Posttransplant Lymphoproliferative Disorders

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Posttransplant lymphoproliferative disorder is a heterogenous group of clonal hyperplasia/neoplasms that can range from benign to highly malignant lesions. Mortality rates can approach 60%. This entity has been on the rise for the last 2 decades with the advent of highly potent immunosuppressive agents. Epstein-Barr virus has shown to play a primary role in more than 90% of the cases. Although standard protocols do not exist for primary prevention and treatment, new agents are emerging that may play a role in treatment and prevention of this debilitating, and at times, fatal disease.

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Review

INTRODUCTION

Posttransplant lymphoproliferative disorder (PTLD) includes a spectrum of lymphoid malignancies of several different forms that occurs secondary to immunosuppression. Lymphoid neoplasms related to transplant recipients were first described in 1968 as a proliferation of primarily B cells. This proliferation occurred secondary to primary immunodeficiency states, solid organ transplant and stem cell transplant.[1-3] Posttransplant lymphoproliferative disorder, which forms the basis of this review, is not very common, but it is a severe complication arising in solid organ transplant recipients.

The monoclonal proliferation of B cells found in PTLD is primarily due to Epstein-Barr virus (EBV) gene products. There is a multitude of risk factors and the pathogenesis is not completely understood. The precursors of PTLD are inclusive of a diverse spectrum of clonal dysplasia including infectious mononucleosis, polyclonal hyperplasia to aggressive non-Hodgkin lymphoma.

EPIDEMIOLOGY

Posttransplant lymphoproliferative disorder occurs in up to 15% of solid organ transplant recipients.[4,5] Global data from large transplant centers show an overall incidence of 6% to 16% with an average 7% incidence.[6,7] Interestingly, its incidence is on the rise and has increased dramatically in recent years. This flare-up of cases is likely due to several reasons, namely, longer life of transplant recipients, use of highly potent immunosuppressive agents such as depleting polyclonal and monoclonal antibodies, and calcineurin inhibitors.

The variability of incidence of PTLD is related to the type of the solid organ transplanted, adult versus pediatric recipients, and the immunosuppressant protocol. It is 4-fold higher in the pediatric population, primarily due to the negative EBV status of children at the time of transplantation. Out of the solid organs that are transplanted, the highest incidence has been reported with intestinal transplant at 19%, followed by heart transplant (2% to 10%), heart-lung transplant (5% to 9%), and liver transplants (2% to 8%).[8] The lowest incidence of PTLD is seen in 2% of kidney transplant recipients.[9] However, the true incidence of PTLD is difficult to be determined as the statistics are generally derived from small-sized studies. Why some organs are associated with a higher incidence of PTLD compared to others is not clear. It may be related to the degree of the lymphoid tissue present within the graft. It can also be due to the fact that certain solid organs such as the heart, lung, and intestine

usually require more intensive immunosuppression as compared to kidney or liver transplantation.

Posttransplant lymphoproliferative disorder occurs most frequently within the first year of solid organ transplant, with a median onset reported at 6 months.[5,6] Some cases have been reported as early as 1 week and as late as 17 years posttransplant.[6,10] The diagnosis of PTLD has historically been associated with a mortality rate of 50% to 80% in patients who have a full-blown monoclonal malignancy.

PATHOGENESIS

The overwhelming majority of PTLD cases are associated with EBV infection. It has been reported that 80% to 90% of cases reveal presence of EBV early RNA, EBV latent membrane protein, and/or EBV DNA.[4,5] These gene products are important in the development of PTLD and will be discussed in further detail. In immunocompetent hosts, EBV usually produces no adverse consequences. However, in immunocompromised persons, such as organ transplant recipients, EBV is triggered into uncontrolled viral replication, resulting in hyperplasia or neoplasm. This will lead to a widespread spectrum of diseases, the worst being a monoclonal proliferation of B cells. This ultimately may lead to graft dysfunction, graft failure, and significant morbidity and mortality for the patient.

Epstein-Barr Virus

The EBV is a lymphotropic herpes virus which is associated with lymphoproliferative disorders.[11,12] In particular, PTLD can arise from a response to primary infection with EBV or from re-activation of the previously acquired virus. The overwhelming majority of adult and adolescent population (up to 95%) has serological evidence of latent EBV infection. Children, who are usually EBV naive, can develop primary infection with EBV.

