ORIGINAL ARTICLES – Clinical science

Human T lymphotropic virus type 1 uveitis after Graves' disease

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Abstract

A distinct clinical entity of uveitis associated with human T lymphotropic virus type 1 (HTLV-I) has been reported previously. During the period between January 1989 and April 1992, 93 patients were observed with HTLV-I uveitis and a significant correlation was found between Graves' disease and HTLV-I uveitis. Sixteen of the 93 patients with HTLV-I uveitis (17·2%) had a previous history of Graves' disease. Fifteen patients were female (15/60, 25·0%) and one was male (1/33, 3·0%). Interestingly, uveitis occurred after the onset of Graves' disease in all cases. On the other hand, none of 222 patients with idiopathic uveitis who were seronegative to HTLV-I had a history of Graves' disease. Although the mechanisms by which HTLV-I causes the correlation between uveitis and Graves' disease are unknown, the present data suggest that immune mediated or autoimmune mechanisms are involved in HTLV-I uveitis.

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Human T lymphotropic virus type 1 (HTLV-I) is a human retrovirus highly endemic in the Caribbean islands, parts of central Africa, and south west Japan (Miyazaki, Kagoshima, and Okinawa).[1] The virus is a causative agent for T cell malignancy such as adult T cell leukaemia/lymphoma (ATL),[2,3] and chronic myelopathy such as HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP).[4,5]

Recently, we have reported seroepidemiological, clinical, and virological studies carried out in an HTLV-I endemic area in Japan which suggest that HTLV-I is also a causative agent for uveitis previously diagnosed as idiopathic: (1) HTLV-I infection was a high risk factor for idiopathic uveitis[6,7]; (2) the idiopathic uveitis seen in HTLV-I carriers had the characteristic clinical feature of being an intermediate uveitis with moderate or heavy vitreous opacities accompanied by mild iritis and retinal vasculitis[8]; and (3) HTLV-I infected cells were detected by polymerase chain reaction (PCR) in all tested samples of aqueous humour from patients with uveitis, but not in control samples from seronegative patients or even from seropositive patients who had other types of uveitis such as Behçet's disease.[9] Our previous data thus indicate that the uveitis in HTLV-I carriers (HTLV-I uveitis) is a distinct clinical entity, though the pathogenic mechanism of HTLV-I uveitis is still not known and remains to be investigated.

More recently, we performed a case-control study comparing the clinical feature of idiopathic uveitis by HTLV-I seropositivity to determine the clinical feature of HTLV-I uveitis.[10] During the case-control study, we observed 93 patients with HTLV-I uveitis and found a high incidence of Graves' disease. Interestingly, the uveitis occurred after the onset of Graves' disease in all cases. The present study reports the cases of HTLV-I uveitis after Graves' disease.

Patients and methods

A total of 93 patients (33 male (median age 44·2 years) and 60 female (median age 47·1 years)) with HTLV-I uveitis and 222 patients (104 male (median age 44·0 years) and 118 female (median age 46·9 years)) with idiopathic uveitis who were seronegative to HTLV-I were reviewed with special attention given to any medical history of Graves' disease. The subjects were patients at Miyata Eye Hospital, located in an HTLV-I endemic area (Miyakonojo, Miyazaki), and at Kurume University Hospital, located in a less HTLV-I endemic area (Kurume, Fukuoka), from January 1989 to April 1992.

The diagnosis of HTLV-I uveitis was made by the following criteria: (1) the serum antibody to HTLV-I was positive by the particle agglutination (PA) assay (Fujirebio, Tokyo) and the enzyme linked immunosorbent assay (ELISA) (Eisai, Tokyo); (2) patients with ATL or HAM/TSP were excluded from our study; and (3) any causes of uveitis with defined aetiology, such as Behçet's disease, Vogt-Koyanagi-Harada's disease, sarcoidosis, toxoplasmosis, tuberculosis, syphilis, and the like, were excluded by routine ophthalmic and systemic examinations. The systemic examination for the diagnosis of uveitis included peripheral blood analysis, blood chemistry, chest *x* ray, tuberculin skin test, serological tests for syphilis and toxoplasmosis, and angiotensin converting enzyme.

