A Report of an Adult Case of Tubulointerstitial Nephritis and Uveitis (TINU) Syndrome, with a Review of 102 Japanese Cases

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Patient: Female, 44
Final Diagnosis: Tubulointerstitial nephritis • uveitis syndrome
Symptoms: —
Medication: Loxoprofen sodium hydrate
Clinical Procedure: Renal biopsy
Specialty: Nephrology

Objective: Rare disease
Background: Although TINU syndrome is characterized by idiopathic TIN with bilateral anterior uveitis, few reports have provided a comprehensive summary of the features of this disorder. Previous reports have suggested that many Japanese patients had HLA-A2 and -A24 (7), but there is no evidence.

Case Report: A 44-year-old female was referred to our hospital due to renal dysfunction in March 2012. After admission, her symptoms improved spontaneously without medication within 2 weeks. In the outpatient clinic, she was diagnosed with idiopathic bilateral anterior uveitis in May, and her renal dysfunction relapsed in November. A renal biopsy showed diffuse TIN. We made a diagnosis of TINU syndrome because we could not explain the origin, and treated her with a systemic corticosteroid. Her renal function and ocular symptoms have been improving. The patient had HLA-A24, -B7, -DR1, -C*07: 02 and -DQB1*05: 01: 01. We collected 102 Japanese cases in PubMed, Ovid MEDLINE, and the Japanese Medical Abstracts Society and compared our case with the previous cases.

Conclusions: This disorder affects primarily young females (median age, 14 years), and the most common symptom is fever (44/102 cases). We conducted a statistical analysis using contingency table and Pearson’s chi-square test, for HLA-A2 and A24, and calculated the odds ratio (OR). There are no significant differences (A2 was present in 7/22 cases and in 19/50 controls, p value (P) 0.61, OR 0.76 (95% confidence interval (CI)) 0.27–2.2; A24 was present in 10/22 cases and in 33/50 controls, P 0.10, OR 0.43, CI 0.16–1.2).

MeSH Keywords: HLA Antigens • Nephritis, Interstitial • Uveitis, Anterior

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Background

Since tubulointerstitial nephritis and uveitis (TINU) syndrome was first reported by Dobrin et al. in 1975 [1], many clinicians have submitted case reports to journals around the world. Many clinicians have inferred that TINU syndrome is an immunological abnormality. More recently, the pathogenesis of TINU syndrome has been gradually becoming clearer. For example, the existence of common antigens present in tubular cells and eyes [2], modified C reactive protein levels [3], and IgG4-related systemic disease [4,5] were all demonstrated to be related to TINU. However, a great deal of uncertainty still remains, such as the optimal treatment and the relevance of the HLA type.

We recently treated an adult patient with this disorder. We collected the previous reports of Japanese cases and compared our case with the average Japanese case. A previous report suggested that particular HLA types are related to this disorder, so patients who have these HLA types tend to be affected with TINU syndrome [6]. Many Japanese patients have HLA-A2 and -A24, which have both been reported to be associated with TINU [7]. To determine the significance of these types in Japanese patients, we conducted a statistical analysis of the reported cases.

Case Reports

A 44-year-old female, who had been healthy until approximately 2 months before admission, was referred to our hospital because of a 2-month history of a low grade fever, weight loss (her weight had decreased by 2.0 kg), and mild renal dysfunction (serum creatinine 1.08 mg/dl) in March 2012. The symptoms had started with common cold-like symptoms, and she had seen a family doctor in late January. She had been taking loxoprofen sodium hydrate and sometimes Chinese herbs (Hochuekkito and Bakumondouto) for approximately 2 months.

At the first admission, she complained of general fatigue, anorexia, and arthralgias. The physical findings indicated cervical lymphadenopathy but no history of skin rash or edema. She had a low-grade fever (37.1°C), and her blood pressure, pulse, and respiration rate were within the normal range.

The laboratory tests showed blood urea nitrogen level of 17.6 mg/dl, creatinine 1.27 mg/dl, and estimated glomerular filtration rate (eGFR) of 37.5 ml/min/1.73 m². The serum levels of total protein, albumin, globulin, electrolytes, lipase, and amylase were normal, as were tests of her liver function. The urinalysis showed that β₂-Microglobulin levels were 184 ng/ml, N-acetyl-β-D-glucosaminidase 23.7 U/liter (normal range 0–10 U/liter). The urinary sediment contained 5–9 red blood cells/high power field (hpf) without any casts. A chest X-ray, ultrasonic abdominal images, and thoracic computed tomography scans were normal. These results and the patient’s clinical history suggested drug-induced tubulointerstitial nephritis, probably due to loxoprofen sodium hydrate. After the administration of NSAIDs was stopped and the patient received rehydration, her renal function and disease presentation gradually returned to normal after 3 days. Therefore, she was discharged from our hospital after 2 weeks. Since then, we have taken a wait-and-see approach. In May 2012, she reported severe pain in both eyes. A general ophthalmologist diagnosed idiopathic bilateral anterior uveitis, but there were no apparent abnormalities of the fundus oculi. The ophthalmologist prescribed topical corticosteroid for the eyes. Three months later, her eye symptoms were found to have improved.

