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Two Cases of Uveitis with Tubulointerstitial Nephritis in HTLV-1 Carriers

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Background: Although the tubulointerstitial nephritis and uveitis (TINU) syndrome has been reported, there are only a few reports in the ophthalmological literature. The ocular findings usually appear later than the renal findings, and a renal biopsy is required for a definitive diagnosis.

Cases: Case 1 was a 15-year-old Japanese girl who was a carrier of the human T lymphotropic virus, type 1 (HTLV-1). She had tubulointerstitial nephritis, anterior uveitis, posterior retinal edema in the right eye, and peripheral vasculitis OU. Case 2 was a 56-year-old Japanese woman who was also a carrier of HTLV-1. Previously she had been diagnosed with Graves' disease, anterior uveitis, and vitreous opacity. Several years later tubulointerstitial nephritis was diagnosed.

Observations: In both patients interstitial nephritis was diagnosed and systemic steroid therapy was effective.

Conclusions: It is difficult for ophthalmologists to diagnose the TINU syndrome because the renal biopsy is performed by a pediatrician or an internist. This may be why ophthalmologic descriptions are rare in cases of TINU syndrome, even though the ocular findings reported in the literature are characteristic. This is the first case report of TINU syndrome in patients with HTLV-1. Ophthalmologists should pay more attention to the uveitis in the TINU syndrome. **Jpn J Ophthalmol 2003;47:372–378** © 2003 Japanese Ophthalmological Society

Key Words: HTLV-1 carrier, nephritis, TINU syndrome, uveitis.

Introduction

The tubulointerstitial nephritis and uveitis (TINU) syndrome was first described in 1975 by Duburin et al as a new syndrome.[1] Although this syndrome has been reported in several papers since then, to the best of our knowledge, there are only a few reports in the ophthalmological literature.[2,3] Of our 2 patients with uveitis and tubulointerstitial nephritis who were positive for HTLV-1, one patient had the TINU syndrome. We reviewed previously reported cases of the TINU syndrome searching for those with descriptions of the ocular involvement in patients with the TINU syndrome.

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Case Reports

Case 1

In October 1998, a 15-year-old Japanese girl felt general fatigue and visited a pediatrician, who found disturbed renal function and referred her to the Department of Pediatrics, Nagasaki University School of Medicine. Interstitial nephritis was suspected because of renal dysfunction without oliguria, serum urea nitrogen of 26.3 mg/dL, creatinine of 2.3 mg/dL, and an immunoglobulin G (IgG) level of 2000 mg/dL. Her red blood cell count was 3.68×10^4 μL, hemoglobin was 11 g/dL, hematocrit was 30.9%, and erythrocyte sedimentation rate was 42.6 mm/hour. Renal biopsy was attempted but was not successful.

In February 1999, the patient complained of blurred vision and ocular pain, and her visual acuity had decreased in both eyes. She visited an ophthalmologist who noted anterior uveitis in both eyes. She received topical

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steroid therapy (Rinderon, 4 times/day) but her symptoms were not alleviated.

She visited our clinic in April 1999, at which time her visual acuity was 1.0 in both eyes. The anterior segment showed severe anterior uveitis in the right eye, and moderate uveitis in the left eye. The chest x-ray showed no evidence of sarcoidosis or other diseases.

Gonioscopy showed an open angle and no nodules, and the vitreous was clear. By fluorescein angiography (FAG), posterior retinal edema was demonstrated in the right eye and peripheral vasculitis in both eyes. The papillae of both eyes were slightly reddish and FAG showed hyperfluorescence. There was leakage at the posterior pole in the right eye (Figure 1).

When she was admitted to our department, the serum C-reactive protein (CRP) was 0.24 mg/dL, IgG was 2073 m/dL, and angiotensin-converting enzyme (ACE) was 15.7 IU/L. There were no specific virus antibody titer findings except for HTLV-1 antibody, which was 45 cut-off index (COI), the urine β2 macroglobulin was 14,300 μg/L, and the urine N-acetyl-β-D-glucosaminidase (NAG) was 14.1 U/g. These results ruled out sarcoidosis and Behçet's disease.