The EBV infects B cells, which differentiate into memory cells. These EBV inclusions in B cells remain in a state of latency for the life of the patient.[13-19] The latently infected B cells carry the virus in a nonreplicative form, with intermittent low-grade replication in the oropharyngeal epithelium (causing infectious mononucleosis). This latent state is also associated with production of viral proteins such as EBV nuclear antigen (EBNA), and latent membrane proteins (LMP).[20] This is the viral mechanism of self-preservation to avoid apoptosis. Most of these latently infected B cells are cleared by cytotoxic T cells (CD8) via immune surveillance. During active immunosuppression and depletion of T cells by antibody-depleting induction therapy, there is no longer a mechanism to clear the infected B cells. With high numbers of infected B cells, there is a propensity for active viral replication that results in further expression of EBV-encoded genes which also include oncogenes. The pathophysiology of transformation of replicative EBV into oncogenic EBV is not fully understood.

The EBNA1 and LMP1 probably play important roles in the oncogenic transformation of *EBV* gene expression. The EBNA1 is needed for maintaining the viral plasmid and allows replication of viral DNA and its transfer to daughter cells. Since EBNA1 is not presented by the major histocompatibility complex class-I molecule on the surface of the infected cells, it does not provoke a cytotoxic T-lymphocyte (CTL) response.[21] The LMP1 is an oncogene capable of inducing malignant transformation as demonstrated in fibroblasts and keratinocytes.[22,23] Transgenic mice expressing LMP1 invariably develop lymphomas.[24] As mentioned before, LMP1 inhibits apoptosis by upregulating anti-apoptotic genes *BCL2* and *A20*.[21]

In consequence, in the immunosuppressed host, the cascade of events begins with EBV seropositivity, lack of checking by CTLs, EBV reactivation and replication, and EBV oncogene transformation/expression, ultimately resulting in lymphoproliferation of B cells.[21,25,26] While the majority of adult solid organ recipients are EBV seropositive, only a small minority develop a full-blown PTLD. This indicates that there are additional stimuli required to trigger full monoclonal proliferation of B cells. These additional stimuli are not clear at present. Local cytokines can cause chronic inflammation which can lead to proliferation of B cells.

The pathogenesis of a minority of PTLDs whose etiology is not associated with EBV is poorly understood. It might be similar to de novo non-Hodgkin lymphomas seen in the general population. These are usually noted to be late in onset and likely represent spontaneous lymphomas arising in immunosuppressed patients.[27,28] Genetic and environmental factors may also play a role.

Other theories exist for non-EBV-related PTLD. The EBV may provide the initial stimulus to B-cell proliferation, and once rapid proliferation ensues, the CTLs attack the tumor, simultaneously eradicating the virus-bearing B cells, making the host EBV negative.[27-29]

T-cell-associated PTLD is extremely rare but has been reported in at least 16 patients to date.[30] Its pathogenesis is unknown. One theory is that EBV may also infect a subtype of T cells that express CD21, thus allowing the enveloping glycoprotein of the virus granted entry into the T cells. Prognosis is very poor for T-cell PTLD with a roughly 50% 1-year survival.[31]

Other potential mechanisms of PTLD include chronic antigenic stimulation by allograft and a possible direct potentiating effect of the immunosuppressive agents.

Immunosuppressive Agents

Posttransplant lymphoproliferative disorder arises for the most part by the T-lymphocyte depleting effect of immunosuppressive agents, leading to unabated EBV replication and oncogene expression. Several different immunosuppressive classes of drugs have come to light in the recent decades, with increasing potencies and a concomitant rise in the incidence of PTLD. The effect of different protocols and their influence on associated PTLD has been looked at in 2 large cohorts of kidney transplant patients.[32,33] Libertiny and colleagues[33] analyzed 1537 kidney transplant recipients over a 23-year period between 1976 and 1998, covering different immunosuppressive protocols: azathioprine and steroids from 1976 to 1983; cyclosporine, azathioprine, and steroids from 1984 to 1989; and more recently, tacrolimus and mycophenolate mofetil between 1990 and 1998. Only 1 case of PTLD was observed prior to the introduction of cyclosporine on the market.

