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Clinical Course of HTLV-I–Associated Uveitis

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Purpose: To define the long-term clinical course and visual outcome of human T-cell lymphotrophic virus type I (HTLV-I)-associated uveitis (HAU).

Methods: We reviewed the clinical data on 96 eyes of 70 patients, 26 men and 44 women, with HAU, with specific reference to recurrence of the disease and long-term visual outcome. The mean follow-up period was 83 months (range, 12–276 months).

Results: The mean age of onset was 42.8 years (range, 7–78 years of age), with men presenting at a significantly younger age. Forty-seven patients had isolated HAU; in 10 patients, HTLV-I–associated myelopathy occurred before or after the onset of HAU; in 14 patients, hyperthyroidism had preceded HAU. A single episode of mild to moderate acute uveal inflammation with resolution in a few weeks or more occurred in 44 (62.9%) patients, and multiple episodes in 26 (37.1%), with a mean interval of 16 months (range, 1–250 months), which affected the same eye, fellow eye, or both. The majority of patients had favorable visual outcome at the last examination, whereas only a few patients suffered poor vision resulting from steroid cataract and retinochoroidal degeneration.

Conclusions: The clinical course of HAU is virtually benign and its visual outcome is favorable, although its recurrence is common. The uveitis is usually isolated and affects a portion of otherwise unremarkable HTLV-I carriers, but it may sometimes be manifest as a symptom of syndromic diseases such as HTLV-I–associated myelopathy or hyperthyroidism. This study describes for the first time cases of HAU that occurred many years before manifestation of HTLV-I–associated myelopathy. **Jpn J Ophthalmol 1999;43:404–409**

Key Words: Clinical course, HTLV-I–associated myelopathy, HTLV-I–associated uveitis, hyperthyroidism, visual outcome.

Introduction

Human T-cell lymphotropic virus type I (HTLV-I)-associated uveitis (HAU) has been recognized as a distinct clinical entity that predominantly affects the anterior uveal tissue and is naturally more prevalent in endemic areas of the retrovirus. Its first description in the late 1980s[1] was followed by many case studies in endemic areas, southwestern Japan in particular,[2–7] and in nonendemic areas,[8–10] which have elucidated the epidemiologic and clinical features of the disease. The disease is characterized by acute granulomatous or nongranulomatous anterior uveitis and vitritis with or without retinal vascular changes. Its course is usually benign and resolves in weeks in apparent response to corticosteroids. However, recurrence of inflammatory episodes is not infrequent.[11–13] HAU occurs not only as an isolated ocular disorder in otherwise healthy HTLV-I carriers but also in association with HTLV-I–associated myelopathy (HAM), a neurologic disease that is evidently caused by the retrovirus.[14,15] To further define the long-term clinical course and visual outcome, we reviewed a large series of cases, most had been followed up on since the middle 1980s.

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Materials and Methods

We reviewed the records on a consecutive series of 70 patients with HAU who were followed up with for more than 12 months between January 1988 and April 1998 at the Kagoshima University Hospital; records before 1988 were also reviewed when they were informative about the previous history of HAU and relevant systemic disorders. Diagnostic criteria were based on clinical findings and presence of serum antibodies to HTLV-I as well as on exclusion of other distinct uveitis entities.[5] The patients were administered corticosteroids and were followed at a 6-month interval after regression of the acute disease, or advised to return whenever symptoms recurred. Routine follow-up examination included history recording, testing visual acuity, slit-lamp biomicroscopy, and ophthalmoscopy. Fluorescein angiography, perimetry, electroretinography, and ocular ultrasonography were also performed in selected patients. Serologic, neurological, and endocrinological studies were also performed when indicated.

The mean follow-up period of the 70 cases was 83 months (range, 12–276 months). Figure 1 illustrates the follow-up period for each case from the first uveitic presentation. Also included is information available on previous history that enabled us to estimate the onset and course of HAU or related systemic disorders, ie, HAM and hyperthyroidism.

