

# Human T Lymphotropic Virus Type-1-associated Myelopathy Manifesting Shortly after Living-donor Renal Transplantation

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## Abstract

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A 38-year-old woman experienced numbness in both lower extremities and spastic paralysis a few months after undergoing living-donor renal transplantation. The patient was negative for human T lymphotropic virus type-1 (HTLV-1) antibodies prior to the procedure; however, she was diagnosed with HTLV-1-associated myelopathy (HAM) based on positive serum and cerebrospinal fluid antibody titers after the surgery. Because the donor was also positive for HTLV-1 antibodies, the infection likely originated from the transplanted kidney. Clinical and imaging improvements were noted following the administration of interferon- $\alpha$ . HAM has been reported to occur after living-donor renal transplantation; however, there are no previous reports of onset within such a short period.

**Key words:** HAM, renal transplantation

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## Introduction

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Human T-lymphotropic virus type 1 (HTLV-1) was discovered in 1980 (1). It is estimated that 15-20 million people are infected with this virus worldwide (2, 3). HTLV-1 is primarily transmitted via cell-to-cell contact (4, 5). Although blood transfusion and organ transplantation are the most efficient modes of viral transmission, most HTLV-1 infections are attributable to transmission from mother to child during breastfeeding or sexual contact later in life (6).

HTLV-1-associated myelopathy (HAM), which is caused by HTLV-1, is a chronic progressive myelopathy characterized by spastic paraparesis, sphincter dysfunction and mild sensory disturbances of the lower extremities (7). The majority of cases of HTLV-1 do not involve clinical symptoms; however, a minority of affected patients (<5%) develop HAM after a long asymptomatic period (8, 9). The onset of HAM is insidious, with neurological symptoms usually appearing in the fourth or fifth decade of life (7, 10). HAM occurs more frequently in cases in which HTLV-1 is acquired through blood transfusion or renal transplantation,

often with a shorter duration of latency (11-16). We herein report a case of HAM caused by renal transplantation from a living donor and discuss possible mechanisms underlying the rapid onset and progression of HAM. To our knowledge, this case involves the most rapid manifestation of symptoms reported to date.

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## Case Report

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The case involved a 38-year-old woman whose parents were from Okinawa and had emigrated to Brazil. The patient herself was born in Brazil, but grew up in Okinawa. She had no history of blood transfusion; however, she had experienced renal failure of unknown origin in 2005 after the birth of her second child and began to receive maintenance blood dialysis in 2010. She subsequently underwent living-donor renal transplantation (donor: real brother) in August 2012, after which oral tacrolimus (5 mg/day) and mycophenolate mofetil (1,500 mg/day) were administered. The patient first experienced numbness in both lower extremities in October 2012. She then developed a gait disturbance in December 2013 and was referred to the neurology



**Figure 1.** Spinal magnetic resonance imaging performed on admission. Areas of intraspinal hyperintensity and swelling are visible from the lower portion of the cervical spinal cord to Th8 on T2WI.



**Figure 2.** Spinal magnetic resonance imaging performed after treatment. The areas of intraspinal hyperintensity on T2WI as well as spinal swelling have almost completely disappeared.

department for an examination in January 2013.

A general physical examination performed on admission revealed no abnormalities, with the exception of an abdominal surgical scar. Neurological testing showed lucid consciousness; however, tremors were observed in the upper extremity posture, thought to be due to adverse effects of tacrolimus. Spasticity of the lower extremities was also noted. Manual muscle testing showed grade 4 muscle weakness in the upper and lower extremities. The patient's deep tendon reflexes were aggravated in the mandibular reflex and upper and lower extremities, and knee and foot clonus was detected. In addition, she was bilaterally positive for the Babinski sign, with numbness in both lower extremities, although no objective abnormalities were found in the sensory system. In contrast, frequent micturition indicated dysfunction of the autonomic nervous system.

A blood examination conducted on admission showed a normal blood count and general biochemical profile. The patient's serum was positive for anti HTLV-1 antibodies on Western blotting and CLEIA ( $> \times 45$ ), with a blood proviral level of 15.0 copies/1,000 peripheral blood mononucleated cells, cerebrospinal fluid (CSF) neopterin level of 51 pmol/mL (reference range:  $< 30$  pmol/mL) and soluble interleukin-2 receptor level of 686 U/mL (reference range: 145-519 U/mL). The proportion of CD4+ cells was 54.4%, while that of CD8+ cells was 31.3% (CD4/CD8=1.74), and a spinal tap revealed an opening pressure of 75 mm H<sub>2</sub>O. The CSF was colorless and clear, with a cell count of 186 (mononuclear: 184) cells/ $\mu$ L and an elevated protein level of 170 mg/dL. The immunoglobulin G index was 0.72, and oligoclonal bands were positive. The CSF was also positive for anti HTLV-1 antibodies on PA ( $> \times 32$ ), while human leukocyte antigen (HLA) testing revealed types A2, A11, B61, B-, DR11 and DR15. Spinal magnetic resonance imaging (MRI)

performed on admission showed a hyperintense area extending from the cervical to thoracic spinal cord on T2WI. Swelling was also noted ranging from the level of the lower cervical cord to the middle thoracic cord (Fig. 1). In addition, brain MRI showed hyperintense areas on both sides of the funiculus lateralis spreading from the anterior horn of the upper cervical spinal cord on T2WI, although no abnormalities were detected in the other horn.

