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Post-Transplant Lymphoproliferative Disease – PTLD

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1. Introduction

Post-transplantation lymphoproliferative disorders (PTLD), one of the most serious complications occurring after transplantation, have been recognized as a complication of organ and cell transplantation for more than 30 years. (Starzl, 1968)

Transplantation of solid organs has been successful in large part due to the development of immunosuppressive regimens that have controlled the recipient's immune system from rejecting the allograft. By suppressing recipient T lymphocytes with cyclosporin or tacrolimus or reversing rejection with antilymphocyte agents such as ATGAM or OKT3, rejection has become a rare cause of allograft loss. (Jain et al., 2000) The “trade off” for this non-specific immunosuppression is the increased risk of the patient contracting opportunistic infections (i. e. viral, fungal and protozoal organisms) and increased risk of malignancies. (Fung et al., 2001) In 1968, lymphoid tumors were first described in transplant patients with a subgroup of these termed “pseudolymphomas” in recognition of their ability to undergo regression after reduction of immunosuppression. (Starzl et al., 1984) “post-transplant lymphoproliferative disease” (PTLD) is now a well recognized complication of solid organ transplantation and therapeutic immunosuppression. As a result, PTLT is a major concern in the post transplant period and also a very complex disease, that encompasses a spectrum of lymphoproliferative disorders that can rise from either cells of B, T or natural killers cell origin. We will focus on the B cell type lymphoproliferative disorders in this chapter. This type is by far the most common and is usually associated with Epstein-Barr virus (EBV) infection. By definition, PTLT is a heterogeneous lymphoproliferation, ranging from benign B cell hyperplasia to aggressive B cell lymphoma, that arise in the setting of bone marrow or solid organ transplantation.

2. Incidence of PTLT

The incidence of various de novo tumors can be very dramatic in the post transplant period, either in the adult or pediatric population. Post-transplantation lymphoproliferative disorders are different from lymphoproliferative disorders that occur in the general population. Although relatively uncommon, the risk of developing lymphoma after transplantation has been reported to be 28 to 49 times greater than that in the general population. (Boubenider et al., 1997) According to the Cincinnati Transplant Tumor Registry (CTTR), which has collected data on more than 6,000 patients, PTLT accounts for 16% of

cancers in transplant recipients compared with 5% in the general population. However, these data are heavily skewed toward kidney transplant recipients. (Penn, 1996)

Although the incidence of PTLD has been reported to be as high as 65% after primary and 30% after reactivation EBV infection, (Birkeland et al., 1999) overall frequency ranges from 1% to 10%. Most estimates are based on relatively small transplant series from individual institutions. (Penn et al., 1998) In an analysis of tumors in 512 patients in the CTTR, PTLD comprised 52% of all tumors. There was a disproportionately high incidence of PTLD among nonrenal allograft recipients compared with renal allograft recipients (81% vs 31%) in this group of patients.

The frequency of PTLD depends on many variables such as the allograft type, for example. Kidney can correspond to 1% to 4% of incidence; heart, 2% to 10%; heart and lung, 5% to 9%; intestine, 19%. (Fizzera, 1992) The overall incidence of PTLD after liver transplantation has been quoted as 2–8.4%. (Wu et al., 2001) In the case of bone marrow recipients, the frequency is 1% to 2% excepting cases of mismatched T-cell-depleted allografts, for which the frequency has been historically as high as 24% (Shapiro et al., 1988). Innovations such as removal of B cells from the marrow allograft have reduced and in some series eliminated this complication. (Cavazzana et al., 1998) Patients who receive allogeneic hematopoietic stem cell transplants also have an approximate 1% risk of developing PTLD. (Gross et al., 1999)

Another variable that influences the incidence of PTLD is definitely the age of the recipient at the time of the transplant. The series of Ho and colleagues, 1988, highlights differences in the frequency of PTLD based on patient age at the time of transplantation. Pediatric patients have a higher frequency of PTLD in general than do adult patients receiving similar allografts, Shapiro and colleagues 1988, reported a 10.1% PTLD frequency in pediatric kidney transplant recipients compared with a 1.2% frequency in the adult renal transplant population; 86% percent of pediatric cases and 50% of adult cases involved a transplant from an EBV-seropositive donor to an EBV-seronegative recipient. Thus, at least part of the difference in frequency between adults and children may be explained by the higher proportion of EBV-seronegative patients in the pediatric as opposed to the adult population.