We noted that her serum creatinine and C-reactive protein levels were barely elevated (1.17 mg/dl and 0.38 mg/dl, respectively), and a screening urine dipstick showed occult blood 1+ in the outpatient clinic in November. Although she had no symptoms at that time, we assumed that she had a relapse of tubulointerstitial nephritis and admitted her to our hospital to perform a renal biopsy (Figure 1).

The renal biopsy showed tubulointerstitial nephritis and normal glomeruli; there were 13 glomeruli, 1 was located just beneath the cortices with global sclerosis, but the other 12 glomeruli were almost normal. The most characteristic optical microscopic finding was the infiltration of mononuclear cells, largely composed of lymphocytes, with a few plasma cells. There was fibrosis involving approximately 80% of the interstitium. Immunofluorescence microscopy revealed that there...
was very weak IgG staining in the glomeruli, but not any other immunoglobulins or complement components. There were no electron-dense deposits detected by electron microscopy.

During hospitalization, an ophthalmologist diagnosed her to have bilateral anterior uveitis, because there was a keratic precipitate, but the retina and vitreous body had nonspecific findings.

As a differential diagnosis, we considered Sjögren’s syndrome, sarcoidosis, IgG4-related systemic disease, Behçet’s syndrome, and infectious mononucleosis. Although further tests were administered, they were all negative. For example, there were no anti-nuclear antibodies, anti-double stranded DNA antibodies, anti-SS-A/B antibodies, anti-neutrophil cytoplasmic antibodies, or anti-Smith antibodies. Chest X-rays showed no characteristic findings of sarcoidosis, such as bilateral hilar lymphadenopathy. Furthermore, at that time, she did not have any overt findings suggesting infection or Behçet’s syndrome. Therefore, we diagnosed TINU syndrome.

We had started a systemic corticosteroid, prednisolone, at 60 mg (1 mg/kg) daily, and tapered the dose for 8 months. Her renal function had stopped deteriorating and started to slowly improve. While the observation is still ongoing, the most recent data showed a serum creatinine level of 0.96 mg/dl and an eGFR of 50.3 ml/min/1.73 m². In addition, the ophthalmological keratic precipitate disappeared in December 2012, and she was able to stop the topical corticosteroids in February 2013. During a follow-up visit, we checked her human leucocyte antigens and alleles; the A locus was A24 and the B locus was B7. The DR locus had DR1, and the allele of C, and the DQB1 were C*07: 02 and -DQB1*05: 01, respectively. HLA-DQB1*05 was reported to be strongly associated with TINU syndrome [7].

Our patient’s serological HLA tests showed -A24, -B7, -DR1 and -DQB1*05: 01: 01, respectively. HLA-DQB1*05 was reported to be strongly associated with TINU syndrome by Ralph et al. [6]. Mandeville et al. suggested that HLA-A2 and -A24 were important antigens associated with this disorder in Japanese subjects, because these 2 antigens had been identified in many (75%) Japanese patients in 2001. Obviously, they also knew that these 2 antigens were often observed in healthy Asian people [7]. In the 102 Japanese cases identified for the present study, we analyzed the findings for 25 cases where the results of HLA typing were reported (Table 1). We conducted a statistical analysis using a 2×2 contingency table and Pearson’s chi-square test for these 2 antigens and calculated the odds ratio (OR). Thanks to the HLA Laboratory, there is extensive data available about the frequency of Japanese serological and genomic HLA tests (Kyoto, Japan), so we were able to obtained data on the HLA results from 50 healthy Japanese subjects. Seven of the 22 TINU patients (32%) had HLA-A2 and 19 of the 50 controls (48%) had it; P value (P) 0.61, OR 0.76, 95% confidence interval (CI) 0.27–2.2. Twelve of the 22 patients (54.5%) had HLA-A24, and 33 of the 50 controls (64%) had it; P 0.10, OR 0.43, 95% CI 0.16–1.2. There were therefore no significant differences in the specific HLA types between those with and without the disease.

