IN PRACTICE

Posttransplant Lymphoproliferative Disorder Following Kidney Transplant

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CASE PRESENTATION

A 67-year-old white man with a history of kidney transplant for hypertensive kidney disease 9 months ago presents for follow-up, concerned by vague abdominal discomfort and loss of appetite. He lost 15 pounds during the preceding 3 months without an obvious cause. He also reports drenching night sweats during the past several weeks. Before his transplant, he had been maintained on hemodialysis therapy for ~1 year, and other than these new concerns, he has done well after receiving a deceased donor organ. Serum creatinine level is stable at 1.3-1.4 mg/dL (estimated glomerular filtration rate, 54-59 mL/min/1.73 m²). Immunosuppressive medications include tacrolimus, 2 mg, twice daily; mycophenolate mofetil, 500 mg, twice daily; and prednisone, 7.5 mg/d. His physical examination is notable for obvious weight loss. Blood pressure is 143/88 mm Hg, pulse is 95 beats/min, and he is afebrile. He has no signs of peripheral lymphadenopathy and has normal cardiopulmonary examination findings. Abdominal examination is notable for a nontender palpable mass in the midepigastric region ~8-10 cm in diameter. He has no hepatosplenomegaly and has a well-healed right-sided abdominal incision. Laboratory data show a serum creatinine level of 1.4 mg/dL (estimated glomerular filtration rate, 54 mL/min/1.73 m²) and otherwise normal extended metabolic panel results. Complete blood cell count is notable for a hemoglobin level of 10.2 mg/dL (previously 12.5 mg/dL) and white blood cell count of 12,000/µL with a normal differential count. Finally, urinalysis is notable for only mild proteinuria. What further evaluation is appropriate to determine the cause of his concerns and laboratory abnormalities?

INTRODUCTION

Kidney transplant is the most definitive treatment of chronic kidney failure. During recent years, transplants have been performed with increasing frequency, with 16,514 kidneys and 836 kidney-pancreas transplants occurring in the United States in 2008 according to the United Network for Organ Sharing.1 Despite the increasing frequency of transplant, there are very real risks for transplant recipients. In addition to being at significantly increased risk of acquiring infections or experiencing transplant rejection, patients also are at risk of developing posttransplant lymphoproliferative disorder (PTLD). This review focuses on the pathogenesis of PTLD after kidney transplant, diagnosis of this life-threatening malignancy, and treatment, including mention of special considerations before a second organ transplant.

PATHOGENESIS

PTLD is a lymphoproliferative disorder that occurs because of impaired T-cell immunity after solid-organ or allogeneic stem cell transplant. These predominantly B-cell malignancies are associated with Epstein-Barr virus (EBV) infections in ~80%–90% of patients with PTLD.2,3 EBV, a member of the herpesviridae family, is fairly ubiquitous and typically infects patients through saliva during their teens or early 20s. Approximately 90% of the adult population has serologic evidence of previous exposure to EBV.4 The virus remains for the lifetime of a previously infected individual in a latent form. It achieves this latency by causing B cells to differentiate into memory B cells that serve as a reservoir from which they can reactivate in the setting of immunosuppression.5 In addition, PTLD not associated with EBV has been described and may be increasing in incidence.6

The mechanism by which EBV-infected memory B cells transform into malignant clonal populations requires the production of 9 viral
proteins that typically are latent in memory cells. These latent proteins in the viral genome can be induced by a master transcription factor, EBV nuclear antigen 2 (EBNA-2). If this transcription factor is active, it can initiate a “growth program” that allows B-cell proliferation. Cytotoxic T cells normally recognize viral particle production in these B cells and destroy them. In patients treated with immunosuppressive medications, cytotoxic T cells are unable to mount an adequate response to keep these cells in check, and B-cell proliferation occurs. In adult solid-organ transplant recipients who develop PTLD, the clonal population of cells originates from host or organ recipient cells that harbor latent virus. The full sequence of events that leads to the transformation of normal B cells into neoplastic cells and what differentiates benign proliferation from malignant transformation are still areas of investigation.