Gao and coworkers[34] reported the incidence of PTLD after heart and heart-lung transplantation over a 30-year period. Recipients were divided into 4 groups according to the immunosuppressive protocol. The first group had been transplanted prior to cyclosporine era, immunosuppressed by azathioprine and steroid only, and the second group had received "triple therapy," namely cyclosporine, steroids, azathioprine. The third group had received triple therapy and induction with murine monoclonal anti-CD3 antibody (OKT-3). The fourth group had been treated withmycophenolate mofetil and tacrolimus. There was no significant difference in the incidence of PTLD (5% to 7%) between the patients of different groups in contrast to the results reported by Libertiny and colleagues.[33] However, when the subset of cyclosporine-treated groups was analyzed according to the dose received, the high-dose cyclosporine regimens had a 10.6% incidence of PTLD versus 5.6% in the low-dose group. Other retrospective studies have also shown a significant rise in the incidence of PTLD since CSA was introduced in the 1980s.

The OKT-3 and polyclonal lymphocyte-depleting antibodies, such as antilymphocyte serum and rabbit thymoglobulin, used as induction agents, have been shown to be a risk factor for development of PTLD. In various analyses, the use of OKT-3 for induction or for treatment of acute rejection has been shown to increase the risk of PTLD by 3- to 4-fold.[9,35-36] Interestingly, there has been recent data indicating that the newest monoclonal lymphocyte-depleting antibody on the market, alemtuzumab may have a protective effect in regard to PTLD. Alemtuzumab is a humanized monoclonal antibody directed against the CD52 receptor of the T cell. Data collected from 59 560 kidney recipients from the Organ Procurement and Transplantation Network/United Network for Organ Sharing database were looked at the various incidences of PTLD, in correlation with various induction agents used.[37] The overall incidence of PTLD was 0.46%, which differed significantly by different induction protocols. Without induction, the incidence was 0.43%. The incidence of PTLD amongst various inducing agents was as follows: 0.38% for basiliximab, 0.33% for daclizumab, 0.67% for thymoglobulin, and 0.37% for alemtuzumab. Thymoglobulin was associated with a significantly increased risk of PTLD. Alemtuzumab, basiliximab, and daclizumab showed a protective effect with fewer incidences of PTLD as compared to no induction. Alemtuzumab was shown to be the most protective drug.[37]

To summarize, the data indicate that the new highly potent immunosuppressive agents, developed in the last 2 decades have had a profound effect on the incidence of PTLD. They also suggest that the area under the curve of total immunosuppression delivered over time and the

individual agents used play a role in the risk of PTLD. Measuring total or cumulative amount of immunosuppression over time is not accurate; thus, excessive immunosuppression often occurs over time, which can lead to life-threatening complications such as PTLD.

CLASSIFICATION

Diagnosis of PTLD relies on biopsy and histopathology examination. It can present in a myriad of diverse histopathologies, making classification cumbersome. Several international meetings have attempted to classify PTLD with confusing results. Until recently, there has been no standard classification accepted. Recently, Knowles and associates[38] studied 28 biopsies of 22 patients with PTLD and described 3 morphological entities, now accepted as the World Health Organization classification: (1) Benign hyperplasia, also known as plasmacytic hyperplasias, is the mildest form arising in the oropharynx and the lymph nodes. It is polyclonal and lacks in oncogene expression and tumor suppressor gene dysfunction. This histology presents clinically as fever and nonspecific lymphadenopathy. (2) Polymorphic B-cell hyperplasias and lymphomas are histopathologic varieties that arise in the lymph nodes and extranodal sites. They can present with local invasion and destruction of nodal histology. These are monoclonal, but lack oncogene expression and tumor suppressor gene dysfunction. (3) Monomorphic lymphomas or multiple myelomas are widespread neoplastic transformation of monoclonal lymphoid tissue with alteration of tumor suppressor genes and expression of oncogenes.[38-45] The first two histopathologic types have a benign course. Their management consists of reduction of immunosuppression with resultant increase in CTL destruction of EBV-infected cells.[46] Antiviral agents may also be used.[47,48]