In children lymphomas are by far the most common tumors, and in the adults is the second most common following skin type lesions. (Penn, 1998) In a recent study 38% and 66% of patients developed a skin cancer after 10 years and 23 years, respectively. (Penn, 1998) This incidence is far greater than in the general population older than 75 years of age (20% to 25%). Malignant lymphomas are the second most common malignancy in transplant patients reported to the CTTR, accounting for 16% of the total tumor incidence. Most lymphomas reported are of the large-cell type; 85% of these are of B-cell origin and 90% to 95% are EBV-related.

Kaposi's sarcoma (KS) accounts for 5.7% of cancers reported to the CTTR. Both nonvisceral (59%) and visceral types (41%) arise. Mortality was higher in patients with visceral KS (53% vs 23%) and remission rates were lower (30% vs 55%). Preventive measures (ie, sunscreen, therapy for oncogenic viruses) and screening measures (ie, mammogram, Pap smear, colonoscopy) are recommended for all age- and sex-appropriate transplant recipients together with an informed approach to the reduction and/or avoidance of drugs with oncogenic potential. (Martinez, 2008)

3. Risk factors

There is a lot of work trying to identify risk factors for PTLD. Clearly, EBV seronegativity is an important factor. This situation occurs when the recipient has not been exposed to EBV virus prior to the transplant and acquires the infection on the setting of immunosuppression. This scenario is often seen in children who are typically immunological naive to the virus and then acquire the virus with the graft, usually from an adult donor who is EBV infected.

PTLD has been documented in three transplant immunosuppression eras: conventional (precyclosporine), cyclosporine, and postcyclosporine. The level of immunosuppression (ie, intensity, type, and amount) is an independent risk factor for PTLD. Ciancio and colleagues, 1997, reported on the incidence of PTLD under different immunosuppressant regimens during an 18-year period. They noted a recent increase in the incidence of PTLD with the advent of newer immunosuppressive agents. By contrast, the use of mycophenolate mofetil in a steroid-free immunosuppressive protocol with concomitant acyclovir therapy was associated with a lower incidence of primary and reactivation EBV infection and PTLD. (Birkeland, 1999)

Efforts have been made to identify a specific immunosuppression that might predispose PTLD. The introduction of calcineurin inhibitor has been associated with an increase in the incidence of PTLD. T cell depletion regimens, especially OKT3, have also been implicated, and more recently, the use of biologics has been followed by an increase in EBV associated tumors. According to CTTR data, the average time after transplantation to the development of lymphomas was 50 months when corticosteroids and azathioprine were used; when CsA was added, this interval dropped to 13 months and when OKT3 was used it dropped to 7 months. Nevertheless, no one particular agent has proven to be associated with the development of this disease. It is more the cumulative amount and the duration of immunosuppression. Prolonged or powerful immunosuppressive therapy in renal transplantation is complicated by the development of an unusually high incidence of malignancy.

