INTRODUCTION

Tubulointerstitial nephritis and uveitis (TINU) syndrome, which is characterized by a combination of acute interstitial nephritis (AIN) and uveitis, is predominant among adolescent girls. Uveitis and pyelonephritis appear at various timepoints, with studies suggesting that more than half of the patients develop ocular symptoms later than AIN. Therefore, early disease recognition may be challenging. This report also describes the reporting and diagnostic problems of TINU cases in female patients whose renal features are primarily due to drug-induced AIN.

CASE

A 15-year-old female patient was admitted to our hospital due to progressive deterioration of her renal function with an increased serum creatinine (sCr) level of 0.95 mg/dl despite having no past history of renal disease. Two weeks prior to admission, she developed a fever >38°C and was empirically treated with azithromycin combined with the occasional use of acetaminophen (ACP) by a local physician; however, her fever persisted. Meanwhile, she started to complain of fatigue and nausea, which prompted referral to our hospital for further workup. Her medical history was unremarkable, except for her prior treatment with escitalopram for developmental disability for 6 months. Upon admission, the patient had a weight of 47 kg (1 kg weight loss), height of 149 cm, temperature of 36.6°C, pulse rate of 90 beats/min, and a blood pressure of 108/65 mmHg. Her bowel sounds were normal. Her abdomen was soft and flat, with lower abdominal tenderness, without rebound pain or palpable masses. The lungs were clear, and heart sounds were normal. No rash, lymphadenopathy, petechiae, or joint swelling were observed. Renal sonography showed no abnormal findings.

Diffusion-weighted images on abdominal magnetic resonance imaging showed heterogeneous high signals in both renal parenchyma and renal enlargement, which were consistent with acute tubular interstitial nephritis. No abnormalities in the fundus were observed. Aside
from renal dysfunction, a serological study revealed an increased C-reactive protein (CRP) level (4.24 mg/dl) and negative findings for antineutrophil cytoplasmic antibody, antiglomerular basement membrane antibodies, anti-SSA/Ro antibodies, and anti-SSB/La antibodies. Urinalysis showed active sediments with six white blood cells and three red blood cells per high-power field. Her urinary protein creatinine ratio was 0.4 g/g·Cr. The urinary β2-microglobulin (b2MG)/creatinine ratio and N-acetyl-beta-d-glucosaminidase (NAG)/creatinine ratio were 3.6 μg/mg-Cr (reference range: <0.3 μg/mg-Cr) and 33.1 U/g-Cr (reference range: 1.6–5.8 U/g-Cr), respectively. A drug lymphocyte stimulation test (DLST) confirmed that the patient had a negative stimulation index (SI) score for ACP but had specific high SI scores for escitalopram of 432% (cutoff value for DLST positivity, 180%). Based on the lack of findings suggesting ocular disease following ophthalmological screening and laboratory results, as well as her clinical history, drug-induced AIN was suspected. The oral administration of escitalopram was stopped. A week after admission, the patient was then found to have anterior bilateral uveitis without any apparent abnormalities of the fundus oculi during a subsequent ophthalmological review. Thereafter, a renal biopsy was performed on the following day. Under a light microscope, five glomeruli were identified within the renal parenchyma. The glomerular structures were preserved, with marked diffuse infiltration of lymphocytes and some eosinophils accompanied by partial destruction of the tubular structures. Immunohistochemistry did not observe any immune complex deposits among the observed glomeruli. A diagnosis of TINU syndrome was thereafter established, and the patient was started on oral prednisolone (PSL) 60 mg daily (1.3 mg/kg/day), to which a favorable response was noted. The patient’s ocular symptoms decreased 1 week after steroid administration, and her urinary b2MG/creatinine ratio and NAG/creatinine ratio decreased to 2.0 μg/mg-Cr and 1.8 U/g-Cr, respectively. PSL was tapered to 45 mg/day for 2 weeks. Her serum creatinine elevated, and the relapse of uveitis was observed during steroid dose reduction, for which oral mizoribine and steroid instillation was started. Given that her eye symptoms could be controlled with steroid eye drops, the dose of the steroid was gradually tapered and discontinued 3 months after the start of steroid administration. No recurrence was observed as of 1 year after the discontinuation. The patient’s clinical course is detailed in Figure 2.

