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HTLV-I-associated myelopathy manifested after renal transplantation

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Abstract

We report a patient with HTLV-I-associated myelopathy (HAM), who developed symptoms of myelopathy 4 years after cadaveric renal transplantation. Since he was seronegative before the transplantation, it is suggested that HTLV-I infection was transmitted via renal graft transplantation. He has been treated with immunosuppressive agents such as cyclosporin A (CsA), mycophenolate mofetil (MMF), and prednisolone (PSL) to prevent graft rejection. This case suggested that these immunosuppressive agents are poorly effective in suppressing either the onset or progression of HAM/TSP.

Keywords: HAM; HTLV-I; Myelopathy; Transplantation; Cyclosporin A; Treatment; Immunosuppressive agents

1. Introduction

Human T-lymphotropic virus type-I (HTLV-I) is an etiologic agent for adult T-cell leukemia/lymphoma (ATL) [1] and HTLV-I-associated myelopathy (HAM)/tropical spastic paraparesis (TSP) [2,3]. Most HTLV-I infections are attributable to transmission from mother to child or to sexual contact later in life while transfusion is perhaps the most efficient mode of viral transmission [4]. There have been some reports of ATL developing in association with organ transplantation [5–7]. To our knowledge, this is the first case of HAM/TSP manifested after organ transplantation.

No treatment to inhibit the progression of the disease has yet been found though corticosteroids were reported to have beneficial effects for the treatment of HAM/TSP [2,8]. Since the activated mononuclear cells are considered to play a role in the pathogenesis of HAM/TSP, down-modulation of their process may be a rational therapy [9]. In fact a few papers suggested beneficial effects by immunosuppressive therapy [10,11] or by immuno-modality therapy [12,13].

We report here a case who was infected with HTLV-I through organ transplantation, and developed HAM/TSP while being treated with immunosuppressive agents.

2. Case report

A 50-year-old man was referred to our department in April 1999 complaining of the difficulty in walking. At the age of 41, he was diagnosed as having chronic renal failure due to chronic glomerulonephritis, and hemodialysis was introduced the following year. In December 1993, at the age of 45, he received cadaveric renal transplantation. The total ischemic time of the graft was 6 h. Since then, he has been treated with cyclosporin A (CsA; 200–125 mg/day), mycophenolate mofetil (MMF; 3000–2000 mg/day), and prednisolone (PSL; 15–7.5 mg/day) to prevent graft rejection up to the present time. Four years later, in December 1997, he felt dysesthesia in lower limbs and urinary disturbance followed by slowly progressive gait

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disturbance. Since these symptoms worsened and muscle stiffness and cramps occasionally occurred, he was referred to our department in April 1999. He has no history of receiving transfusions of blood products prior to or after renal transplantation.

Deep tendon reflexes were exaggerated in lower more than upper limbs with bilateral ankle clonus and positive pathological reflexes such as Babinski's and Wartenberg's signs. Muscle tonus was increased especially in lower limbs and the gait was spastic. Upper limb strength was normal, but mild muscle weakness was observed in lower limbs. He complained of hypesthesia and hypalgesia in distal lower limbs and of dysesthesia below the level of Th10 and in both hands. Cystometry revealed an atonic bladder. No cerebellar signs or extrapyramidal signs were seen.

Blood examination showed normal renal function, WBC 6570/μl, CD4+ cells 65.7%, CD8+ cells 18.4%, and soluble IL-2R 641 U/ml (normal <530). ATL-like cells with lobulated nuclei were found in the blood. Peripheral lymphocytes showed a increased spontaneous proliferation (patient 25 300 cpm, mean of two controls 5900 cpm) [14]. Cerebrospinal fluid (CSF) examination revealed that cell count was 12/mm^3 (mononuclear cells 90%, polymorphonuclear cells 10%), protein was 68 mg/dl, and IgG index was 0.69 (normal, <0.7). ELISA and Western blotting of blood samples identified antibodies to HTLV-I. Particle agglutination test revealed that CSF was positive for HTLV-I (>×32; normal, –) and cytomegalovirus (2.59; normal, <0.20). The class of the antibodies to cytomegalovirus has been IgG since it was first examined 2 weeks after renal transplantation. Antibodies to HTLV-I in his blood sample was negative when examined a day before renal transplantation. No abnormal findings were detected by MRI of brain and spinal cord and by chest X-ray film. Nerve conduction study showed normal latencies in posterior tibial, peroneal, and sural nerves and slightly prolonged latency in median nerve.

3. Discussion

The clinical manifestations and laboratory findings of this patient fulfilled the diagnostic guideline for HAM/TSP [2,8]. Though this patient has antibodies to cytomegalovirus in addition to HTLV-I, the class of the antibodies has been IgG since it was first examined 2 weeks after the transplantation and the titer has not been changed. He denied the experiences of sexual intercourse except with his wife, and he has never received blood transfusions which are possible causes of HTLV-I infection, and antibodies to HTLV-I were negative 1 day before the transplantation. The serological screening for HTLV-I from this organ donor was not performed. Together, these facts suggested that HTLV-I in this patient was transmitted by cadaveric renal transplant, though the possibility that HTLV-I was infected via hemodialysis performed immediately before the transplantation cannot be completely eliminated.

The characteristic laboratory findings in HAM/TSP are the increased HTLV-I proviral load in the peripheral blood [15], the increased spontaneous proliferation of peripheral blood lymphocytes (PBL) [14,16], and exaggerated HTLV-I-specific cytotoxic T lymphocytes (CTL) [17]. Thus, the activated T cells and exaggerated CTL response to HTLV-I are considered to play a role in the pathogenesis of HAM/TSP, and therapeutic strategies for HAM, therefore, include antiviral and immunosuppressive agents. CsA acts at the G0 phase by inhibiting calcineurin/calmodulin phosphatase activity required for IL-2 gene transcription in T-helper cells [18], and PSL decreases cytokines (e.g., IL-1, -2, -6) and cell surface molecules (e.g., ICAM-1, LFA-1) [19,20]. Both agents inhibit lymphocyte proliferation through different mechanisms [21]. CsA inhibited the spontaneous proliferation of the HAM/TSP-derived lymphocytes, and is suggested to be a potential agent for HAM/TSP treatment [11,22]. PSL was reported to have beneficial effects on HAM/TSP [2,8]. MMF is an inhibitor of the type 2 isoform of inosine monophosphate dehydrogenase (IMPDH) expressed in activated T and B lymphocytes [23], and inhibits the proliferation of both T and B cells [24]. Thus these immunosuppressive agents, CsA, PSL, and MMF inhibit lymphocyte activation through different mechanisms, and synergistic effects are expected. The development of HAM/TSP in this single case while being treated with immunosuppressive agents suggested that these drugs may not be enough to suppress activities of lymphocytes in vivo or to inhibit progression of the disease, and further studies are necessary to find out more efficient immunosuppressive agents in HAM/TSP treatment.

Two points should be emphasized in this report. The first is that it is possible to cause HAM/TSP by the infection of HTLV-I via organ transplantation. The second is that the immunosuppressive treatment for HAM/TSP other than CsA and MMF should be considered.

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