As previously mentioned, there is also a range in the incidence depending on the type of organ transplanted. Whether it has to do with the lymphoid compartment that is transferred with the graft, the alloreactivity of the graft or the amount of immunosuppression required in the transplant is unclear. Several studies have implicated concurrent cytomegalovirus (CMV) and/or hepatitis C infection as risk factor for the development of PTLD, but that also has remained unclear. And finally several articles have been published looking for the role of cytokine gene polymorphisms in the genesis of PTLD. (Martinez, 2010)

Reports have suggested that underlying disease may represent a risk factor for PTLD. Shpilberg and colleagues, 1999, suggest that, in liver transplant patients, underlying autoimmune disorders such as autoimmune hepatitis or primary biliary cirrhosis may predispose to PTLD. An even more striking association was reported in one series of patients who underwent liver transplantation for treatment of Langerhans cell histiocytosis (Newell et al., 1999). In this group, two thirds of patients developed PTLD. Underlying hepatitis C virus (HCV) infection was also found to be associated with a 10.5% frequency of PTLD in one series, whereas liver transplant for other diseases was associated with a 1.7% frequency. (Hezode et al., 1999) Although patients with HCV were noted to have a higher requirement for immunosuppression with antilymphocyte

antibodies, the authors observed that an increased risk remained even after this variable had been accounted for.

Risk factors for PTLD
• EBV seronegativity
• Type and duration of immunosuppression
• Type of organ transplanted
• Concurrent CMV and/or HCV infection?
• Cytokine gene polymorphisms?

Table 1. Risk factors for PTLD

4. Epstein Barr Virus (EBV)

EBV is a B lymphotropic DNA gamma herpes virus and it infects cells through CD21, a complement receptor (CR2), using HLA class II as a co-receptor. Once infected, persists in the cell as episome in subset of latently infected memory B cells. Using this strategy the virus is very effective, as EBV infects over 90% of the population. In addition to the PTLD, this virus is known to cause infectious mononucleosis in the general population and also has a strong association with Burkitt's lymphoma, Hodgkin's lymphoma, and other tumor of epithelial origin such as nasopharyngeal carcinoma. (Snow et al., 2006)

Understanding the life cycle of EBV in a healthy person can help us in the pathogenesis of PTLD. Typically is transmitted through the saliva and infects B cells. One of two things can happen, it can set up a lytic infection where virus particles are produced and the cells are lysed and the viral particles are released to infect other cells, or it can set up a latent infection, expression of the define viral genes, including EBV Nuclear Antigen (EBNAs) and Latent Membrane Protein 1 (LMP-1) proteins. By expressing these two antigens, the cell is now able to proliferate autonomously and becoming essentially a lymphoblast. Cytotoxic T cells and NK cells control the expansion of these cells. (Cohen, 2000)

Eventually the expression of LMP-2 antigen is shutted off and the cell exists the cell cycle, goes on to a type 2 latency state, and goes through germinal center reactions and emerges as a memory B cell, where the virus persists. Occasionally the cell can reactivate the virus and produces additional viral particles or can revert into the lymphoblast-like activity.

5. Mechanisms of oncogenesis

One of most important protein involved in the genesis of these tumors is the LMP-1, the major oncogene of EBV. It has been demonstrated that it is sufficient by itself for transformation of rodent fibroblast and is also necessary for transformation of human B cells. In an infected B cell that is undergoing a latent state, LMP-1 is expressed in the membrane of the cell via an expression of multiple spanning domains. The cytoplasmic region, signaling domain, of the molecule does not have intrinsic kinase activity, but via tumor tips, C Terminal Activating Regions (CTAR1 and CTAR2), allows the recruitment of various

adaptor proteins from the cell, activating a number of cellular signaling pathways. These cellular signaling pathways are responsible for the oncogenic function of the virus. (Martinez et al., 2008)

It has been shown that tumor derived LMP-1 contains unique mutations, in position 212 and 366 (Vaysberg et al., 2008). Also, the wild type form of LMP-1 expressed on the B cell induces only a transient activation, known as benign or weakly oncogenic. In contrary, tumor derived LMP-1 is able to induce activation of various proto-oncogenes. These mutations identified in tumor derived LMP-1 may account for the oncogenic function of EBV.

