ELSEVIER

Influence of Immunosuppression in HTLV-1–Positive Renal Transplant Recipients

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THE USE OF IMMUNOLOGY suppression in renal transplant patients enables opportunistic development of not only infections, but also malignancies.[1] One such example is the RNA retrovirus human T cell lymphotrophic virus–1 (HTLV-1). This retrovirus has been implicated in causing the lymphoproliferative disorder, Adult T-cell leukemia/lymphoma (ATL). ATL is an insidious disease, usually presenting after a long latency period and exhibiting low morbidity. HTLV-1 had also been associated with others such as HTLV-1–associated myelopathy (HAM/TSP), HTLV-1–associated bronchopneumonopathy, HTLV-1–associated arthropathy, uveitis, Sjögren's syndrome, and glucose tolerance disorder.[2]

MATERIALS AND METHODS

From 1985 through 1997, 152 renal transplants were performed in Okinawa, Japan. In each of these, the patients were screened with preoperative and postoperative HTLV-1 titers. Appropriate screening for ATL[3] and HAM[4] was performed on the basis of physical examination and laboratory data.

The incidence of HTLV-1 in potential kidney recipients was obtained from the Japan Organ Transplant Network (JOTN) information obtained from hemodialysis patients. The background incidence of HTLV-1 positively for all Okinawa was obtained from the Red Cross.

RESULTS

In Okinawa, of the 152 renal transplants, 15 (9.9%) were HTLV-1–positive (Table 1). Of these, 9 underwent living-related kidney transplants, 6 received cadaveric kidneys. The patients range in age from 26 to 49 (mean, 39.5) years. The preoperative HTLV-1 titers revealed that 8 were positive preoperatively and another 6 were negative preoperatively, and converted after transplantation. One patient's preoperative status was unknown. The immunosuppressive agents used after kidney transplant included cyclosporine A, steroids, azathioprine and mizoribine. Antithlymphocyte globulin was used as induction therapy immediately after

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Table 1. HTLV-1–Positive Renal Transplant Cases in Okinawa, Japan (1985–1997)

Case	Present age of recipient	Follow-up after transplant	Immunosuppression drugs	HTLV-1* donor recipient	Kidney prognosis	ATL HAM	
1	36	10 y	4 mo	CyA + MZ + PSL	+ → −	LD lost	No
2	40	10 y	1 mo	CyA + MZ + PSL	+ → −	LD function	No
3	49	9 y	9 mo	CyA + AZ + PSL	− → +	LD lost	No
4	38	7 y	7 mo	CyA + AZ + PSL	+ → −	LD function	No
5	37	7 y	5 mo	CyA + AZ + PSL	+ → +	LD function	No
6	36	6 y	1 mo	CyA + AZ + PSL	+ → −	LD function	No
7	26	5 y	0 mo	CyA + AZ + PSL + ALG	+ → +	CD function	No
8	48	4 y	4 mo	CyA + MZ + PSL + ALG	+ → ?	CD function	No
9	46	3 y	11 mo	CyA + AZ + PSL + ALG	+ → +	CD lost	No
10	48	4 y	6 mo	CyA + MZ + PSL + ALG	? → +	LD function	No
11	36	4 y	4 mo	CyA + AZ + MZ + PSL + ALG	+ → −	CD lost	No
12	42	3 y	11 mo	CyA + AZ + MZ + PSL + ALG	+ → +	CD lost	No
13	32	3 y	2 mo	CyA + MZ + PSL + ALG	? → +	LD function	No
14	39	1 y	11 mo	CyA + AZ + MZ + PSL + ALG	− → +	CD function	No
15	40	8 y	6 mo	CyA + MZ + PSL	+ → −	LD function	No

Abbreviations: CyA, cyclosporine A; AZ, azathioprine; MZ, mizoribin; PSL, prednisolone; ALG, antilymphocyte globulin; LD, living related donor; CD, cadaveric donor.

*This data reveals the result of pretransplant HTLV-1 titers of donor and recipient.