3 | DISCUSSION

Establishing a clinical diagnosis of drug-induced AIN is exceedingly difficult given the numerous types of medications associated with AIN. Although AIN often occurs less than 2 weeks after drug exposure, it has been shown to vary from days to months depending on the drug.2 However, a diagnosis of AIN may be established through knowledge of the patient’s medical history and specific laboratory tests, such as DLST.2–5 In fact, DLST has been regarded as a useful diagnostic test for various types of drug hypersensitivity, including drug-induced AIN, by measuring drug-induced T cell proliferation in vitro.6,7 In the current case, considering that the patient showed a specific high score for escitalopram in DLST, the patient’s renal abnormality was initially considered to have been attributed to drug-induced AIN. We believe that the subsequent development of TINU syndrome in our patient may have been caused by the additive, synergistic, or cumulative effects of the drugs, including escitalopram. Although DLST results are not absolute, T cell-mediated mechanisms have been proposed to play a major pathogenic role in TINU syndrome, which necessitates drug induction.2,7 Case information on prior drug use as an estimated risk for TINU syndrome continues to accumulate.7–10 However, similar inducers have been identified in both isolated AIN and TINU syndromes.2,7,8 Unfortunately, determining the exact contribution of each is quite difficult. Whether AIN without TINU syndrome and uveitis is a different phenotype of the same pathology is particularly important and crucial issue that needs to be extensively investigated.11 As such, we note that recent studies on the pathogenic role of modified CRP (mCRP) can irreversibly dissociate

FIGURE 1  (A) There was no glomerular sclerosis, mesangial proliferative, glomerular basement membrane change. (B) Marked diffuse infiltration of lymphocytes and some eosinophils accompanied by partial destruction of the tubular structures. (A, B) PAS staining, ×200
from native CRP in TINU syndrome. This is because it can be one of the common target autoantigens in kidney and eye tissue. Interestingly, serum levels of anti-mCRP autoantibodies may play a role in distinguishing patients with TINU syndrome from those with AIN. Unfortunately, such a procedure is inapplicable to the current patient. Moreover, HLA-type analysis is progressing in TINU syndrome, with reports showing that HLA-DQA1, HLA-DQB1, and HLA-DRB1 are associated with the onset. The HLA type in the current case was unknown, with the patient not consenting to genetic testing. Identifying the patient’s mCRP and HLA types may have helped establish a diagnosis, and we believe that similar cases will benefit from such tests in future. The main treatment for AIN is to discontinue or reduce the dose of the problematic drug. Corticosteroid therapy has shown no clear benefits after discontinuation of the problematic drug. One study showed that 72% of patients with TINU syndrome who did not use systemic steroids were expected to spontaneously recover from renal dysfunction. In contrast, another report revealed that two out of four patients who did not receive steroids progressed to chronic renal failure, with one patient developing end-stage renal failure. Several reports have suggested corticosteroid administration may shorten the course of renal failure. Considering that no improvement in the renal function of the current patient was observed following drug discontinuation, PSL was started at 60 mg/day (1.3 mg/kg/day). The interval between drug discontinuation and start of steroid treatment was approximately 3 weeks. Immediately after starting PSL treatment, the patient’s renal function improved. This finding is consistent with that reported in previous studies, which showed that patients often respond to PSL doses of 1–2 mg/kg/day. Many authors agree with corticosteroid treatment for patients with TINU syndrome who have advanced renal failure similar to AIN.

The response to systemic steroid administration is good; however, long-term administration may be necessary because approximately half of the patients experience relapse when the dose is reduced. Therefore, concomitant use of immunosuppressive drugs is considered in cases of recurrence of uveitis, but there is no established therapeutic drug. Immunosuppressive drugs were used in combination in 11 of 123 cases with TINU syndrome, according to global reports. Cyclosporine, a drug that inhibits calcineurin dephosphorylation enzyme activity, is indicated for Behcet’s uveitis; however, because of concerns about the side effects of renal dysfunction, we selected mizoribine, which is a metabolic antagonist with relatively fewer side effects. Mizoribine is an immunosuppressive drug that inhibits purine synthesis in nucleic acid metabolism and suppresses both cell-mediated and humoral immunities by inhibiting the proliferation of T and B lymphocytes.

Simultaneous use of topical ocular steroids and immunosuppressants may be essential due to the prolonged and/or recurrent uveitis associated with this syndrome.

4 | CONCLUSION

Distinguishing between late-onset TINU syndrome and drug-induced AIN remains difficult given that patients with TINU syndrome may develop uveitis long after the onset of AIN. Therefore, ophthalmic examination is required not only upon diagnosis but also continuously
or when eye symptoms (e.g., photophobia and conjunctival suffusion), elevation of urinary β2MG, and relapse of urinary findings (e.g., hematuria and proteinuria) are observed.

AUTHOR CONTRIBUTIONS
K. Yukiko and T. Hiroshi cared for the patients and designed the project. N. Koji and K. Shohei collected clinical information. All authors have read and accepted the manuscript.

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CONFLICT OF INTEREST
All authors declare that they have no conflict of interest relating to this case report.

DATA AVAILABILITY STATEMENT
All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

ETHICAL APPROVAL
This case study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The article is exempt from Kumamoto University Ethical Committee approval as a single case is not required for approval.

CONSENT
Written informed consent for examinations and to publish their cases including images was obtained from our patient and her parents.

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