Posttransplant Lymphoproliferative Disorder With Lung Involvement in a Renal Transplant Recipient

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Abstract

Posttransplant lymphoproliferative disorder is one of the most important complications of solid-organ transplant in terms of malignancy. Here, we report a case of Epstein-Barr-virus–negative posttransplant lymphoproliferative disorder of T-cell type, involving the lung, in a renal transplant recipient.

A 23-year-old woman received a living-related renal transplant in 2002. She presented with a 6-month history of weight loss, malaise, night sweats, and lymphadenopathy 6 years after the transplant. Chest radiograph showed miliary opacities. We performed a biopsy of the submandibular mass and computed-tomography–guided transthoracic needle biopsy of the lung. Pathological investigation of lymphadenopathy and lung were inconsistent with posttransplant lymphoproliferative disorder of T-cell type. After the diagnosis of posttransplant lymphoproliferative disorder, her immunosuppressive regimen was modified, and she was treated with cyclophosphamide, doxorubicin, vincristine, prednisolone, ifosfamide, carboplatin, and etoposide chemotherapies, which resulted in partial remission.

Posttransplant lymphoproliferative disorders may be seen as an atypical presentation; the differential diagnosis should be thought of pulmonary infiltrates in renal transplant recipients.

Key words: *Posttransplant lymphoproliferative disorder, T-cell lymphoma, Renal transplant*

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Introduction

Posttransplant lymphoproliferative disorder is a recognized complication of solid-organ transplant in terms of malignancy.[1-3] The risk of the developing posttransplant lymphoproliferative disorder is clearly related to immunosuppressive regimens. Because transplant patients undergo immunosuppressive treatment for a long time, the risk of posttransplant lymphoproliferative disorder is higher in these patients compared with the general population.[1, 4, 5] Posttransplant lymphoproliferative disorders occur more commonly in the first years posttransplant[1, 3, 5]; they show an increased risk of occurrence in younger and older patients, and more frequently in children. Increased risk of posttransplant lymphoproliferative disorder in children may result from the fact that children are more frequently Epstein-Barr-virus–seronegative compared with adults during transplant.[2, 6] As many as 80% of cases of posttransplant lymphoproliferative disorder are positive for Epstein-Barr virus. They are typically of B-cell origin, T-cell lymphomas, or natural-killer–cell lymphomas in the transplant recipients, and are also classified as *posttransplant lymphoproliferative disorder*.[4, 7] The prognosis for posttransplant lymphoproliferative disorder is poor, with most patients dying despite treatment.[7] We report a case of posttransplant lymphoproliferative disorder with pulmonary involvement in a patient after renal transplant.

Case Report

A 23-year-old woman with end-stage renal failure resulting from focal segmental glomerulosclerosis received a living-related renal transplant from her mother in 2002. Her immunosuppressive regimen consisted of cyclosporine, azathioprine (75 mg/d),

and prednisolone (5 mg/d × 1 y). Because of cyclosporine toxicity, the regimen was replaced by tacrolimus, mycophenolate mofetil, and prednisolone. There were no episodes of rejection.

Six years later, she presented with a 6-month history of weight loss, malaise, night sweats, and lymphadenopathy. On examination, her vital signs were within normal limits. She had multiple lymphadenopathies on her neck, bilateral axilla, and inguinal areas with a size of nearly 2 to 3 cm in length and diameter. Breath sounds were diminished. Liver and spleen were enlarged. Laboratory data on admission were a white blood cell count of 7610/mm^3 with normal differential, hemoglobin of 9.7 g/dL, platelet count of 233 000/mm^3, normal electrolytes and liver functions, blood urea nitrogen of 15 mg/dL, creatinine of 1.5 mg/dL, and an elevated level of lactate dehydrogenase of 339 U/L. Results of a chest radiograph showed miliary opacities (Figure 1). The results of a Mantoux test were negative. Positron emission tomography/computed tomography revealed an intense hypermetabolic uptake in bilateral submandibular, axillary, chest, splenic area, para-aortic, mesenteric, iliac and inguinal conglomerate lymph nodes, and both lungs.