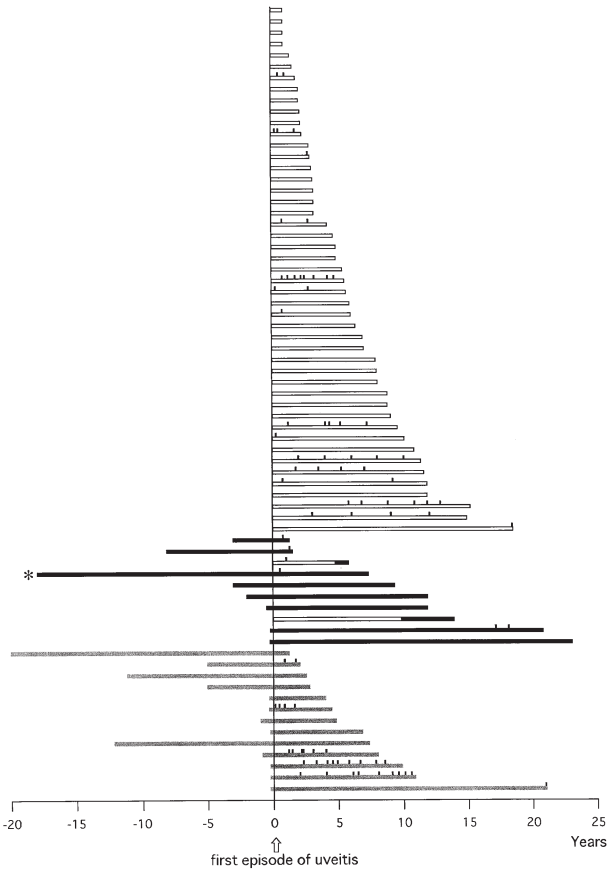

Figure 1. Clinical course of HAU. Length of horizontal bars represents duration of follow-up for each case. Open bars, 47 cases with isolated ocular disease, follow-up beginning from its first episode; black bars, 10 cases with HTLV-I–associated myelopathy (HAM), including two cases of HAU followed by manifestation of HAM and one case (star on left side of bar) of combined HAM and hyperthyroidism; gray bars, 13 cases with hyperthyroidism. Length of left side bars before the onset of uveitis indicates interval between systemic disease onset and uveitis onset. Small rectangles on bars indicate recurrence of uveitis.

Results

Patient Characteristics

The 70 patients with HAU included 26 men and 44 women. The mean age of onset in men was 34.8 years (range, 7–60 years), more than a decade earlier than in women (48.1 years; range, 12–78 years) (P = .006).

As summarized in Table 1, 47 cases had isolated ocular disease and otherwise remained unremarkable, whereas 10 and 14 cases were complicated by HAM and hyperthyroidism, respectively.

Clinical Features of HAU

Initial symptoms and signs in those patients seen between the late 1980s and middle 1990s have been described previously[1,3,11,13] and were the same as seen in later additional patients. In brief, the majority of cases presented with acute visual blurring and/or floaters. Examination revealed mild to moderate anterior segment inflammatory signs such as ciliary injection and cells in the anterior chamber, and vitritis signs such as fine granular or membranous vitreous opacities. Some cases had retinal vascular changes including venous dilatation, granular deposits over vessels, and cotton-wool spots. Corticosteroids were administered topically in 25 patients (35.7%), periocularly in 10 (14.3%), and orally in 35 (50.0%). The acute uveal disease resolved completely within a few weeks to 10 months (mean, 2 months), but occasional cases had prolonged vitreous opacities.

Recurrence

During the follow-up period, 44 cases (62.9%) developed unilateral uveal disease and 26 cases (37.1%) bilateral, resulting in a total of 96 eyes of 70

Jpn J Ophthalmol
Vol 43: 404–409, 1999

Table 1. HTLV-I–Associated Uveitis: Case Categories

Related Disease	Number of Cases	Male/Female	Age of Onset of Uveitis Mean (Range)	Recurrent Cases of Uveitis
Isolated HAU	47	22/25	43.0 (7–78)	15 (31.9%)
HAU with HAM	9	3/6	31.0 (10–55)	4 (44.4%)
HAU with hyperthyroidism	13	1/12	51.5 (25–71)	6 (46.2%)
HAU with HAM and hyperthyroidism	1	0/1	44	1 (100%)
Total	70	23/44	42.8 (7–78)	26 (37.1%)

HAU: HTLV-I associated uveitis; HAM: HTLV-I–associated myelopathy.

cases being affected. Of the bilateral cases, 19 (73.1%) developed concurrent episodes in both eyes and 7 (26.9%), on separate occasions.