The diagnosis of Graves' disease was based on established criteria which included: clinical and chemical hyperthyroidism, combined with diffuse enlargement of the thyroid. Hashimoto's

thyroiditis, idiopathic myxoedema and non-autoimmune thyroid diseases including multinodular nontoxic goitre, autonomously functioning thyroid nodule multinodular toxic goitre were excluded.

If the patients had a history of Graves' disease or had had any episodes of the disease, they were referred to the department of internal medicine, Kumamoto University Hospital for systemic examinations that included (1) serum anti-HTLV-I antibody to confirm the seropositivity of HTLV-I, (2) tests of thyroid function, and (3) detailed review of the history of Graves' disease and the therapy for the disease.

THYROID FUNCTION TESTS

Serum thyroxine (T4), triiodothyronine (T3), free T4, and free T3 levels were measured by radioimmunoassay using commercially available kits (Amersham International Ltd, Buckinghamshire). Serum thyroid stimulating hormone (TSH) levels were measured by a radioimmunometric assay (Amersham International Ltd). Anti-thyroglobulin and anti-thyroid microsomal antigen titres were determined using commercially available kits (Fujirebio Inc, Tokyo).

Results

Sixteen of the 93 patients with HTLV-I uveitis (17·2%) had a previous history of Graves' disease. Fifteen patients were female (15/60 (25·0%), median age 48·0 years) and one was male (1/33 (3·0%), 25 years). Table 1 summarises the profile of the 16 patients. On the other hand, none of the 222 patients with idiopathic uveitis who were seronegative to HTLV-I had a history of Graves' disease. The difference was statistically significant ($p<0·001$).

The diagnosis of Graves' disease had been made by local physicians based on the clinical and chemical hyperthyroidism before the patients developed uveitis. At the onset of Graves' disease, all 16 patients were suffering from signs and symptoms of thyrotoxicosis, such as goitre, weight loss, changes in temperature preference, shakiness of hands, and mood changes. In all 16 patients, uveitis occurred after the onset of Graves' disease and the time interval from the onset of Graves' disease to HTLV-I uveitis ranged from 7 months to 12 years (Table 1).

THYROID FUNCTION TESTS AT THE ONSET OF UVEITIS

Thyroid function tests were carried out in 15 of the 16 patients at the time of uveitis (Table 2). As shown in the table, at the onset of uveitis, the ranges of free T4 and free T3 were 0·31–3·64 ng/dl and 1·79–12·11 pg/ml, respectively. Free T4 levels were above normal in two and were below normal in three of the 15 patients. Free T3 levels were above normal in two and were below normal in four of the 15 patients. Antithyroglobulin and antithyroid microsomal antibodies were positive in two and 10 of 15 patients, respectively.

Table 1 HTLV-I uveitis after Graves' disease

Case	Age/sex	Onset of Graves' disease	Symptoms of Graves' disease	Diagnosis of HTLV-I uveitis	Interval to HTLV-I uveitis	Treatment for Graves' disease	Anti-HTLV-I antibody	
							PA titre	ELISA
1	55/F	1976	Goitre General fatigue	1988 April	12 Years	Methimazole	×256	+
2	60/F	1980 May	Goitre Palpitation	1991 March	11 Years	Methimazole	×4096	+
3	50/F	1983	Goitre Sweating	1991 May	8 Years	Methimazole	×1024	+
4	60/F	1985 June	Palpitation Weight loss	1991 June	6 Years	Methimazole	×1024	+
5	38/F	1985 August	Goitre Palpitation Sweating	1990 October	5 Years	Methimazole	×512	+
6	54/F	1985	Palpitation	1988	3 Years	Methimazole	×8192	+
7	51/F	1986	Goitre Sweating	1989 June	3 Years	Methimazole	×2048	+
8	27/F	1988 April	Goitre Palpitation Sweating	1990 October	18 Months	Methimazole	×4096	+
9	25/M	1990 March	Weight loss Ophthalmoptosis Shakiness of hands	1991 June	15 Months	Radioactive iodine +methimazole	×1024	+
10	42/F	1988 August	Goitre Palpitation Sweating	1989 October	14 Months	Methimazole	×4096	+
11	30/F	1990 August	Goitre Palpitation Sweating	1991 October	14 Months	Methimazole	×256	+
12	70/F	1989 December	Mood changes	1990 December	12 Months	Methimazole	×512	+
13	49/F	1988 March	Goitre General fatigue Sweating	1988 December	9 Months	Surgical thyroidectomy +methimazole	×512	+
14	41/F	1989 June	Goitre Palpitation Sweating	1990 January	8 Months	Methimazole	×512	+
15	36/F	1991 January	General fatigue Palpitation	1991 August	7 Months	Methimazole	×4096	+
16	57/F	1986 November	Goitre Palpitation General fatigue	1987 July	7 Months	Methimazole Surgical thyroidectomy	×4096	+