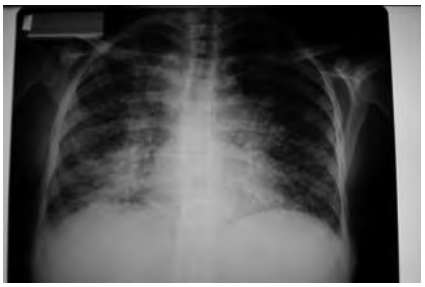

Figure 1. Radiograph of the lung before treatment.
Reticulonodular miliary pattern is observed in the lower lobes of both lungs.
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The excisional biopsy of the submandibular lymph node showed diffuse effacement of the structure by small- and medium-sized lymphoid cells having irregular nuclear outlines with inconspicuous nucleoli and scattered immunoblasts (Figure 1). Atypical lymphoid cells demonstrated positive for CD3, CD5, CD7, and CD4, and had a negative reaction to CD20, CD138, CD23, CD21, CD8, CD30, Cyclin D1, Bcl-6, TdT, granzyme-B, perforin, kappa, lambda, and EMA on immunohistochemistry. Transbronchial lung needle biopsy also showed atypical lymphoid infiltration, same as the lymph nodes (Figure 2). Immunohistochemically, atypical lymphoid cells demonstrated CD3, CD4, and CD5 positivity. Atypical cells were negative for Epstein-Barr virus on in-situ hybridization using the Epstein-Barr virus EBER1 RNA in both lymph nodes and the lungs. The histologic and immunohistochemical findings were monomorphic posttransplant lymphoproliferative disorder of peripheral T-cell lymphoma (not otherwise specified type) Epstein-Barr–virus negative. Epstein-Barr–virus DNA PCR was not detected by in-situ hybridization.

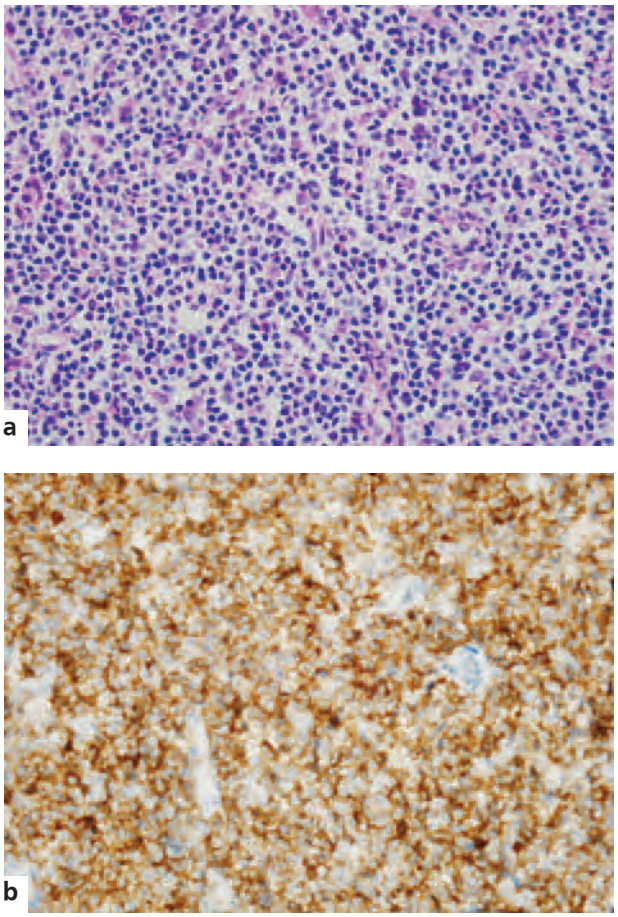

Figure 2. Lymph node biopsy.
(a) Lymph node biopsy characterized by diffuse nodal involvement. The tumor is composed predominantly of small cells, with scattered, large, transformed cells and nuclear irregularities (H&E ×400).
(b) CD3 is expressed by neoplastic cells with a strong cytoplasmic and membranous pattern (immunoperoxidase ×400).