The patient had been negative for serum HTLV-1 antibodies prior to undergoing renal transplantation; however, she was diagnosed with HAM on admission based on high levels of HTLV-1 antibodies in the blood and CSF combined with clinical features consistent with the disease. The clinical motor function was grade 5 according to Osame's Motor Disability score. Interferon- $\alpha$  treatment was therefore administered, and the patient received 3 million units/day continuously for four weeks. Spinal MRI performed one month after therapy showed almost complete resolution of the intraspinal regions of high intensity on T2WI as well as the spinal swelling (Fig. 2). One month after the initiation of therapy, the patient's gait disturbance improved; the Osame's Motor Disability score decreased to grade 4.

## Discussion

The unique characteristic of this case is the early onset of HAM following living-donor renal transplantation. The development of HAM after following renal transplantation has been reported in six cases to date (12-16) (Table). In previous cases, the period between transplantation and the onset of HAM ranged between 17 months and 7 years (mean: 3.3 years) after cadaveric renal transplantation and only 10 and 11 months after living-donor renal transplantation (16). Therefore, the two-month period to onset observed in the present case is much shorter than that previously reported.

Vertical transmission was also considered as a source of

**Table. Cases of Human T Lymphotropic Virus Type-1-associated Myelopathy after Renal Transplantation**

Reference	Age/ gender	HLA typing	Donor	Period after transplantation	Immunosuppressants	Treatment	Effect
12	32/M	A24	mother	11 months	CsA/MZR/ AZA/mPSL	IFN- $\alpha$ →PE	temporarily improved
13	54/M	none reported	CD	4 years	CsA/MMF/mPSL	none reported	none reported
14	56/M	none reported	CD	7 years	CsA/MZR/mPSL	PE	none reported
15	54/F	A2	CD	2 years	CsA/mPSL	oral prednisolone	not effective
	57/M	A2	CD	2 years	CsA	oral prednisolone	none reported
16	54/M	DR4, DR9	sister	10 months	CsA/mPSL	IFN- $\alpha$	improved
present case	38/F	A2, A11, B61, B-, DR11, DR15	brother	2 months	TAC/MMF	IFN- $\alpha$	improved

CD: cadaveric renal transplantation, CsA: cyclosporin, MMF: mycophenolate mofetil, mPSL: methylprednisolone, MZR: mizoribine, AZA: azathioprine, TAC: tacrolimus, IFN- $\alpha$ : Interferon- $\alpha$ , PE: plasma exchange

HTLV-1 infection in this case; however, the patient was negative for this virus before undergoing renal transplantation. The donor blood examined after the onset of HAM was found to be positive for HTLV-1 antibodies on Western blotting and chemiluminescence enzyme immunoassay (CLEIA) ( $\times 43.4$ ). The patient was subsequently found to be positive for serum HTLV-1 antibodies after transplantation, likely due to transfer of these antibodies from the donor, who was a carrier of HTLV-1, suggesting conversion following renal transplantation. Renal transplantation is not normally considered to be a risk factor for the onset of HAM in HTLV-1-carrier recipients (17, 18). Other reports of the development of HAM following renal transplantation have also described the possible transmission from an infected donor (12-16). However, reports of causative correlations between infection from an HTLV-1-carrier donor and the onset of HAM are rare.

A high titer of HTLV-I-infected cells (virus quantity) has been reported to correlate with the risk of onset, as well as the prognosis, of HAM (19). The development of HAM occurs more quickly in the setting of living-donor transplantation than in that of cadaveric renal transplantation, likely due to the direct transfer of a high quantity of the virus to the transplant recipient. The proviral DNA levels in this case were high. However, because the measurement methods were not uniform, it is difficult to compare our findings with the results of other studies. In addition, methylprednisolone and cyclosporin (CsA) were used in combination as immunosuppressive drugs for post-living-donor renal transplantation in previous reports (12-16), but not in the present case. Caillard et al. reported that patients treated with tacrolimus are at greater risk of developing post-transplant lymphoproliferative disorders than those treated with CsA after renal transplantation (20), and Kawano et al. reported that all patients (three) in their study who developed adult T-cell leukemia (ATL) after undergoing living-donor liver transplantation received tacrolimus, whereas the remaining three patients who received CsA did not (21). Steroid therapy has also been suggested to be effective in cases of HAM due to its anti-inflammatory effects (22-24). Therefore, the differences in immunosuppressive drugs and lack

of steroid use in the present case may account for the early onset observed in our patient.

The class I allele HLA-A2 has been reported to have a preventive effect against the development of HAM in patients infected with HTLV-1 (25). However, this allele was detected in three cases of HAM, including the present case (8), suggesting that the onset of HAM after transplantation does not correlate with this defense mechanism.

Reports of HAM onset following renal transplantation are rare. Therefore, further analyses of the pathology and treatment of this disease are required.

**The authors state that they have no Conflict of Interest (COI).**

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