The association between EBV and the malignant proliferation of lymphocytes is not unique to transplant recipients and immunosuppression. The virus also is believed to have a key role in neoplastic transformation in other malignancies, including nasopharyngeal cancer, Burkitt lymphoma, Hodgkin lymphoma, and AIDS-related non-Hodgkin lymphoma. EBV-related malignancies also are seen in patients with congenital immunodeficiency syndromes, such as X-linked lymphoproliferative disorder, and in aging individuals as their immune systems become senescent.

Classification of PTLD is fairly complicated, with subgroups defined by whether they arise from a single cell (monoclonal) or multiple cells (polyclonal). They are subdivided further by cell morphologic characteristics, categorized as monomorphic if the cells are homogeneous or polymorphic if they are heterogeneous. The most recent World Health Organization classification of hematopoietic disorders published in 2008 is based on these characteristics (Box 1). It ranges from polyclonal hyperplastic lesions, which are more benign in nature, to polymorphic lymphoid proliferations to true monoclonal lymphomas. Diffuse large B-cell lymphoma and immunoblastic lymphoma are the most common subtypes, and Hodgkin lymphoma, plasma cell neoplasms, and T-cell PTLD are seen less frequently.

**Box 1. Pathologic Classification of PTLD**

- **Early lesions**
  - Plasmacytic hyperplasia
  - Infectious mononucleosis-like lesion
- **Polymorphic PTLD**
- **Monomorphic PTLD**
  - B-Cell neoplasms
    - Diffuse large B-cell lymphoma
    - Burkitt lymphoma
    - Plasma cell myeloma
    - Plasmacytoma-like lesion
  - T-Cell neoplasms
    - Peripheral T-cell lymphoma, not otherwise specified
    - Hepatosplenic T-cell lymphoma
  - Classical Hodgkin lymphoma-type PTLD

Abbreviation: PTLD, posttransplant lymphoproliferative disorder.

*Classified according to lymphoma they resemble.
Source: Swerdlow.

Compared with other patients receiving solid-organ transplants, kidney transplant recipients develop PTLD at substantially lower rates. Multiple series have reported an incidence range of 1%-4.5%, with higher rates in the pediatric population. Despite the fairly low incidence, the absolute number of PTLD cases in kidney transplant recipients is fairly large because of the relatively large number of kidney transplants and long survival of these patients. Kidney transplant recipients comprise the second largest group of solid-organ transplant recipients with PTLD in the United States, outnumbered by only heart transplant recipients.

Mortality from PTLD in solid-organ transplant recipients can range from 40%-60%, and several factors have been found useful in determining prognosis. Factors implicated in poor prognosis include the involvement of multiple sites, tumor monoclonality, central nervous system (CNS) involvement, and late-onset PTLD (onset > 1 year after transplant). Leblond et al found that Eastern Cooperative Oncology Group performance status > 2 (individual is unable to work, but spends < 50% of waking hours in bed) also was associated with poor outcome. More recently, Ghobrial et al showed that CD20 positivity was associated with a better outcome, noting that T-cell PTLD, plasma-cell PTLD, and CD20-negative large cell lymphomas were associated with worse outcomes.
RISK FACTORS

Risk factors for the development of PTLD should be considered for every patient after solid-organ transplant. First, EBV-negative serostatus at the time of transplant confers an increased risk of developing PTLD. In one series, this was associated with an incidence of PTLD 25-50 times higher than in recipients who were EBV seropositive. According to another series, in the first year after transplant, EBV-naive patients had a 20-fold higher risk of developing PTLD than patients who had been exposed to EBV in the past. Mismatching EBV-negative recipients with EBV-positive donors is associated with primary EBV infection and the highest risk of developing PTLD.

Type of organ transplant also is believed to be associated with developing PTLD. According to several series, intestinal transplant showed the highest incidence (19%-30%), followed by heart-lung (9%), lung (8%), heart and liver (~3%), and kidney (1%-3%). Several explanations for this have been proposed, including differences in the degree and type of immunosuppression required for different organs, as well as differing amounts of donor-derived lymphoid tissue.

Children appear to show a higher risk of developing PTLD compared with adults. They have lower rates of prior infection with EBV, putting them at increased risk of developing primary infection after transplant. The lower rates of prior EBV exposure result in many EBV-seronegative pediatric patients receiving kidneys from EBV-seropositive donors, contributing to the increased risk.