The pretransplant and posttransplant Epstein-Barr–virus status of the patient was not known. No analyses about other viral causes (eg, HTLV-1 and -2, or HHV-8) were performed. Results of a bronchoscopy were normal. Bronchoalveolar fluid examination was normal; no acid-fast bacilli or malignant cells were seen. Also, the results of a

polymerase chain reaction test for tuberculosis, and a tuberculosis culture of the fluid were negative. A computed-tomography–guided transthoracic needle biopsy showed atypical lymphoid cells that were positive for CD3 and CD5 and negative for CD8 and CD30 (Figure 3). Results of a bone marrow aspirate and core biopsy were normal. No disorder related to tuberculosis was reported either in the bone marrow or lung biopsies.

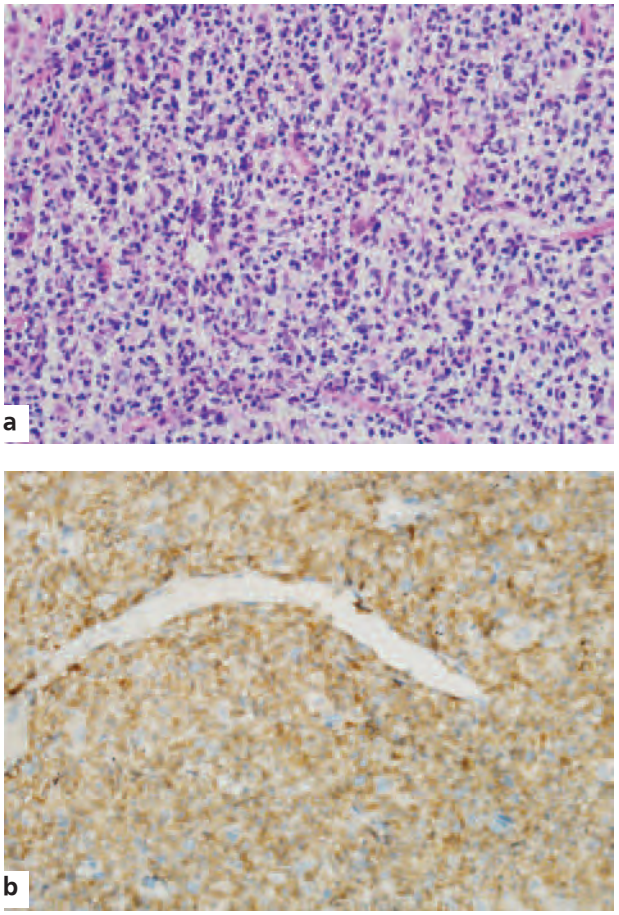

Figure 3. Lung biopsy.
(a) In a lung needle biopsy, small- and medium-sized atypical lymphoid cells with convoluted nuclei are shown (H&E ×400).
(b) CD3 is expressed by neoplastic cells with a strong cytoplasmic and membranous pattern (immunoperoxidase ×400).

The final diagnosis was Epstein-Barr-virus–negative posttransplant lymphoproliferative disorder, T-cell type, involving the lung. Tacrolimus and mycophenolate mofetil were discontinued, prednisolone was maintained, and sirolimus was introduced to the treatment with a dosage of 2 mg/d. Miliary pattern in the lung disappeared on the sixth day of treatment (Figure 4). The patient was initially treated with 6 cycles of CHOP. Because of an incomplete response to this chemotherapy, she was given 6 cycles of ifosfamide cisplatin etoposide chemotherapy. She has been followed in partial remission without any treatment. She had planned to undergo autologous hematopoietic stem cell transplant; however, she did not accept any other treatment.

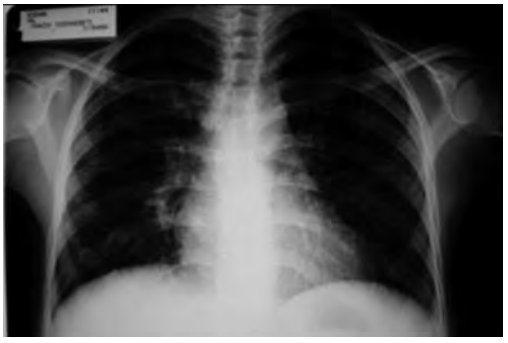

Figure 4. Radiograph of the lung after treatment. Miliary pattern was not observed.