PA titre=particle agglutination titre. ELISA=enzyme linked immunosorbent assay.

Table 2 Thyroid function at the time of uveitis onset

Case	TSH (μU/ml)	T3 (ng/ml)	T4 (μg/dl)	Free T4 (ng/dl)	Free T3 (pg/ml)	Antibodies to	
						Thyroglobulin	Microsome
2	0·07	4·53	7·12	0·31	4·40	<100	102 400
3	<0·06	1·93	26·84	2·98	8·12	<100	6 400
4	<0·06	1·41	15·47	1·63	4·75	<100	<100
5	0·51	1·76	7·30	0·65	4·73	<100	6 400
6	0·89	1·12	11·84	0·95	2·67	<100	25 600
7	0·70	1·14	10·31	0·81	3·37	<100	<100
8	0·69	1·43	13·19	1·47	4·69	<100	100
9	0·09	2·87	19·02	3·64	12·11	<100	6 400
10	1·41	1·12	11·84	0·71	2·60	400	102 400
11	4·35	1·33	17·68	1·13	4·50	<100	1 600
12	2·12	0·87	7·07	0·52	1·79	<100	<100
13	3·66	1·19	17·92	0·89	4·17	<100	6 400
14	4·15	1·00	12·66	0·87	2·90	<100	<100
15	1·78	0·79	13·41	0·93	2·80	400	1 600
16	1·86	0·64	4·97	0·68	2·32	<100	<100
Normal value	0·36–3·25	0·7–2·1	4·5-12·0	0·7–1·7	2·7–5·5	<100	<100

TSH=thyroid stimulating hormone, T3=triiodothyronine, T4=thyroxine.

CASE REPORT

A 25-year-old man (case 9 in Table 1) was referred to the radiology clinic at the Kumamoto University Hospital with chief complaints of tremor, weight loss (60 kg to 50 kg in a year), and tachycardia in March 1990. At his first presentation, his pulse rate was 102 per minute and the thyroid function test disclosed hyperthyroidism: thyroid stimulating hormone (TSH), <0·06 U/ml; T3, 5·19 ng/ml; T4, 24·99 μg/ml; free T4, 4·0 ng/dl; and free T3, 27·32 pg/ml. Antibodies to thyroglobulin and microsome were <100 and 6400, respectively. High uptake of gadolinium by thyroid was demonstrated by syntchigram (84·0% at 3 hours and 66·6% in 24 hours) and diffuse swelling of the thyroid was shown by echogram. Based on the clinical and laboratory findings, the patient was diagnosed as having Graves' disease and treated with methimazole. In late June 1991, he had floaters and decreased vision in his left eye of acute onset. The signs progressed with time and he was referred to our uveitis clinic on 31 August 1991. At the first presentation, the best corrected visual acuity in his left eye was 0·6 and the intraocular pressure was 12 mm Hg by applanation tonometry. The left eye had moderate iritis with ciliary injection and a moderate number of cells (40–50 cells/field). There were no nodules in the iris and the trabecular meshwork. Ophthalmoscopy disclosed mild vitreous opacities with fine cells and membranous opacities (Fig 1). The patient was treated with systemic prednisolone (30 mg/day) for 1 week, after which treatment was slowly tapered. The vitreous opacities decreased in 4 weeks on prednisolone treatment and the visual acuity of his left eye was 1·2 on 1 October 1991. The diagnostic laboratory examinations for uveitis were normal except for the serum antibodies to HTLV-I which were positive by ELISA and ×256 by PA. The examinations of thyroid function at the time of uveitis onset disclosed hyperthyroidism as shown in Table 2.