A renal biopsy during her hospitalization showed only slight fibrosis and a few inflammatory cells in the interstitial tissue (Figure 2) because her renal function was gradually returning to normal. On the basis of the clinical features and biopsy findings, she was diagnosed as having the TINU syndrome.

She was treated with intravenous Predonine at an initial dose of 80 mg/day. The dose was gradually reduced and replaced by the oral form. When the cumulative intravenous dose reached 420 mg and the total oral dose 110 mg, the vasculitis and papillitis had almost disappeared. There was no papillitis or edema in the posterior pole. FAG also showed a reduction of hyperfluorescence and vasculitis in the posterior pole (Figure 3).

The patient was then treated with topical steroids, but in September she had recurrent uveitis and was readmitted to our hospital. Tests showed serum CRP was 0.04 mg/dL, IgG was 973 mg/dL, HTLV-1 antibody was 40.5 COI, urine β2 macroglobulin was 750 μg/L, and the urine NAG was 7.8 U/g. Her visual acuity was 1.2 OD and 1.5 OS. The anterior segment showed severe anterior uveitis with many cells and fine keratic precipitates in both eyes. At this time there were many exudates in the peripheral

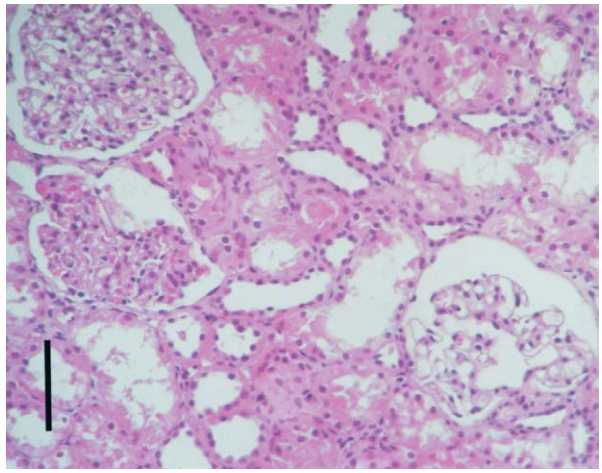

Figure 2. Light microscopy of the renal biopsy specimen in case 1. Hematoxylin-eosin staining shows some fibrous change and interstitial inflammation. Bar = 80 μm.

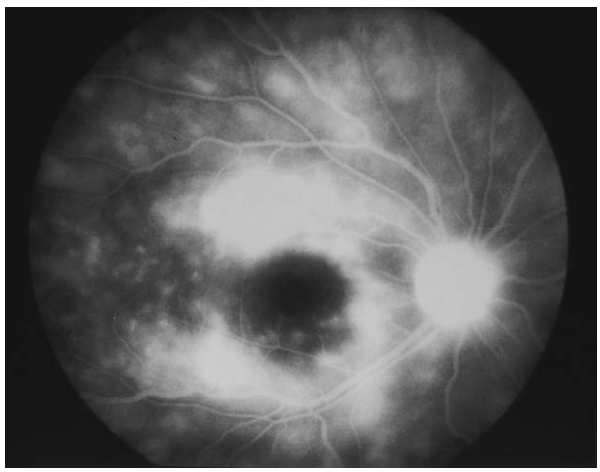

Figure 1. Case 1: fluorescein angiography of the right eye of a 15-year-old Japanese girl on her first visit to our clinic. Hyperfluorescence of the papillae and leakage at the posterior pole are visible.