A number of various cytokines is produced by EBV infected B cells, and in many cases the actual viral gene itself has been identified to be responsible for inducing the production of cellular cytokine. Some of these cytokines, especially IL-10, functions as autocrine growth factor for these tumor cells.

Also, EBV is very effective at immune evasion, a characteristic that allows for the virus to coopt and borrow a number of different cellular pathways to allow it to persist and avoid detection by the immune system. (Martinez & Gruji, 2008)

6. Classification

Lymphoproliferative lesions are currently classified according to histologic parameters. Histologic findings refer to the microscopic appearance and characteristics of the tissue. Polymorphic lesions contain a proliferation of cells with varied morphologic structure, whereas monomorphic PTLDs generally contain a uniform population of cells. With the rapid progress in molecular diagnostic techniques, including DNA array technology, it is likely that the classic approach will soon be supplemented or superseded by more comprehensive molecular approaches. (Nalesnik et al., 2000)

The features of PTLD have been categorized by the World Health Organization in 1997 and revised in 2008. It classifies PTLD into four different categories. Early lesions can be the reactive plasmacytic B cell type hyperplasia or infectious mononucleosis-like syndrome. Those are often seen as consequence of a primary disease. Various types of B cells infiltrating the lesion characterize the polymorphic PTLDs, including small B cells and lymphoblast plasma cells, and those are often seen in children. The monomorphic PTLD include those that are T cell or natural killer (NK) cell origin as well as the B cell lymphomas, the most common B cell lymphomas. They usually look like diffuse large B cell lymphomas. Finally, the classic Hodgkin lymphoma type PTLD, is diagnosed as in the non-transplant patients. (Martinez, 2010)

Classification of PTLD
• Early
• Polymorphic PTLD
• Monomorphic PTLD
• Classic Hodgkin lymphoma-type PTLD

Table 2. Classification of PTLD

7. Staging

The stage of PTLD represents the extent of the disease. For example, it can be local or disseminated and nodal or organ involvement. In approximately 50% of cases, multiple organs or sites are involved at the time of presentation. (Boubenider et al., 1997) The lymph nodes and GI tract are the 2 most common sites. No formal system of PTLD staging exists, and it is suggested that the standard Ann Arbor classification with Cotswold modification, which is used to stage non-Hodgkin's lymphomas, be used when possible in reporting cases. (Paya et al., 1999)

The cases are placed into one of four stages (I-IV), based upon the sites of involvement, the number of lymph node regions involved and the presence or absence of systemic symptoms or of bulky or extended disease. Apart from these four stages, there is a subclassification, in which "E" indicates extra-nodal involvement; "A" to indicate the absence or "B" to indicate the presence of systemic symptoms (weight loss, fever, or night sweats) and "X" to denote bulky disease, which is more than 10cm in maximum dimension or involves more than one third of the chest diameter (seen on chest x-ray).

All organs known or suspected to be involved in PTLD and the evidence for their involvement (histologic, radiologic, and/or biochemical) should be recorded. The presence or absence of allograft involvement should also be explicitly stated for each case. (Preiksaitis & Keay, 2001)

Stage	Criteria
I	In 1 lymph region only
II	In ≥ 2 lymph regions on the same side of the diaphragm
III	In the lymph nodes, spleen, or both and on both sides of the diaphragm
IV	Extranodal involvement (eg, bone marrow, lung, liver)

Table 3. Cotswold Modification of Ann Arbor Staging of Hodgkin Lymphoma and Non-Hodgkin Lymphoma

8. Clinical presentation

Due to the complexity of the disease, clinical presentation can be quite variable, depending on the type of immunosuppression, type of organ transplanted and type of PTLD. Generalized systemic illness symptoms, such as fever, sweats, malaise, and rapid enlargement of tonsils or cervical nodes are commonly seen in PTLD patients. In some cases the nodes are involved, and sometimes it presents as a localized disease and sometimes as a disseminated disease.