Other risk factors for developing PTLD after solid-organ transplant include simultaneous primary infection with cytomegalovirus (CMV) and being within 1 year of transplant. In several series of children, patients who developed primary infection with CMV after transplant had a 4-6-fold higher risk of developing PTLD. It is believed that the inflammatory cytokines released in the presence of a primary infection with CMV make the milieu more supportive of EBV proliferation. Timing also has a role because patients most frequently develop PTLD within the first year after transplant, possibly related to the higher degree of immunosuppression during this period. Although rates of developing PTLD are highest in the first year after transplant, the risk of developing the disorder remains increased indefinitely. The 10-year risk of developing PTLD in solid-organ recipients is ~12-fold higher than the risk of lymphoma in the general population. Finally, several small studies have attempted to identify HLA subtypes associated with a higher risk of PTLD, but these results still await confirmation in large-scale epidemiologic studies.

SURVEILLANCE/EBV PCR MONITORING

Surveillance for EBV through polymerase chain reaction (PCR) monitoring was suggested as a way to make early diagnosis easier. An early study of 35 adult solid-organ transplant recipients showed low sensitivity for this assay. Controversy continues to surround the method of surveillance because there is still no consensus about how to determine EBV positivity. As in the previously mentioned study, one can measure EBV viral load in peripheral blood using PCR, measure the ex vivo spontaneous growth of EBV-transformed B cells, or determine the number of EBV-infected peripheral-blood mononuclear cells. Although it can be less reliable in patients on immunosuppressive medications, serologic testing of EBV viral capsid antigen or nuclear antigen antibodies is considered more specific for EBV disease. All these serologic markers increase before a diagnosis of PTLD, with a peak occurring around the time of diagnosis. It has been suggested that although PCR monitoring may not be useful for diagnosis, several studies have shown that DNA levels decrease as patients receive therapy, indicating that following up EBV viral load may be helpful in monitoring response to therapy. Unfortunately, although viral load level may decrease, this does not always correlate with objective tumor response to therapy. Additionally, recurrent PTLD after successful treatment is not detected easily by variations in EBV viral load because the level changes less predictably with recurrent disease.

Clinical trial guidelines recommend following up EBV viral loads for patients considered to be high risk of PTLD, including pediatric patients and patients who are seronegative with a seropositive donor.
2-arm prospective controlled study of adult transplant recipients that aimed to determine which primer sets might be the most efficacious for PCR diagnosis, what normal ranges for these assays should be, and whether it was more efficacious to measure intracellular EBV versus the more convenient method of performing free plasma EBV PCR. We found that measuring free plasma EBV PCR was a more effective tool than measuring intracellular EBV because of a high likelihood that immunosuppressed transplant recipients would have chronic low levels of latent EBV. Results also indicated that the primer set targeting EBNA-1 had the greatest sensitivity (77%) and specificity (100%). We found that screening simultaneously for multiple EBV genes (EBNA, EBV-encoded RNA [EBER], and latent membrane protein [LMP]) was the best approach for ruling out EBV-related PTLD. This study provides evidence to support the use of EBV PCR to help diagnose EBV-related PTLD earlier with the hope that early treatment will reduce mortality.43

**CLINICAL PRESENTATION**

Patients can present in a variety of ways, from nonspecific symptoms of weight loss, malaise, and fever to more severe organ dysfunction or infectious complications. It is important to keep PTLD in the differential diagnosis of ill patients after transplant because their disease can range from being indolent to rapidly progressive and life threatening. Median onset of PTLD is ~6 months after transplant, but it has been reported from 1 week to 9 years after transplant.44,45 In our center, we have encountered several cases of patients who presented well into the second decade posttransplant, with 1 patient presenting 17 years after kidney transplant.

Early symptoms of PTLD can be nonspecific and difficult to pick up. An infectious mononucleosis-like syndrome with lymphadenopathy, weight loss, fever, and increased transaminase levels is common. Gastrointestinal symptoms also are common, including diffuse abdominal discomfort or distension, loose bowel movements, and even bleeding or bowel perforation.25 All newly found masses or skin lesions should be biopsied or removed in patients on immunosuppressive therapy because of the high malignant potential seen in this group of patients. Table 1 lists the most common presenting symptoms and signs in our series of 148 patients with PTLD.