A considerable proportion of cases showed recurrence of uveitis during the follow-up, as illustrated in Figure 1. Only a single episode occurred in 44 (62.9%) of 70 cases, whereas multiple episodes developed in 26 (37.1%) cases, either in the same eye or in the fellow eye. The frequency of recurrence ranged from 1 to 9, as illustrated in Figure 2: 1 recurrence in 9 cases, 2 in 5 cases, 3 in 2 cases, 4 in 2 cases, and more than 4 in 8 cases. Although not statistically significant, syndromic cases tended to recur more frequently; 11 (47.8%) of 23 cases complicated with HAM or hyperthyroidism had recurrent uveitis, as did 15 (31.9%) of the 47 isolated cases.

The relapse period in recurrent cases was variable, as illustrated in Figure 3. The mean interval between episodes was 16 months; over 90% of cases showed recurrent disease within 3 years.

Ocular Complications

Most of the episodic ocular disease showed a complete remission, leaving no clinical trace. However, sequelae of inflammation leading to sight-threatening complications occurred in a few eyes. Of 96 affected eyes, 3 had retinochoroidal degeneration, 2 had glaucoma, and 5 had corticosteroid-induced cataract. Such complications as chronic cystoid macular edema, retinal necrosis, or others secondary to recurrent uveitis were not seen in any of the eyes.

Visual Outcome

Figure 4 illustrates a comparison of visual acuity between the first and last presentation. At the last examination, 90% of affected eyes had best-corrected visual acuity of 0.5 or more. Visual acuity improvement of more than 1 line was found in 61 eyes (63.5%). Recurrence of HAU did not affect the long-term visual outcome. On the other hand, 4 eyes (4.2%) had poor visual outcome with final visual acuity of 0.1 or less because of the complications mentioned above.

Related Systemic Disorders

Of the 70 cases of HAU, 23 (32.9%) developed HAM or hyperthyroidism along with ocular disease. One of these cases had a combination of the three disorders, ie, HAU, HAM, and hyperthyroidism. Nineteen (43.2%) of the 44 women and 4 (15.4%) of the 23 men had these HTLV-I–related systemic disorders, the incidence being higher in women (P = .022). It is noticeable that none of the cases had adult T-cell leukemia, another hematologic malignancy caused by HTLV-I.

Ten (14.3%) cases were affected with HAM (Figure 1). Eight cases had developed this neurological disease before the onset of uveitis, whereas the remaining 2 cases had developed clinical manifesta-

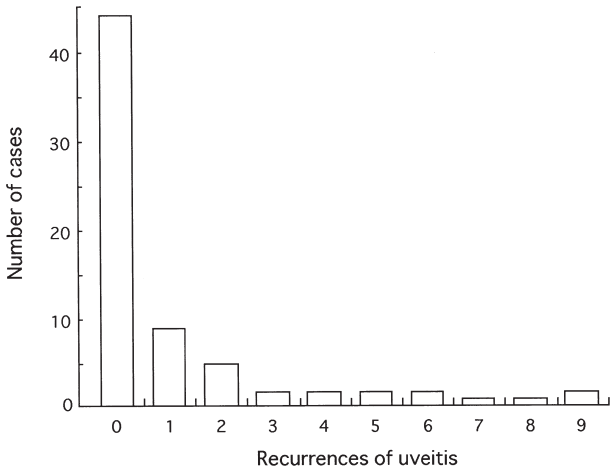

Figure 2. Frequency distribution of recurrence of uveitis, as counted for affected patients. Number 0 indicates only a single episode of disease.