Discussion

The present study reported for the first time a close relation between Graves' disease and uveitis in HTLV-I carriers. In a series of 93 patients with HTLV-I uveitis, 16 patients (17·2%) had a previous history of Graves' disease and all 16 developed uveitis after the onset of Graves' disease. The time interval from the onset of Graves' disease to uveitis varied from 7 months to 12 years. As a result of the treatment for Graves' disease, nine patients had normal thyroid function at the time of uveitis and two patients (cases 12 and 16) had hypothyroid function, though four patients (cases 3, 4, 9 and 11) still had hyperthyroid function.

Although the mechanisms by which HTLV-I causes the high correlation between uveitis and Graves' disease are unknown, three hypotheses could be considered. Firstly, an excess of thyroid hormone may modify the immune response or activate the virus replication and/or expand the number of HTLV-I infected lymphocytes. Then these circulating and/or locally infiltrating HTLV-I infected cells may affect the intraocular tissues, leading to uveitis. The second hypothesis concerns the effects of the medication used to treat Graves' disease (methimazole). The changes in thyroid hormone from high level to normal or low level caused by the medication or the agent itself could be related to the development of uveitis. The third hypothesis is that there might be a correlation between HTLV-I infection and Graves' disease similar to the high association between HTLV-I infection and uveitis.

As for the first hypothesis, it does not seem to reconcile with the fact that many of the patients were euthyroid or even hypothyroid at the time of uveitis, although the hypothesis could explain the order of the onset of the two diseases – that is, from Graves' disease to uveitis in all 16 patients. The second hypothesis is most unlikely because no significant incidence of uveitis has been reported in patients with Graves' disease on antithyroid drugs. As for the third hypothesis, we carried out a seroepidemiological survey in a large number of patients with Graves' disease to determine if there is any significant association between HTLV-I infection and Graves' disease.[11] The seroprevalence of HTLV-I in patients with Graves' disease was 78/1177 (6·6%) (male; 14/260 (5·4%), female 64/917 (7·0%)) and this was significantly higher than that of control, 44/852 (5·1%)[11] ($p<0·05$, by logistic model[12]). This result indicates that there is a significant association between HTLV-I infection and Graves' disease. However, it is still unknown why Graves' disease occurred before the onset of uveitis in the 16 patients. It can be hypothesised that the eye is more resistant to the changes caused by HTLV-I infection than is the thyroid, because the eye is isolated and protected from the systemic circulation by the blood-ocular barrier.

The high association between Graves' disease and idiopathic uveitis in HTLV-I carriers suggests that HTLV-I infection produces changes in the immune system which predispose to autoimmune disease, since both Graves' disease and idiopathic uveitis are considered to be immune mediated or autoimmune diseases. It is well known that HTLV-I is transmitted to CD4 positive T lymphocytes and the HTLV-I infected T lymphocytes express interleukin 2 receptors and produce a variety of lymphokines, indicating that HTLV-I infected lymphocytes