PTLD, similar to other lymphoid neoplasms, can be localized or disseminated. Table 2 lists the frequency of organ involvement in our series of 148 patients with PTLD. There often is extran-
odal involvement at presentation, occurring in up to two-thirds of patients. The CNS can be the only site of disease, and involvement is reported in 8%-30% of patients. Not infrequently, solid-organ transplant recipients can present with transplant involvement and dysfunction, which must be differentiated swiftly from other causes, including transplant rejection, infection, and medication toxicity. Clinical deterioration after treatment of presumed rejection with increased immunosuppression should prompt concern for possible PTLD. Kidney involvement with PTLD is fairly common after kidney transplant, but also can be seen after other solid-organ transplants, occurring in up to 18% of patients. Usually, these cases of PTLD are solid kidney masses, with the transplant affected in approximately one-third of cases. Notably, one study of 1,474 kidney transplant recipients found that all 14 patients who developed PTLD presented with decreased kidney function, and 10 patients had disease localized near the transplant.

Imaging should include computed tomography (CT) of the chest, abdomen, and pelvis with contrast media, if possible. Guided by signs and symptoms, additional imaging of the CNS or gastrointestinal tract or other areas is recommended, and all suspicious lesions should be biopsied. Biopsy specimens should contain enough tissue to evaluate cellular morphologic characteristics and tissue architecture, as well as allow for immunohistochemical staining (Fig 1). Pathologic examination also should include flow cytometry, which can help determine clonality using light-chain restriction and determine the cell of origin. When the cell of origin is unclear or clonality needs to be determined, molecular studies can be used to test for rearrangement of immunoglobulin chains or T-cell receptor at the DNA level. Biopsy specimens also should be tested for the presence of EBV using EBER-targeted RNA in situ hybridization. Alternative stains for LMP-1 or LMP-2 are less sensitive for EBV, but are specific enough for the diagnosis of EBV-positive PTLD.

In addition to imaging and pathologic examination, peripheral-blood plasma should be tested using PCR to determine EBV viral load. Whole-blood EBV PCR may be substituted, but with lower specificity and positive predictive value. Bone marrow aspirate and biopsy are needed to complete the staging and determine bone marrow involvement for patients with suspected sys-

![Figure 1](image_url)
temic involvement of disease. It probably is unnecessary in patients who present with a localized lesion and normal blood cell counts. Staging laboratory tests include a complete blood cell count with white blood cell count manual differential and a basic metabolic panel with calcium, magnesium, phosphate, uric acid, and lactate dehydrogenase levels (Box 2).

**Box 2. Evaluation of Newly Diagnosed PTLD**

**Initial Studies**
- History and physical examination
- Bloodwork
  - CBC with differential, extended metabolic panel
  - Lactate dehydrogenase
  - Uric acid
- Biopsy specimen
  - Morphology
  - Flow cytometry
  - Immunohistochemistry
- CT/PET of neck, chest, abdomen, and pelvis

**Additional Studies**
- Immunoglobulin and T-cell receptor gene rearrangement studies
- CT or MRI of brain
- Upper and lower gastrointestinal endoscopies
- Analysis of cerebrospinal fluid, including cytology and flow cytometry

Abbreviations: CBC, complete blood cell count; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; PTLD, post-transplant lymphoproliferative disorder.

*Indicated for specific cases.

Adapted from Foon et al with permission of McGraw-Hill.

Primary prophylaxis is to use them in combination with arginine butyrate. Through induction of the lytic phase of EBV gene expression, arginine butyrate can induce the expression of thymidine kinase. This enables ganciclovir to be phosphorylated into its active form. Several studies have attempted to investigate the use of ganciclovir with arginine butyrate in both solid-organ and bone marrow transplant recipients with PTLD and have had moderate success.

**Local Therapy**

Localized PTLD does not always require systemic therapy. Surgery or radiation can be used in patients presenting with localized disease, such as a skin lesion or a single gastrointestinal lesion, thus sparing the patient the consequences of systemic therapy and withdrawal of immunosuppression. Local therapies used in conjunction with reduction of immunosuppression have resulted in very low PTLD-related mortality rates. In addition, there has been some success when surgery or radiation is combined with the use of rituximab. In patients who require palliative therapy or emergent therapy for advanced disease, local field radiation therapy can be used.