Discussion

Secondary malignancies are the most-important long-term complications of solid-organ transplants. Among them, lymphoproliferative disorders are the second most-common type of malignancies after cancers of skin in solid-organ recipients.[3]

Posttransplant lymphoproliferative disorders include mainly atypical B-cell lymphoproliferation, Hodgkin disease, and T-cell lymphomas. Immunohistochemical typing shows that most posttransplant lymphoproliferative disorders originate from B lymphocytes, while the rest are of T-cell origin, and rarely of null-cell origin.[1, 2, 4, 8] Epstein-Barr virus plays a major role in the pathogenesis of posttransplant lymphoproliferative disorder, and Epstein-Barr virus seronegative patients have higher rates of posttransplant lymphoproliferative disorder compared with those who are seropositive.[1, 3-6, 8, 9] Despite not being routinely used, recently, monitoring of Epstein-Barr virus-DNA load after a transplant has increasingly been used to identify individual patients at risk of developing posttransplant lymphoproliferative disorder.[4] Epstein-Barr virus was investigated by in-situ hybridization in our case, but we could not detect Epstein-Barr virus in the pathological specimens.

Beside Epstein-Barr virus-seronegative status, *cytomegalovirus* disease, use of cyclosporine,

tacrolimus, antilymphocytic antibody, and OKT3, the number of methylprednisolone pulses, acute rejection episodes, genetic predisposition, and younger age have all been suggested as risk factors for development of posttransplant lymphoproliferative disorder.[1, 3-5, 7, 9] However, there is no definite evidence of a single immunosuppressive drug causing posttransplant lymphoproliferative disorder in renal transplant recipients. Although there is uncertainty about which immunosuppressive drug is a risk factor for developing posttransplant lymphoproliferative disorder[4, 7]; among them, sirolimus is thought to have anticancer effect.[3, 10] So, it should be convenient to add sirolimus to these patients. Also, our patient was treated with tacrolimus and mycophenolate mofetil, which were replaced with sirolimus after the diagnosis of posttransplant lymphoproliferative disorder had been made.

Although extranodal involvement including the kidneys, spleen, liver, skin, and intestinal tract is common,[4, 9] pulmonary involvement has been reported in 5 cases by Hanson and associates,[11] and 1 case of pleural primary effusion by Melo and associates.[12] Among these cases, only the ones reported by Hanson and associates were posttransplant lymphoproliferative disorder of the T-cell type. Lung involvement was biopsy proven in only 2 patients, with focal effacement of the pulmonary architecture by lymphomatous process, with areas of necrosis and peripheral lymphatic tracking and also with frequent infiltration of the small pulmonary vessels by lymphoma cells, while the airways were relatively spared.

In our case, a lung biopsy showed atypical lymphoid infiltration with CD3 and CD5 positivity. Immunophenotyping analysis was different from our patient in that all patients were positive for CD8. Three cases reported by Hanson and associates were tested for both T-cell and B-cell gene rearrangement showing clonal rearrangement of T-cell type in all 3 cases. However, we could not perform gene rearrangement analysis in our patient. Also, instead of the lymph nodes, bone marrow involvement was more common in the cases reported by Hanson and associates, whereas lymph node involvement was prominent in our patient.

To the best of our knowledge, this case is the sixth one of posttransplant T-cell lymphoproliferative disorders involving the lung. On presentation, the patient, who was Epstein-Barr virus seronegative, had lymphadenopathy, and a chest radiograph showing miliary opacities in bilateral lungs resembling tuberculosis. The long immunosuppressive treatment and patient's symptoms led us to suspect tuberculosis and other agents causing pneumonia. However, microbiological studies could not demonstrate any causative agent. Therefore, we decided to perform a lung biopsy, which resulted in a diagnosis of posttransplant lymphoproliferative disorder of the T-cell type.

In summary, posttransplant lymphoproliferative disorder of the T-cell type is often atypical in its presentation and the prognosis is poor. An early diagnosis may allow patients to be treated earlier and thus, improve their chance of survival.

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