The gastrointestinal tract is a common site of extra nodal disease and it can cause abdominal pain with hemorrhage and may perforate, leading to acute abdomen. Central nervous system disease may also occur causing symptoms secondary to local necrosis and tumor mass effect. However, PTLD can occur at any site. For example, isolated skin involvement has been noted, (McGregor et al., 1993) and gallbladder involvement has been observed in one case as well (Heller et al., 2000). Disease limited to the graft is a common manifestation

of early PTLD. Its differentiation from acute cellular rejection in this situation is critically important. Lesions may be limited and progress slowly, or the patient may present with a fulminant, multiple-system, sepsis-like syndrome. This last form is an uncommon presentation, occurring in approximately 1% of cases (Nalesnik et al., 2000). PTLD may resemble a self-limited infection or be indistinguishable from non-Hodgkin lymphoma. An unexplained infectious syndrome in a transplant recipient should raise the suspicion of PTLD. A mononucleosis syndrome may occur early after transplantation, particularly in association with a primary EBV infection. This presentation is particularly common in the pediatric population, and indeed, in some cases it is infectious mononucleosis. Otolaryngologic symptoms and findings are often the first manifestation of PTLD in children. (Posey et al., 1999) Patients may present with tonsillitis, tonsillar necrosis, lymphadenitis, sinusitis, and otitis media. There is a tendency for more severe upper airway symptoms, including airway obstruction. It should also be noted that the underlying process in these cases, ie, infectious mononucleosis vs frank tumorous PTLD, cannot always be inferred from the clinical picture alone.

PTLD can present as early as less than a month or lately as several years after transplantation. In a series of 71 liver transplant recipients in a pediatric population the incidence of PTLD was 9.85%. The median time from the first symptoms to the initial treatment was 9.7 days (Wiederkehr et al., 2010). In general, however, PTLD is remarkable for a short post-transplantation time of onset. In the CTTR, the latest case occurred 25 years after transplantation. As a general rule patients who present as late onset (>1 year) have more aggressive tumours with poorer prognosis (Molnar & Keung, 2001).

PTLDs that do not contain EBV tend to arise at a later time than those that do contain the virus. In one series, 50% of EBV-positive PTLDs arose by 6 months following transplantation, whereas the 50% mark for occurrence of EBV-negative PTLDs was not reached until 5 years after transplantation (Leblond et al., 1998). PTLDs of T-cell origin are uncommon and may also arise later in the posttransplantation course, but a case of a monoclonal T-cell tumor arising 2 months after transplantation has been described. (Kim et al., 1999)

A PTLD that occurs later is more likely to be circumscribed anatomically and to be associated with a more gradual clinical course. In this situation, extranodal disease with visceral involvement is common with gastrointestinal, pulmonary, or central nervous system (CNS) symptoms. Lymphadenopathy is painless, and atypical lymphocytes may or may not be present in the white blood cell differential count.

Most patients with PTLD present with at least 1 tumor. About two thirds of these tumors are extranodal, and about one third are nodal. (Penn, 1994) There is a tendency to involve specific sites. The gastrointestinal tract is involved in about 26% of cases and CNS in about 27% of cases (Chen et al., 1993). The allograft can also be involved. In this case, the frequency of involvement varies according to the specific type of allograft. PTLDs that arise in lung or intestinal transplant recipients involve those allografts in up to 80% of cases. The reason for this is not known. However, it is interesting that the lung and bowel are transplanted with a large indigenous lymphoid population. PTLDs that occur in patients receiving other types of allografts, such as liver and kidney, involve the allograft in about one third of cases (Cohen, 1993). In contrast, the transplanted heart is only rarely involved with these tumors (Hanasono, 1995).