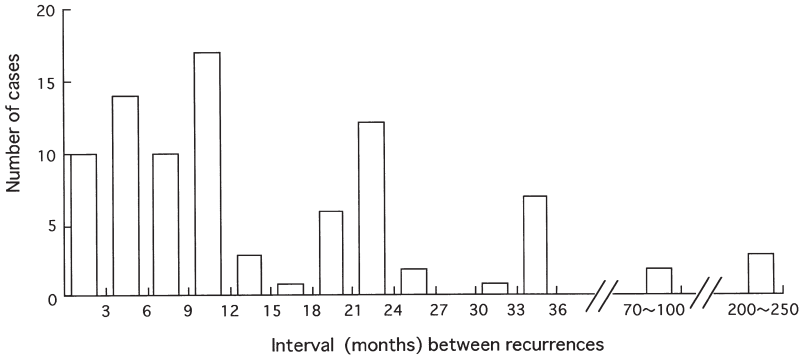

Figure 3. Frequency distribution of relapse period of uveitis, estimated for interval (month) between exacerbations. Mean interval between exacerbations was 16 months (range, 1–250 months). About 60% of recurrences occurred within 12 months.

tions of HAM 4 or 11 years after the development of HAU, as described below for one of the cases.

Fourteen (20.0%) cases had accompanying hyperthyroidism, which preceded HAU or occurred at its first presentation, as illustrated in Figure 1. These cases developed uveitis in close association with thiamazole therapy for the management of endocrinological dysfunction. In 6 cases, acute uveal inflammation occurred soon after initiation of thiamazole administration; notably one of these cases had recurrent uveitis at the beginning of repeat thiamazole therapy.

Case Report

This case represents an instance of HAU that was followed by the development of HAM. A girl presented in 1983 with blurred vision and floaters in her right eye when she was 13 years of age. Best visual acuity was 0.6 OD and 1.2 OS. Mild anterior uveal reactions, fine membranous vitreous opacities, and retinal periphlebitis were noted. Etiology-undefined uveitis was the diagnosis with unremarkable systemic and laboratory studies. Oral corticosteroids were effective on uveal reactions, with retention of slight vitreous opacities and retinal vascular sheathing. She was followed up with regularly, and, aside from transient, mild anterior uveal reactions, vitreous opacities and retinal vascular sheathing, remained unchanged. Examination in 1987 at 17 years of age revealed right best visual acuity of 0.9, nearly clear anterior chamber, decreased vitreous opacities, and retinochoroidal atrophic spots scattered in the equator. Thereafter, mild anterior uveal reactions recurred, which resolved in a few weeks with topical corticosteroids. In early 1995, at 25 years of age, it was noted that she had trouble walking. She was admitted to our hospital, and neurologic examination revealed abnormalities compatible with HAM; the titer of antibodies to HTLV-I was 8,192 in serum and 512 in cerebrospinal fluid. Ocular examination at this time showed no active uveitis with stationary retinochoroidal atrophic focal lesions, but right best vision was 0.4 because of corticosteroid-induced posterior subcapsular lens opacities.

Discussion

The acute phase of HAU usually lasts for a few weeks, probably is shortened by corticosteroids, and resolves with no clinical trace. Its clinical course is characterized by recurrence of uveal inflammation.[11,12] The above results from an average follow-up of 83 months indicate that about 60% of cases de-