RISK FACTORS

Multiple risk factors have been suggested including the intensity of immunosuppression, small bowel or heart-lung transplantation, simultaneous cytomegalovirus disease, young age, male sex, white race, and simultaneous hepatitis C infection.[2] The most important risk factor is transplanting organ from an EBV-seropositive donor to an EBV-seronegative recipient, and the incidence of PTLD has been shown to be 20- to 50-fold higher in EBV-seronegative recipients as opposed to seropositive recipients.[38,40-51]

The immunosuppressive agents used are likely the second most important risk factor, after the recipients' EBV-seronegative status. The arrival of new more potent agents, use of multiple drugs for maintenance immunosuppression, and induction with powerful depleting antibodies have resulted in increasing incidence of PTLD.[2,33,39,52,53]

Interestingly, concurrent infection with cytomegalovirus can lead to a 4- to 6-fold increase in the incidence of PTLD. The pathophysiology behind this is not clear, but it may be related to the effects of increased cytokines due to cytomegalovirus infection that can modulate EBV replication.[40] Other factors such as age, race, gender, and concurrent infections with other viruses (eg, hepatitis C virus) have also been reported.[2,54-56]

DIAGNOSIS AND CLINICAL FEATURES

The clinical presentation of PTLD is highly diverse and heterogeneous. Roughly, 50% of cases present with fever, 30% with lymphadenopathy and weight loss, and 30% with central nervous system involvement. Up to 15% of PTLD cases may present with acute abdomen and perforated intestine. Extranodal sites can involve almost any organ, most commonly the kidney, liver, and bowel. Isolated central nervous system involvement can also be seen in PTLD.[39,57-59] This is significant, since only 1% of non-Hodgkin lymphomas are confined to the central nervous system in the general population.

Serological testing is readily available, but is generally not useful for diagnosis. In children, primary EBV infection can be determined by seroconversion with development of antibodies to viral capsid antigens and EBNA1. Over the past decade, EBV-DNA polymerase chain reaction has replaced serological testing. A positive EBV-DNA polymerase chain reaction implies greater viral loads and is suggestive of viral replication. One caveat to this is that EBV-DNA with low-grade viremia may be detected at all times in immunosuppressed patients.

Transplant recipients fail to produce detectable EBNA1 antibodies in primary infection. Similarly, seropositive recipients may develop decreasing titers despite high EBV loads while developing PTLD.[32,60]

Thus, serological testing remains unreliable in the face of any form of immunosuppression. Cytology has also a limited role in the diagnosis of PTLD. Imaging studies such as computed tomography, magnetic resonance imaging, ultrasonography, and plain radiography can be utilized as part of the initial evaluation, which may also include endoscopy, lumbar puncture, or body fluid aspiration.

Biopsy remains the gold standard and is necessary in all cases for diagnosis. The EBV-positive neoplastic PTLD is a B-cell lymphoproliferation with a broad continuum, which can vary from the presence of monoclonal cells to oligoclonal cells, ultimately replacing the native tissue structure. The LMP1 can also be demonstrated on immunofluorescence and can differentiate PTLD from transplant rejection. Other markers such as CD19, CD20, CD21, and CD22 that are found on B cells can also differentiate PTLD from rejection.[61]

TREATMENT

To date there is no standard evidence-based treatment of PTLD. This is due to lack of multicenter trials to specifically support one treatment modality over another in the established PTLD cases. Despite the lack of a standard protocol, the universal first maneuver in over 90% of cases is reduction of immunosuppression. This is a pathophysiologically sound first step that has been shown in various studies to be effective at diminishing EBV-inciting B-cell proliferation in one-third to one-half of the patients.[62]