**Reduction of Immunosuppression**

The cornerstone of therapy for patients with PTLD has been reduction of immunosuppression. This approach initially was outlined in 1984 and has been used successfully many times since then. Reducing the degree of immunosuppression allows restoration of the natural T-cell–mediated immune response against EBV-infected B cells. Ideally, a lymphoma-specific immune response will result while sparing an immune attack on the transplant. The goal when reducing the amount of immunosuppression is to find a dose that allows restoration of an immune
response against the lymphoma without causing transplant rejection.

There are significant risks associated with reduction of immunosuppression. Transplant rejection occurs in up to 39% of solid-organ recipients regardless of whether they respond to treatment. The risk of rejection varies by organ transplant type; patients who received heart and lung transplants have the highest risk of acute organ rejection. Rejection also is not tolerated as well in patients who have life-sustaining organ transplants, such as heart, lungs, and liver. Fortunately, for kidney transplant recipients, reduction of immunosuppression can be more aggressive because it is relatively easy to follow up creatinine and electrolyte

Figure 2. A suggested algorithm for the diagnosis and treatment of post-transplant lymphoproliferative disorder (PTLD). Clinical presentation is highly variable and all patients should undergo a diagnostic biopsy, imaging, and laboratory tests for staging and prognostication (see Box 2 for more details). Patients with 0-1 poor prognostic features and no signs of rejection can be treated with reduction of immunosuppression initially. Other patients should be treated with rituximab and/or cytotoxic chemotherapy according to their disease features. Selected cases can be treated with surgery or radiotherapy, either alone or in combination with other modalities. Abbreviations: CNS, central nervous system; CT, computed tomography; EBV, Epstein-Barr virus; LDH, lactate dehydrogenase; PCR, polymerase chain reaction; PET, positron emission tomography; XRT, radiotherapy. Adapted and reproduced from Tsai et al with kind permission of Springer Science and Business Media.
values to monitor for rejection. These patients also have lower rates of transplant rejection than most other solid-organ transplant recipients in this clinical situation.47,63

There is no standard method of reducing immunosuppression. It should be individualized for every patient and it is important to assess various patient characteristics first, including transplant type, relative risk of transplant rejection, extent and severity of PTLD, and the immunosuppressive drugs being administered.2,45,63 Usually mycophenolate mofetil and azathioprine are discontinued first, and steroid and calcineurin inhibitor doses are reduced.2 As one would expect, it is necessary to continue close monitoring of patients during reduction of immunosuppression to ensure early detection of acute rejection.

Response to reduction of immunosuppression can be predicted by multiple factors. Perhaps surprisingly, EBV serostatus does not predict response, and this method of treatment should be first line in both EBV-positive and EBV-negative patients who develop PTLD.6,64,65 Indicators of a poor response to reduction of immunosuppression include bulky disease, lactate dehydrogenase level > 2.5 times the upper limit of normal, organ dysfunction, and multiple visceral sites of disease.6,45 For patients lacking these features, the response rate to reduction of immunosuppression is as high as 89%.

Anti–B-Cell Antibodies

Use of medications targeting B-cell antigens is common in patients with PTLD because the malignancy usually comprises B-cell proliferation. As expected, response rates to these medications typically are good, ranging from 50%-80%.66-69 Nevertheless, some patients do not respond to these medications as favorably as others. Risk factors for a poor response to anti–B-cell therapy include late-onset PTLD (onset > 1 year after transplant), CNS involvement, and involvement of multiple viscera.63 Some subtypes of PTLD that lack expression of CD20, such as T-cell PTLD, and some tumors with plasmacytic differentiation are not likely to respond to anti–B-cell antibodies.