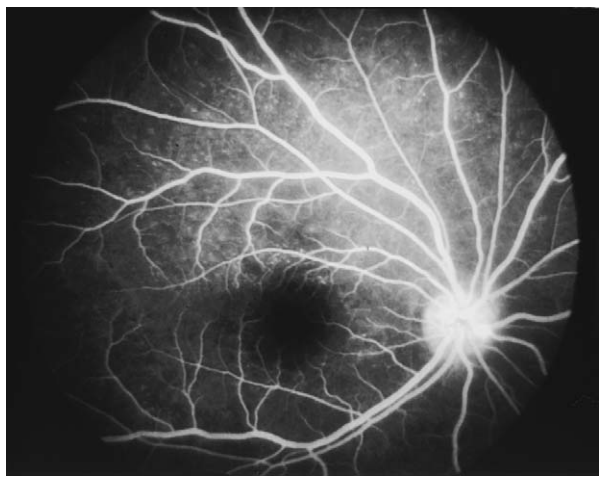

Figure 3. Case 1: fluorescein angiography after systemic steroid therapy shows reduction of hyperfluorescence of the papillae and the posterior pole.

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retina and papillitis in both eyes. There were no remarkable changes in the posterior pole of the retina.

She was treated with intravenous Predonine again at an initial dose of 80 mg/day with a gradual reduction and replacement by the oral form. When the total intravenous dose was 420 mg and the total oral dose was 120 mg, the exudates, papillitis, and anterior uveitis had almost disappeared.

Case 2

In September 1993, a 56-year-old Japanese woman was referred to our Department complaining of many floaters and decreased visual acuity in her left eye. Anterior uveitis and vitreous opacities were noted in the left eye (Figure 4). Her corrected visual acuity was 0.9 OD and 0.3 OS. Chest x-rays showed no evidence of sarcoidosis or other diseases. Her serum examination was normal (CRP 0.12 mg/dL, ACE 14.6 IU/L, and lysozyme 5.5 μg/mL), and urine NAG was 3.6 U/g but antibody to HTLV-1 was demonstrated by particle agglutination (PA) assay and enzyme-linked immunosorbent assay. There were no specific clinical findings of sarcoidosis or Behçet's disease, such as aphtha, erythema, or nodules.

This patient had a history of Graves' disease since July 1992 and a renal disorder, but the details were not known. At that time her serum-free triiodothyronine (FT3) was 10.1 pg/mL, serum-free thyroxine (FT4) was 3.72 ng/dL, and thyroid-stimulating hormone (TSH) was <0.05 μU/mL.

She was treated with oral thiamazole (Mercazole) 30 mg/day, and her FT3, FT4, and TSH were normal in September 1993 at her first visit to our clinic. She was diagnosed as having HTLV-1–associated uveitis and Graves' disease, and she was treated with systemic Predonine at an initial dose of 60 mg/day. Corticosteroid was gradually reduced and when the total systemic Predonine dose reached 810 mg, the vitreous opacity had decreased.

Moderate uveitis recurred a few more times and the cataract gradually progressed. She was admitted to our Department for cataract surgery in March 2000. The postoperative course went well, but renal dysfunction was noted (microhematuria and proteinuria 0.384 g/day), and she was transferred to the Internal Medicine Department. Her serum blood urea nitrogen was 30 mg/dL, creatinine was 1.3 mg/dL, urine β2 macroglobulin 720 μg/L, and urine NAG 7.4 U/g. A percutaneous renal biopsy showed interstitial nephritis with internal edema, infiltration of lymphocytes, and glomerular mesangial proliferation (Figure 5).

Discussion

The association of TINU is also called the renal ocular syndrome, and its pathogenesis remains unclear. Because there are no clinical criteria for the TINU syndrome, it is usually necessary to exclude other systemic diseases, such as systemic lupus erythematosus and sarcoidosis. Although the etiology of the TINU syndrome remains unknown, it is most likely an immunological disorder.

