IgM (mg/dL)            | 23.0       | 4.8-105.0       |
| Anti-nuclear antibody  | <1.40      | <1.40           |
| SS-A antibody (U/mL)   | <0.50      | <0.50           |
| SS-B antibody (U/mL)   | <0.50      | <0.50           |
| Angiotensin-converting enzyme (U/L) | 6.6 | 8.3-21.4 |
| Soluble IL-2 receptor (U/mL) | 469 | 122-496 |
| Cryoglobulin           | Negative   | Negative        |
| MPO-ANCA (U/mL)        | <0.50      | <3.50           |
| PR3-ANCA (U/mL)        | <0.50      | <2.50           |
| Urinary N-acetyl-β-glucosaminidase (U/L) | 48.0 | 0.3-15.0 |
| Urinary β2-microglobulin (μg/mL) | 21.51 | <0.29 |
| Urinary protein-to-creatinine ratio (g/g) | 0.10 | <0.15 |

3. Discussion

AIN is caused by a variety of disorders including allergic, infectious, and autoimmune diseases, and most frequently by drug allergies. Renal biopsy is useful for a definitive diagnosis of AIN by verifying the presence of “tubulitis” and determining the cell type of inflammatory infiltrate. Eosinophilic infiltration generally indicates that an allergic reaction is involved in the pathogenesis of AIN. However, eosinophilic infiltration can also be observed in some rare autoimmune disorders such as tubulointerstitial nephritis with uveitis (TINU), eosinophil granulomatosis with polyangiitis, and Kimura’s disease. [4] The latter two diseases have specific clinical symptoms and can cause glomerular lesions; however, it may be difficult to distinguish TINU from DI-AIN.

When DI-AIN is suspected, the putative offending drug(s) should be promptly discontinued. However, it may be difficult to identify the offending drug(s) due to polypharmacy. A recent study reported that 36.8% of elderly patients in the United States take > 5 medications. [8] Unfortunately, there are no definitive ways to select one or more offending drugs from many other drugs in patients with DI-AIN. Although the LST, an in vitro test for type IV allergic reactions, has been utilized to determine the offending drug(s) in...
patients with DI-AIN, it has an inadequate diagnostic sensitivity, and is therefore not widely recommended. Indeed, the patient in the present case experienced repeated AIN recurrence even after zoniamide discontinuation (as indicated by the positive LST result), suggesting that it was not the offending drug. Furthermore, it is usually difficult to discontinue "all" medications, since abrupt discontinuation of pivotal drugs such as anticoagulants and antiepileptics can lead to life-threatening events. Consequently, offending drugs may be continued if they cannot be replaced with appropriate alternatives. In the present case, recurrent eosinophilic interstitial nephritis might have been caused by the difficulty in discontinuing carbamazepine.

Recent studies have suggested the benefits of early corticosteroid therapy for DI-AIN; most patients with DI-AIN experience no recurrence after corticosteroid therapy and discontinuation of the offending drug. However, in some cases, AIN recurs with steroid tapering, leading to corticosteroid dependency. As mentioned above, at least two factors contribute to corticosteroid dependency in eosinophilic interstitial nephritis: 1) the presence of underdetermined autoimmune processes, and 2) the difficulty in discontinuing the offending drug. Corticosteroid-dependent AIN is usually treated with repeated courses of corticosteroids to prevent disease progression. Although minimizing corticosteroid exposure is important for reducing adverse effects, there is little evidence regarding alternative management. MMF has been a therapeutic option for recurrent AIN caused by autoimmune disorders such as sarcoidosis and Sjögren's syndrome. In an earlier case series, eight patients with corticosteroid-dependent AIN underwent MMF treatment. This study included two patients with DI-AIN and MMF (1500 mg daily) successfully stabilized serum creatinine levels for over 25 months in both patients without complications. In a recent retrospective cohort study of 22 patients with recurrent AIN, 2 of 6 patients with DI-AIN underwent MMF treatment. One patient treated with a corticosteroid followed by MMF showed renal function improvement, whereas another with advanced renal failure showed no response to MMF treatment. These reports suggest a satisfactory tolerability and the steroid-sparing effect of MMF in corticosteroid-dependent DI-AIN. The present case experienced no obvious MMF-related adverse effects, including leukopenia and gastrointestinal symptoms. The scarcity of corticosteroid-dependent eosinophilic interstitial
nephritis unfortunately makes it difficult to verify the efficacy of MMF in controlled trials. Although the benefits and risks require further verification in larger case studies, MMF may be considered as a candidate for the management of corticosteroid-dependent eosinophilic interstitial nephritis, with due attention to the common adverse effects.

4. Conclusion

It should be recognized that eosinophilic interstitial nephritis can recur even after corticosteroid therapy and discontinuation of the putative offending drug, leading to corticosteroid dependency. Undetermined autoimmune processes and polypharmacy contribute to corticosteroid dependency in patients with eosinophilic interstitial nephritis including DI-AIN. MMF may have a steroid-sparing effect under these conditions. However, the benefits and risks of MMF therapy for corticosteroid-dependent eosinophilic interstitial nephritis must be verified in larger case studies.

Author contributions

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Figure 2. Clinical course of the patient with a trend of serum creatinine levels. Values on the blue steps indicate the daily dosage (mg) of prednisolone (PSL). A daily dose of 1500mg daily of mycophenolate mofetil (MMF) was added to the corticosteroid therapy.
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