Several anti–B-cell drugs have been used to treat PTLD. Early studies focused on medications targeting CD21 and CD24, with complete response rates of 63% and long-term survival of 46%.70 Within the past 10 years, studies have focused more on the anti-CD20 antibody rituximab, showing good results.69 This medication has a favorable side-effect profile; the most common adverse events are infusion-related reactions. These reactions generally are mild and include fever, chills, and mild hypotension in up to 77% of patients with lymphoma during their first infusion. The rate of reactions decreases with subsequent infusions, and life-threatening transfusion reactions are extremely rare. Other serious complications occur rarely, including delayed neutropenia, tumor lysis syndrome, and progressive multifocal leukoencephalopathy.71,72

Rituximab’s proposed mechanism of action in patients with PTLD may explain why it is potentially more efficacious in these patients than in those with traditional non-Hodgkin lymphoma. Anti-CD20 antibodies bind to B cells and induce clearance of the cells, but also induce destruction by antibody-dependent complement-mediated lysis or apoptosis. Some hypothesize that these antibodies serve to “activate” a patient’s immune system against EBV-infected B cells, aiding destruction of the malignancy and preventing its recurrence.63

Other anti–B-cell antibodies have not been evaluated systematically in patients with PTLD, but it is hypothesized that their use in PTLD may be similar to that in non-Hodgkin lymphoma. These antibodies include anti-CD20 antibodies coupled with radioactive iodine-131 (tositumomab) or yttrium-90 (ibrutinomab), anti-CD22 (epratuzumab), anti-CD80 (galiximab), and others that currently are in various stages of development.

Cytotoxic Chemotherapy

For patients in whom reduction of immunosuppression is ineffective or not a viable option or in patients with rapidly progressive or life-threatening disease, chemotherapy can be used as an alternative or additional treatment.60 The regimens used are similar to those used to treat non-Hodgkin lymphoma, including, among others, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone with or without rituximab) and proMACE-CytaBOM (prednisone, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine, and methotrexate).63 Unfortunately, although these chemotherapeutic regimens are highly effective, they put
patients at significant risk of infections and other complications, resulting in significant morbidity and mortality in solid-organ transplant recipients.73-75 Despite this, a study in 2003 of kidney transplant recipients with PTLD showed that using CHOP after a reduction in immunosuppression resulted in a complete remission rate of 63% and median disease-free survival of 10.5 years.76

Limitations of using chemotherapy to treat patients with PTLD are numerous and include suboptimal performance status, dose-limiting organ dysfunction, drug-drug interactions, and high potential for infectious complications. Chemotherapy typically is administered to patients who have Eastern Cooperative Oncology Group performance status of 0-1 (either no limitations in activity or restrictions in only strenuous activity). Patients with poor performance status often are not candidates for chemotherapy, and their management requires careful consideration and consultation with an experienced oncologist. As expected in kidney transplant recipients, organ dysfunction that limits chemotherapy use often is related to the kidney, but also can be hepatic or cardiac in nature. In addition, chemotherapy use can be limited by infectious complications. These factors result in treatment-related mortality of ~20%-50% with chemotherapy despite good tumor responses.63,73

One recent study directly compared patients who received rituximab followed by chemotherapy when their PTLD progressed with patients who received chemotherapy followed by rituximab after disease progression. All patients failed to respond to reduction in immunosuppression alone.60 The overall response rate for patients who received rituximab was 68%, and median time to treatment failure was not reached within the 19 months of follow-up. Patients with EBV-positive disease were significantly more likely to respond to rituximab and achieve a complete response than patients with EBV-negative disease. Patients who received chemotherapy (various regimens) achieved an overall response rate of 74%, and median time to failure was 10.5 months. Although the overall response rate was somewhat higher for patients treated with chemotherapy, the associated toxicities were significant. Fifty-two percent of patients treated with chemotherapy were hospitalized for infections and 6% ultimately died of complications related to chemotherapy. The debate regarding when to use rituximab versus chemotherapy and how to use them in combination continues with no current consensus recommendations.

Cellular Immunotherapy

Cellular immunotherapy for patients with PTLD involves reinfusion of T cells into a recipient with a goal of targeting a patient’s EBV-associated lymphoma.77 Early studies of cellular immunotherapy involved patients undergoing allogeneic stem cell transplant using the readily available donor-derived T cells to target the tumor. Initial work with donor lymphocyte infusions in stem cell recipients was promising, with a greater than 90% response rate, but a significant risk of graft-versus-host disease.78