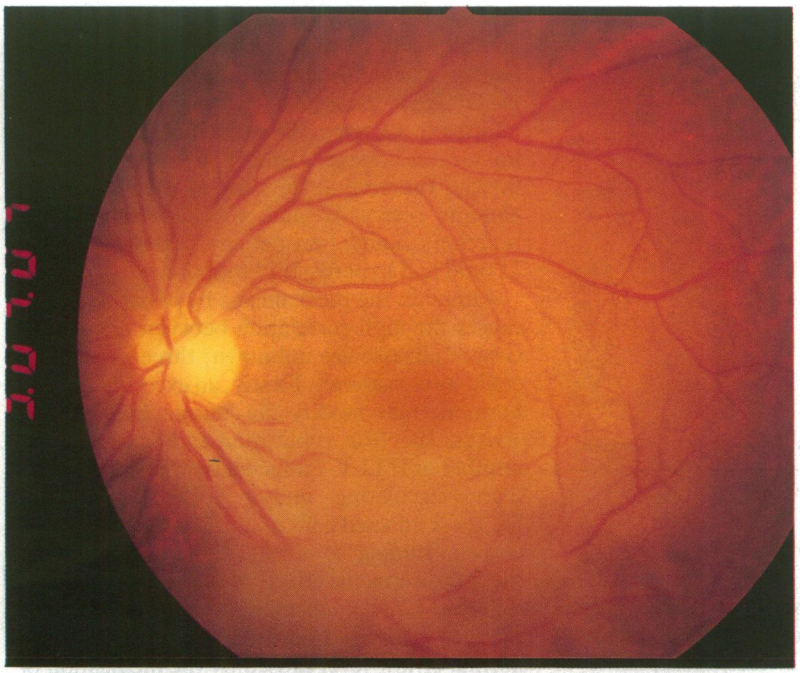

Fig 1A

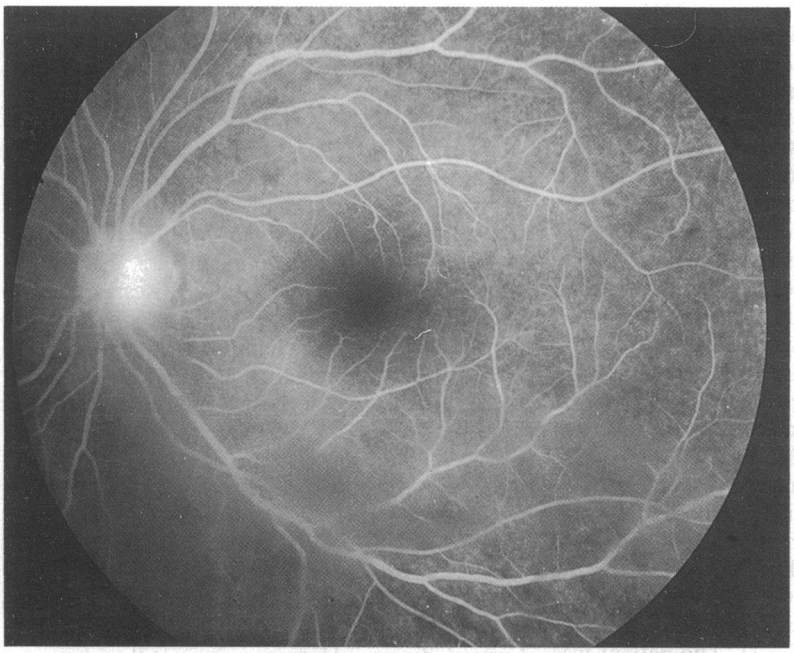

Fig 1B

Figure 1 Ophthalmoscopic view (A) and fluorescein angiography (B) at the time of onset of HTLV-I uveitis (August 1991) (case 9; a 25-year-old man). Fine cells and mild membranous opacities were present in the vitreous body near the retinal blood vessels at the posterior pole of the fundus.

are activated T lymphocytes.[13] It is well documented that the activated lymphocytes play a significant role in the development of uveitis.[14] There are several case reports suggesting an association of human retroviruses and autoimmune diseases: Sjogren's syndrome,[15] multiple sclerosis,[16] or thrombocytopenic purpura[17] in association with HTLV-I infection, and Sjogren's syndrome-like illness[18] or thrombocytopenic purpura[19 20] in association with HIV infection. The present cases of HTLV-I uveitis after Graves' disease together with these previous reports implicate a significant role of retroviruses in autoimmune disease and, further, the pathogenesis of diseases with infectious/autoimmune overlap. It is unknown whether the two autoimmune processes (uveitis and Graves' disease) in our patients occurred independently as a part of the infection with HTLV-I or that there might be a link between the two. This should be answered in future by examining whether there are cross reactive epitopes in thyroid antigens and ocular antigens to HTLV-I (or HTLV-I infected T lymphocytes).

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