Over 70 cases of TINU have been described to date, but because most of these reports have been from the fields of internal medicine and pediatrics, the ophthalmological findings are not often clear or detailed. In only 25% of

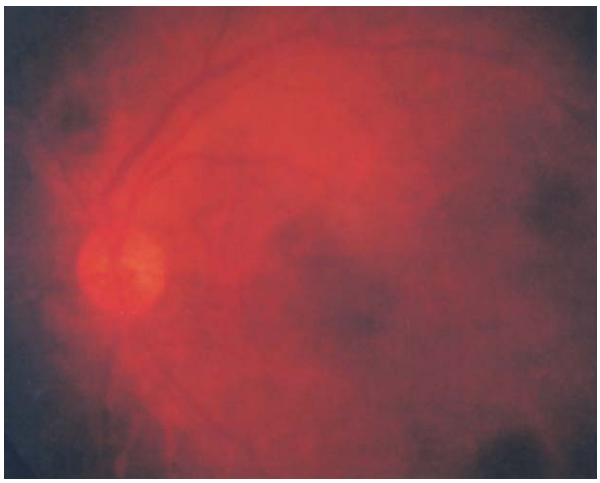

Figure 4. Fundus of left eye in case 2, a 56-year-old Japanese woman, shows vitreous opacity and anterior uveitis.

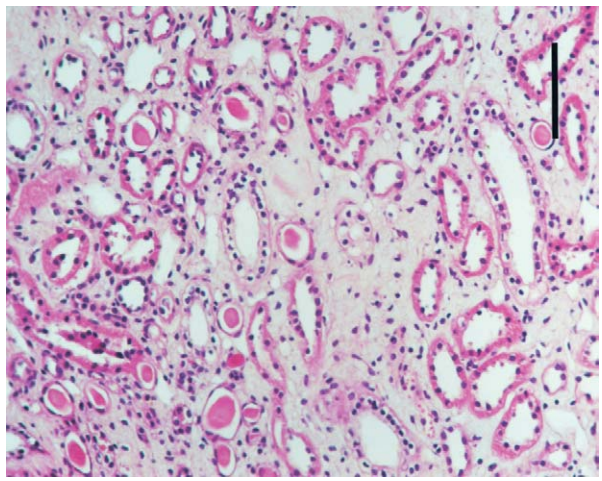

Figure 5. Light microscopy of the renal biopsy specimen in case 2. Hematoxylin-eosin staining shows interstitial nephritis with internal edema, infiltration by lymphocytes, and glomerular mesangial proliferation. Bar = 150 μm.

the reports is there clear evidence of posterior uveitis, but in the ophthalmological literature (Table 1),[2,3] the incidence of posterior uveitis in patients with the TINU syndrome is 50%. As far as we know, almost all the TINU patients reported in the Japanese ophthalmological literature had posterior uveitis (Table 2).[4–11]

The clinical features of the TINU syndrome described previously[10] are: it is more frequently observed in girls about 15 years of age; the general symptoms precede the ocular symptoms and there may be a long interval between the two. All the patients have anterior uveitis and most have bilateral uveitis, none has posterior uveitis alone. Anterior uveitis responds well to corticosteroid therapy. The erythrocyte sedimentation rate is high; and there is hypergammaglobulinemia, in particular, a high IgG. These features were present in our case 1.

We reviewed the Japanese ophthalmological literature and found some additional features (Tables 1 and 2), eg, TINU syndrome is often complicated by uveitis in the posterior pole and is seen as hyperfluorescence of the optic disc and posterior retina. The posterior uveitis is sometimes complicated by peripheral vasculitis but the visual acuity is almost normal. The TINU syndrome sometimes occurs in elderly patients.

It is interesting that our 2 patients were HTLV-1 carriers, and it is also known that HTLV-1 is associated with herpes anterior uveitis (HAU). Because the criteria for TINU syndrome and HAU are unclear, these diseases should be differentiated from other diseases causing uveitis. HAU has been tentatively defined as an idiopathic uveitis of otherwise asymptomatic HTLV-1 carriers. Many patients with HAU have granulomatous changes, retinal vasculitis, vitreous opacities, and/or cotton wool spots.[12] However, in our case 1, the TINU syndrome was diagnosed because of the patient's clinical course and the ophthalmological findings.