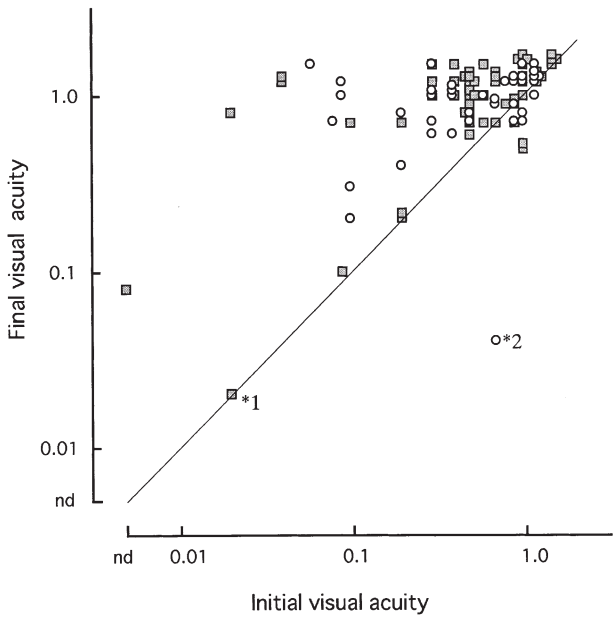

Figure 4. Comparison between best visual acuities on initial and final examination. Ninety-six affected eyes of 70 cases. Squares represent cases with single episode; circles, cases with multiple episodes. *1, patient with diabetic retinopathy; *2, patient with steroid cataract.

Jpn J Ophthalmol
Vol 43: 404–409, 1999

velop no further episode whereas the remaining cases have multiple exacerbations up to 9 times. The time interval between episodes varies but most frequently is within 1 year. Complete relief is likely if remission has lasted for 3 years. Because the recurrence rate appears not to depend on the age of onset, sex, or intensity of inflammation, it is hard to predict at initial presentation whether there will be recurrence. It is, however, remarkable that each episode of uveal inflammation is virtually self-limited or responsive to corticosteroids and that the long-term visual outcome is usually favorable, irrespective of repeated episodes, except for occasional cases of moderate permanent visual loss resulting from inflammatory sequelae such as retinochoroidal atrophy or secondary glaucoma. This essentially benign course with favorable visual outcome even after multiple recurrence provides a striking contrast to other uveitis entities such as Behçet's disease in which recurrent inflammation may lead to a progressive visual decline.

HAU occurs, not only as an isolated ocular disorder in otherwise healthy HTLV-I carriers, but also as part of HTLV-I–related systemic diseases.[1,11] The distinct uveitis entity was first described in patients with HAM, a neurologic disease that affects adults carrying HTLV-I and predominantly involves the pyramidal tracts. HAM is characterized by a slowly progressive spastic paraparesis presenting with symptoms and signs such as gait disturbance, spastic bladder, and sensory disturbance.[14,15] The uveitis in patients with HAM is similar to that in isolated HAU,[11,12] but according to our results, it is more likely to recur. Previous reports[1,11,13] described identification of HAU during the follow-up of HAM; the uveal inflammatory disease became manifest during the course of chronic progressive neurological disease. In this study, two cases presenting initially with isolated HAU developed features compatible with HAM many years later. In conjunction with the established etiologic role of HTLV-I in HAM, the new findings provide additional evidence that nonspecific uveitis in HTLV-I carriers is caused by the retrovirus and gives insight into the pathological mechanism of HAU. Immune-mediated intraocular reaction is thought to be relevant to the pathogenesis of HAU: intraocular T-cells activated by HTLV-I contribute to constitutive cytokine production, thereby causing intraocular inflammation.[16] The recurrent feature of HAU might reflect the changing immunologic status of individuals carrying HTLV-I. It is tempting to speculate that subtle episodic inflammatory processes might occur in the spinal cord during the long, insidious course of HAM.

Case studies of HAU reported the association of hyperthyroidism or Graves' disease in 6 (7.9%) of 76 patients in one study[17] and 16 (17.2%) of 93 patients in another study.[18] Our study confirms these previous reports, demonstrating that 14 (20.0%) of 70 HAU patients had hyperthyroidism. It is noteworthy that many cases had a uveitic episode shortly after initiation of thiamazole administration. One case had recurrent uveitis after each initiation of antithyroid therapy. An additional description is the case with concomitant association of HAU, HAM, and hyperthyroidism. The detection of antibodies to HTLV-I in the thyroid tissue of HAU[19] and the high prevalence of thyroid autoantibodies in HTLV-I carriers,[20] suggest that the characteristic uveitis in HTLV-I carriers is caused by an immune-mediated or autoimmune pathological mechanism modified by the retrovirus.

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