Discussion

Tubulointerstitial nephritis and uveitis (TINU) syndrome was first reported by Dobrin et al. in 1975 [1]. Over 200 cases have since been reported by physicians all over the world. Mannideville et al. assembled 133 cases and reported that this disorder affects primarily young females (the median age of onset is 14 years), with about 3 times as many females as males developing the syndrome. They also mentioned that the tubulointerstitial nephritis (TIN) generally precedes the uveitis by a few months, and proposed criteria for diagnosing this disorder. They also mentioned that the tubulointerstitial nephritis (TIN) generally precedes the uveitis by a few months, and proposed criteria for diagnosing this disorder. They also mentioned that the tubulointerstitial nephritis (TIN) generally precedes the uveitis by a few months, and proposed criteria for diagnosing this disorder. They also mentioned that the tubulointerstitial nephritis (TIN) generally precedes the uveitis by a few months, and proposed criteria for diagnosing this disorder.
We first diagnosed the present patient with drug-induced tubulo-interstitial nephritis (TIN) because of her clinical course and the results of the lymphocyte transformation test (LTT), which is called the drug-induced lymphocyte stimulation test (DLST) in Japan. Domenico et al. suggested that drug-induced TIN could cause TINU syndrome [9]. We hypothesized the patient could have developed TINU syndrome because she had an allergic susceptibility to loxoprofen sodium hydrate, Hochuekkito, or Bakumondoto. However, the LTT has been disputed, and has been concluded to be an insufficient method. Moreover, some reports have pointed out that Chinese herbs have mitogenic effects [10]. Although the challenge test is the most reliable method of diagnosing allergic patients, it is difficult to perform the test in most cases because of the risk (e.g., anaphylactic shock) and ethical concerns. Therefore, many clinicians have noted the presence of basophils and their functions in allergic inflammation, and have recently focused on a new method, the basophil activation test (BAT) [11,12]. We performed the BAT in the present case and obtained contradictory results to the LTT. The BAT is still being optimized, but it is a favorable method to elucidate the cause of allergic disorders [11–13]. There have been no previous reports about performing the BAT for tubulointerstitial nephritis. Further study is needed to evaluate the results and their significance for individual patients.

Table 1. The serological and genomic HLA typing.

| No. | HLA-A | HLA-B | HLA-C | HLA-DQ | HLA-DR |
|-----|-------|-------|-------|--------|--------|
| [14] | A24/A31 | Bw54/Bw55 | Cw1/Cw3 | – | DR4/DRw6 |
| [14] | A24/A31 | Bw48/Bw7 | Cw7 | – | DR4/DRw12 |
| [14] | A24/A2 | Bw54/Bw61 | Cw3 | – | DRw8 |
| [14] | A24/A33 | Bw52/Bw60 | Cw3 | – | DRw8 |
| [15] | A11 | B54/B35 | Cw1/Cw3 | DQB1 0401 | DR4(DRB1 04051) |
| [16] | – | – | – | – | DR6/DR9 |
| [16] | – | – | – | – | DR4/DR6 |
| [17] | A2/A11 | Bw62/Bw46 | Cw4 | – | – |
| [17] | A2/A11 | B54/B35 | Cw1/Cw3 | – | DR4/DR11 |
| [17] | A24/A26 | B70/B51 | Cw7 | – | DR4/DR2 |
| [17] | A26/A11 | Bw61/Bw46 | Cw3 | – | – |
| [17] | A2/A24 | B55/B62 | Cw1/Cw7 | – | DR12 |
| [18] | A9 | Bw54 | C1 | – | DR4 |
| [19] | A24/A33 | B44 | Cw3 | – | – |
| [20] | A24(9)/A26(10) | B35/Bw62(15) | Cw3 | – | DRw12(5) |
| [21] | A24/A26 | B7/56 | C04011/C0702 | – | B101/B104 |
| [22] | A11/A24 | B54/B61 | Cw1/Cw3 | DQ1 | DR14 |
| [23] | A2/A33 | B44/B61 | Cw3 | DQ13/DQ1/DQ4 | DR4 |
| [24] | – | – | – | – | DR4/DR12 |
| [25] | A2/A11 | Bw48/Bw54 | Cw1 | – | – |
| [26] | A33 | B44/B61 | C3 | DQ1/DQ3 | DR9/DR13 |
| [26] | A26 | B61/B62 | C3/C7 | DQ1/DQ3 | DR8/DR9 |
| [27] | A29 | Bw52/Bw59 | Cw1 | – | – |
| [28] | A2/A24 | B51/B61 | Cw10/Cw14 | – | DR4/DR14 |
| Our patient | A24 | B7 | C*07: 02/~ | DQB1 05: 01: 01 | DR1 |

Number is same as references. Each report described serological or genomic HLA typing. The bar (–) was unsurveyed or undescribed articles.
Conclusion

We assembled characteristics of Japanese patients and found no significant differences between both HLA antigens and TINU syndrome in Japanese patients.

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