It is known that a strong correlation exists between HTLV-1–associated uveitis and Graves' disease. Three hypotheses to explain this correlation[13] are as follows: (a) an excess of thyroid hormone may modify the immune response or activate virus replication and/or increase the number of HTLV-1–infected lymphocytes; (b) the medication (Methimazole) used to treat Graves' disease may reduce thyroid hormone from a high to a normal or low level, which might be related to the development of uveitis; and (c) there might be a correlation between HTLV-1 infection and Graves' disease similar to the close association between HTLV-1 infection and uveitis. In

Table 1. Clinical Features of Tubulointerstitial Nephritis and Uveitis syndrome in English Literature

Author	Age	Sex*	Findings in Anterior Segment	Findings in Posterior Segment†	Fluorescein Angiographic Findings†	Biopsy Findings
Salu et al[3]	66	F	Keratic precipitates in left eye Iritis in right eye		No registry	Edema of interstitial tissue Dense infiltration of lymphocytes and plasmocytes Neutrophils, and some eosinophils Swollen endothelium in small blood vessels
Rosenbaum et al[2]	43	F	Iritis in both eyes Ocular hypertension in left eye	CME in both eyes Peripheral intraretinal hemorrhage	CME in both eyes	Interstitial nephritis
	13	M	Precipitates Iritis in both eyes		No registry	Interstitial nephritis
	42	F	Conjunctivitis of the left eye Iritis in both eyes	Exudate in both eyes Intermediate uveitis in both eyes	No registry	Interstitial nephritis
	54	F	Iritis in both eyes		No registry	
	52	M	Iritis in both eyes	Intermediate uveitis in both eyes Exudate in left eye	No registry	

*F: Female; M: Male.
†CME: cystoid macular edema.

Table 2. Clinical features of Tubulointerstitial Nephritis and Uveitis Syndrome Japanese Literature

Author	Sex*	Age	Findings of Anterior Segment	Findings in posterior Segment	Fluorescein Anglographic Findings	Urine β2 Microglobulin	Urine NAG†	Biopsy Findings
Deguchi et al	F	15	B) Iritis	B) Papillitis and papilledema	B) Hyperfluorescence of the disk	14300 μg/L	14.1 IU/L	Fibrosis and inflammatory cells in interstitial tissue
			B) Fine keratic precipitates	B) Edema in posterior retina	B) Leakage in the posterior retina			
				B) Peripheral vasculitis				
Maruyama et al[4]	M	13	R) Iritis	B) Papillitis and papilledema	B) Hyperfluorescence of the disc	16364 μg/L	12.9 IU/L	Edema of interstitial tissue
			B) Fine keratic precipitates	L) Exudete in the peripheral retina	L) Leakage in the peripheral choriocapillars			Thickening of the tubular basement membrane
	M	18	L) Iritis	L) Papillitis	B) Hyperfluorescence of the disc	18760 μg/L	11.6 IU/L	Edema in interstitial tissue
			L) Fine keratic precipitates	L) Vitreous opacity	B) Leakage in the peripheral retina			Dense infiltration of lymphocytes
				R) Papillitis				Thickening of the tubular basement membrane
Ureta et al[5]	F	13	L) Ciliary injection		L) Leakage in the disc	0.98 mg/dL		Infiltration of lymphocytes
			L) Fine keratic precipitates		B) Leakage in the peripheral vessel			Thickening of the tubular basement membrane
			L) Iritis					Destruction of glomerulotubular structure
	M	17	B) Ciliary injection	R) Vitreous opacity and exudate	B) Leakage in the disc	5.16 mg/dL	14.51 IU/L	Infiltration of lymphocytes
			B) Fine kiratic precipitates	B) Edema in the posterior retina	B) Leakage in the peripheral choriocapillaris			
				B) Splinter hemorrhage				
				R) Papillitis				
Kobayashi et al[6]	F	12	R) Ciliary injection	B) Vitreous opacity	B) Hyperfluorescence in retinal vessels	12.2 mg/dL	29.4 U/L	Dense infiltration of lymphocytes and plasmocytes
			B) Fine keratic precipitates	B) Nodule of the retinal vessel				
			B) Iritis	B) Exudate				
			B) Iris nodule					
			B) Angle hypopyon					