Subsequent studies using EBV-specific cytotoxic T lymphocytes (CTLs) have been performed in solid-organ transplant recipients with PTLD. Because T-cell targeting is HLA specific, EBV-specific CTLs must be HLA-matched to the recipient, and donor lymphocyte infusion usually is not a viable option.8,79 Earlier attempts to expand autologous lymphokine-activated killer cells by ex vivo incubation with interleukin 2 resulted in a modest response in 4 of 7 patients with EBV-positive disease, but with concomitant rejection in some patients.26

A later attempt in using autologous pretransplant-harvested CTLs in a prophylaxis study resulted in effective reduction of EBV viral loads. This group showed survival of EBV-specific clones up to 3 months after the infusion.80

Interestingly, active CTLs also can be obtained from some solid-organ recipients after transplant and initiation of immunosuppression.81-83 Reinfusion of these cells as preemptive therapy when the EBV viral load increases or as therapy for established PTLD appears promising, but requires extensive time and expense and is not successful in all patients.84

More recently, several groups have attempted to use tissue banks to store EBV-specific CTLs for various HLA types. Haque et al85 performed a trial with 8 patients using partially HLA-matched CTLs from a tissue bank. The patients had EBV-positive PTLD, and 2 were kidney transplant recipients. In this small study, 4 of 8 patients had a complete response to the reinfused CTLs, even without reducing their levels of
immunosuppression. This pilot study was followed by a phase 2 multicenter clinical trial of 33 adult patients with EBV-positive PTLD (13 kidney transplant recipients) in whom prior conventional treatment modalities had failed. They compiled a bank from 100 different donors of various EBV-specific CTLs. The overall response rate after infusion of these cells was 52%. The authors note that patients who received the closest HLA-matched CTLs had better responses at 6 months. Investigation into this promising approach to therapy for patients with treatment-resistant disease is ongoing.

Retransplant

Perhaps one more optimistic point for patients who develop PTLD after kidney transplant is the opportunity for complete withdrawal of immunosuppression and removal of the transplant. Hemodialysis therapy can be initiated in place of the transplant, and patients can look forward to the possibility of retransplant. One series of 12 patients showed that successful treatment of PTLD can result in years of continued transplant function and that successful retransplant is feasible using a standard immunosuppressive regimen. Other small studies found that after transplant failure due to PTLD, retransplant 1-2 years after completion of therapy is safe and rarely results in relapse of PTLD.

In our institution, 8 kidney transplant recipients underwent retransplant after achieving remission from PTLD, and the relapse rate was 0%. There are no randomized trials investigating the amount of time that should pass before retransplant.

CONCLUSION

PTLD is an uncommon complication of solid-organ and stem-cell transplant. It is linked closely with immunosuppressive therapy, and in most cases results from uncontrolled proliferation of EBV-transformed lymphocytes. The incidence in kidney transplant recipients is low, and the highest risk is seen within the first year after transplant, although the risk is never eliminated. To detect these tumors early, a high level of suspicion should be maintained, and when diagnosed, management should be handled by an experienced team that includes a nephrologist, oncologist, and transplant surgeon to overcome this potentially life-threatening complication. Although many patients can be treated successfully using reduction of immunosuppression, immunotherapy, and chemotherapy, there are still multiple areas that require further research. These include, among others, the role of EBV viral load monitoring, novel monoclonal antibodies, and cellular therapy.

CASE REVIEW

The patient underwent CT of the abdomen and pelvis to further evaluate the epigastric mass. The scan showed retroperitoneal lymphadenopathy and a mass near the stomach that was concerning for PTLD. A CT-guided biopsy was performed, and stains for EBV were positive. Staging was completed with chest CT that showed no evidence of disease. He was treated initially with reduction of immunosuppression, which included decreasing the tacrolimus dose by 50%, holding mycophenolate mofetil therapy, and decreasing prednisone dosage to 5 mg/d. Creatinine, extended metabolic panel, and complete blood cell count results were monitored weekly, and after 4 weeks, he had moderate improvement in appetite and level of energy. However, repeated CT of the chest, abdomen, and pelvis showed stable disease, and the patient received 4 weekly doses of rituximab, 375 mg/m², resulting in resolution of the epigastric mass and lymphadenopathy. Creatinine level temporarily increased from 1.4 to 1.8 mg/dL (estimated glomerular filtration rate, 40 mL/min/1.73 m²), but later returned to baseline. After 3 years, he is free of disease and with a functioning transplant.

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