Significant reductions should be made in the dose of immunosuppressive drugs, as concomitant chemotherapy that is needed in PTLD cases with malignant transformation will provide umbrella immunosuppression to prevent allograft rejection. To what degree, however, one should reduce immunosuppressive dose is unknown. Reduction of immunosuppressants will also depend on serial measurements of graft function and clinical status of the patient. A serious complication of reducing immunosuppression is rejection of the allograft. If this occurs, sirolimus would be the most suitable agent for maintenance of immunosuppression. It has antiproliferative properties (due to direct inhibition of cell cycle) in lieu of other agents such as tacrolimus and cyclosporine. Sirolimus has also been shown to reduce interleukin-10 secretion, cell cycle arrest, and apoptosis, and significant delay or even inhibition of solid tumor growth. Interleukin-10 is a necessary autocrine growth factor and has been shown to activate transcription growth factors.[63,64]

Some centers will perform weekly EBV-DNA polymerase chain reaction and monitor the clinical status and graft function while immunosuppressant doses are reduced in a stepwise fashion. Transplant biopsy may be necessary if graft function begins to decline, and also to differentiate altering function from primary PTLD versus new onset rejection. The ultimate goal is to reduce immunosuppression to a degree that will allow increased counts of CTLs to counter against EBV-infected B-cells inducing B-cell proliferation. This can be monitored by looking for a lymphocytic response as would be seen in a viral infection in a normal host.

The second line of treatment includes utilizing therapies other than reducing immunosuppression to increase CTLs. Examples of this include administering potent cytokines like interferon-α and anti-interleukin-6 antibodies.[65]

Rituximab (anti-CD20 monoclonal antibody) can be utilized for refractory cases. It neutralizes B-cell expression of CD20, and thus, halts replicative stimulation of EBV leading to B-cell proliferation.[66] The major drawback of this approach is serious adverse effects such as sepsis and tumor lysis syndrome.[67] In all PTLD cases associated with overt malignant transformation/lymphoma, primary chemotherapy should also be administered. Standard regimens are available such as cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) and cyclophosphamide, doxorubicin, etoposide, prednisone, bleomycin, cytarabine, methotrexate, and leucovorin (ProMACE-CytaBOM), with ancillary rituximab.[68]

Newer therapies include passive transfer of antibodies (intravenous immunoglobulin), local radiation for localized lymphoma, and adoptive immunotherapies such as autologous cloned CTL or human leukocyte antigen-matched CTL infusion.[69]

Antiviral agents are often administered along with the reduction of immunosuppression in PTLD; however, little to no evidence exists for improving outcome. Recent studies have examined the prophylactic role of antivirals in preventing PTLD. Data that does exist for the use of antivirals is conflicting. The efficacy of currently available

antiviral agents, such as acylcovir and gancylcovir that do inhibit EBV viral replication, is not well studied; however, they do not affect latent oncogenic viruses.[47,48] Currently, different antiviral prophylactic regimens are routinely administered for up to several months posttransplant.

PROPHYLAXIS

As PTLD is mostly a consequence of EBV infection, prophylactic measures have been studied with varying degrees of success. Use of antiviral therapy, as was discussed above, is an example of this.

Epstein-Barr virus vaccination is a potential approach for reducing the incidence of PTLD in high risk patients, ie, EBV-seronegative recipients. The vaccine would expose naive recipients to EBV to induce seroconversion. Vaccine consisting of gp350 (viral envelope capsid) has been shown to have good immunogenic response in adult volunteers.[70] Studies are currently underway in seronegative children awaiting solid organ transplantation in the United Kingdom. This will hopefully shed some light on the efficacy of this modality. There is also a European controlled trial underway to this effect.

Some data have suggested that meticulous posttransplant EBV surveillance followed by appropriate reduction of immunosuppression and preemptive antiviral therapy may prevent PTLD while preserving graft integrity.[51]

CONCLUSIONS

Posttransplant lymphoproliferative disease remains on the rise as a serious complication of solid organ transplantation. The overwhelming majority of cases are EBV related B-cell tumors arising from impaired immunity. Additional knowledge of molecular mechanisms involved in activation of virus from latency and expression of oncogenic genes is needed to illuminate potential genetic and molecular targets to prevent and treat PTLD. Improved knowledge of virology and standardized histopathology, along with standardized protocols for immunosuppression reduction, and the use of second-line drugs is an important first step in managing the current disease burden. Further prophylactic and therapeutic regimens are also needed to be studied in a randomized controlled fashion in large-sampled, and preferably, multicenter trials.

CONFLICT OF INTEREST

None declared.

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