(*continued*)

Table 2. *Continued*

Author	Sex*	Age	Findings of Anterior Segment	Findings Position Segment	Fluouescein Anglographic Findings	Urine β2 Microglobulin	Urine NAG†	Biopsy Findings
Kimura et al[7]	F	10	B) Ciliary injection	R) Papillitis	R) Leakage in the disc and retina	80000 μg/L	7.7 U/L	Infiltration of monocytes
			B) Fine keratic precipitates	R) Vitreous opacity				Fibrosis of interstitial tissue
			B) Iritis					
	F	62	L) Ciliary injection	Invisible due to fibrin		639450 μg/L	23.6 U/L	
			L) Iritis					
			L) Iritis					
Tekebayashi et al[8]	F	18	B) Fine precipitates	R) Vitreous opacity	B) Leakage in the disc and peripheralretina	2063 ng/mL	6.9 U/L	Partial thickening of the tubular basement membrane
			B) Iritis	B) Papillitis				Fibrosis of interstitial tissue, infiltration of lymphocytes
								Proliferation of mesanglum
Taniyama et al[9]	F	14	B) Ciliary injection	B) Anterior vitritis	B) Hyperfluorescence of the disk	8000 μg/L	17.1 U/L	Infiltration of many lymphocytes and some eosinophils
			B) Iritis	B) Papillitis and papilla edema				Edema in interstitial tissue
			B) Fine precipitates					
Aso et al[10]	F	42	R) Fibrin in AC	L) Soft exudate				Infiltration of round cells, lymphocytes, and eosinophils
			B) Iritis	B) Papillitis and papilla edema	B) Hyperfluorescence in the peripapillary area			
				B) Papillitis and papille edema				
				B) Vitreous opacity				
				R) Blot hemorrhage				
Kubota et al[11]	F	53	L) Ciliary injection	B) Posterior retinal edema	L) Leakage in the posterior retina	Increase		Infiltration of small round cells involving neutrophils
			L) Iritis	L) Vitreous opacity				
			L) Iritis nodule					
			R) Fine keratic precipitates					

*F: Female; M: Male.
†NAG: N-acetyl-β-D-glucosaminidase.

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addition, there are some reports that HTLV-1 is associated with collagen diseases, such as rheumatic disorders[14] and Sjögren's syndrome.[15] We suspect that there is a subgroup of TINU syndrome cases caused by HTLV-1 infection. There is some possibility that the TINU syndrome might be related to immunological disorders, and that the HTLV-1 infection may trigger these autoimmune diseases.

In case 2, the uveitis occurred 1 year after the onset of Graves' disease, and tubulointerstitial nephritis was diagnosed 7 years later. HTLV-1 carriers often have Behçet's disease or sarcoidosis, especially in the Kyushu district, where the incidence of HTLV-1 is high. In this patient, we could rule out sarcoidosis and Behçet's disease on the basis of the laboratory data and clinical findings. Therefore, our diagnosis for this patient was HTLV-1–associated uveitis with Graves' disease. It is possible that she had had tubulointerstitial nephritis earlier. The relationship between HTLV-1 infection and TINU syndrome is uncertain, but cannot be overlooked.

There are no distinct clinical criteria for the TINU syndrome but renal biopsy is necessary for its diagnosis. The decision for the biopsy is usually made by the internist or pediatrician. Therefore, there are only a few ophthalmological reports of patients with TINU confirmed by renal biopsy. Our examination of previous reports showed that the ocular findings in TINU were characteristic.

This is the first report describing posterior uveitis in TINU syndrome. Some cases of uveitis of unknown etiology may belong to the category of TINU. Ophthalmologists should pay more attention to uveitis and the TINU syndrome because TINU may become a clinical entity in patients with uveitis.

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