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Table 2. Incidence of HTLV-1 in Blood Donors From Okinawa, Japan (1994)

Age	Gender	Odds ratio (%)
10s	M	1.21
	F	1.22
	Total	1.22
20s	M	1.6
	F	1.47
	Total	1.54
30s	M	3.79
	F	4.85
	Total	4.05
40s	M	6.87
	F	8.13
	Total	7.17
50s	M	8.62
	F	13.56
	Total	10.09
Total	M	3.86
	F	3.37
	Total	3.68

the operation in all cadaveric and one living related donors. Follow-up times range from 1 year and 11 months to 10 years and 4 months. There have been no cases of disease related to HTLV-1 in any of our patients to date. One patient (case no. 5) had evidence of the smouldering type[5] of ATL pretransplant; however, there were no abnormal lymphocytes detected during his postoperative surveillance. Recent data obtained from the Red Cross show the incidence of HTLV-1 in Okinawa to be 3.2% to 4.2%, overall, although the incidence increases proportionally with increasing age (Table 2). Of the 359 hemodialysis patients registrated with JOTN awaiting renal transplant, 42 (11.7%) are HTLV-1–positive, 301 are HTLV-1–negative and in 14 cases, the HTLV-1 status is unknown. Compared with the general population of Okinawa, these rates are high.

DISCUSSION

ATL is a T-lymphocyte monoclonal proliferative disorder that is caused by HTLV-1 infection. The incidence of HTLV-1 shows distinct geographic variation. There are three major endemic populations of HTLV-1 in the world, Japanese living in southern Japan, Africans in central Africa, and inhabitants of the Caribbean basin.[6] Okinawa, which is in southern Japan, is an endemic area of HTLV-1. Management of HTLV-1–positive individuals with respect to kidney donations is an important issue in Okinawa. Although HTLV-1 has five subtypes (Asia type, the Pacific Ocean type, the Atlantic Ocean type, Central Asia type, Malaysian type), these have no role in clinical medicine. Despite the fact that Okinawans have the Atlantic Ocean type and inhabitants of Kyushu, Japan, have the Asian type,[7] there is no cross-reactivity seen.

In nonimmunocompromised persons, HTLV-1 infection is a relatively insignificant problem. The morbidity of ATL is 0.1% to 0.2% per year with a cumulative morbidity up to age 70 years of 2% to 5%.[8] The average age of onset of ATL is 57 years and it does not often affect persons younger than 40 years old.[9] Male and female infection rates are similar at 1.2:1. The known routes of transmission of the HTLV-1 virus are from mother to infant via breast feeding (vertical transmission), husband to wife via semen (horizontal transmission), or via blood transfusion. However, there are not known reports of the development of ATL associated with horizontal transmission or after blood transfusion. Occurrence of ATL in the setting of immunosuppression is unknown. We reviewed those patients with HTLV-1 who underwent renal transplantation in the past. The literature documents three cases[10–12] in which HTLV-1–positive recipients developed ATL after transplant. But the HTLV-1 status of the recipient before transplant was not known.

A related issue is the development of HAM/TSP, which is a chronic immunological inflammation of the spinal cord that results in spastic spinal paresis. Although there are no documented cases of ATL after transfusion of HTLV-1–positive blood, there are multiple reports of the development of HAM.[13] Although there are no reported cases of HAM after kidney transplantation, this association with blood transfusion makes it more worrisome.

According to the JOTN donor criteria, because it is not clear how these problems will manifest in an immunocompromised patient, kidneys from HTLV-1–positive donors are not considered appropriate for organ donation, even if the recipient is also HTLV-1–positive. A parallel model exists in examining ATL in HTLV-1 patients after blood transfusion. With blood transfusions, the literature reports no cases of ATL, but does report the development of HAM. In our cases, ATL, HAM or HTLV-1–associated disorders did not occur after kidney transplantation.

In Okinawa, the current JOTN criteria excludes 3% to 5% of the population as kidney donors. Because the occurrence rate of ATL and HAM in immunocompromised patient is unknown, we believe this topic deserves further investigation. A consideration should be made for allowing the transplantation of HTLV-1–positive donor kidneys to HTLV-1–positive recipients, once patients are made aware of the possibilities of developing either HAM or ATL. With the high numbers of HTLV-1–positive patients on hemodialysis who are awaiting kidney donation, the inclusion of otherwise healthy HTLV-1–positive persons in the pool of donors could greatly improve the odds of successful kidney transplants.

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