9. Diagnosis of PTLD

The diagnosis of PTLD requires an awareness of the myriad appearances of this syndrome. Isolated or systemic lymphadenopathy or "lumps and bumps" that suddenly appear should include PTLD in the differential diagnosis. (Nalesnik et al., 2000) Abdominal pain, particularly with evidence of intestinal bleeding, raises the possibility of PTLD in the GI tract. In one pediatric series, diarrhea and/or gastrointestinal bleeding in the presence of active EBV infection was associated with PTLD in 43% of cases. (Cao et al., 1998) Persistent headaches or CNS symptoms suggest localization to the brain. Upper respiratory tract infections that may be associated with lymphadenopathy or that do not resolve after a course of antibiotics should raise a suspicion of PTLD.

Several laboratory assays have applicability in suggesting or supporting the diagnosis of PTLD. Badley and colleagues, 1996, demonstrated monoclonal gammopathy in 71% of transplant recipients with and in 27% of transplant recipients without PTLD. A separate study showed that PTLD developed in 9% of all transplant recipients who had monoclonal gammopathy. (Pageaux, 1998)

The gold standard is the analyses of histology of the biopsy tissue. (Dusenbery et al., 1997) The first effort is to identify the virus, usually done by looking for EBV encoded RNA (EBER) or LMP-1 with immunohistochemical stain. Clonality and phenotyping can also be done to identify the origin of the cells involved in the tumor.

The term 'PTLD' encompass the full range of EBV-related lymphoproliferative states, including benign processes. However, when not otherwise specified, PTLD should refer to the neoplastic end of the PTLD spectrum. Neoplasia should be defined by two of the following three characteristics: (1) destruction of the underlying lymph node architecture; (2) monoclonality (regardless of morphology); (3) evidence of EBV infection in the neoplastic cells. (Loren et al., 2003)

Regarding serology, it is not diagnostic of PTLD rather than a tool to identify primary infection or reactivation. Epstein-Barr viral serologic testing may be used to evaluate the presence of recent or remote infection and thus may provide indirect information relevant to the diagnostic workup for PTLD. However, a diagnosis of EBV infection, active or remote, is not synonymous with a diagnosis of PTLD. For example, one study (Smets et al., 2000) of EBV-seronegative pediatric liver transplant recipients showed an 80% conversion rate to seropositivity within the first 3 months after transplantation. Of these patients, approximately 85% were asymptomatic and only 15% developed PTLD.

Of the various serologic assays for EBV infection, IgM antiviral capsid antigen (IgM-VCA) is particularly useful in detecting active infection. In one study, IgM-VCA antiviral capsid antigen level was elevated an average of 5 days after a detectable rise in circulating EBV genomes shown by polymerase chain reaction (PCR) assay. (Bodeus et al., 1999) Quantitative estimation of the number of EBV genomes in the peripheral blood by use of the PCR assay provides a more useful correlate of the EBV infection types most likely to be associated with PTLD.

This technique was applied following the observation that patients with PTLD had early and spontaneous outgrowth of virus when peripheral blood cells were cultured in vitro. (Rooney et al., 1995) Such outgrowth does not occur in "normal" EBV-positive patients. It

was subsequently shown that patients with PTLD had elevated numbers of circulating viral genomes. Hanasono and colleagues, 1995, showed that normal EBV-positive patients had less than 2,000 viral genomes per microgram of blood cell DNA, whereas the number of genomes was increased 10- to 100-fold in patients with PTLD. Rowe and colleagues found an increased risk of PTLD when the number of circulating EBV genomes exceeded 500/105 peripheral blood lymphocytes. Furthermore, regression of PTLD was associated with a decrease in the number of circulating viral genomes, indicating that this parameter also served as a useful means of monitoring therapy. (Rogers et al., 1998)

Some tests done for confirmation of diagnosis of PTLD are HE staining, which is important to determine the morphology of the tumor and the extent of infiltration and tissue architecture destruction; phenotyping of B cells, NK cells or T cells; Ki-67 which is an important marker for the proliferative index and shows how rapidly the tumor is dividing; and EBER staining to confirm the presence of the virus itself.

10. Radiographic features

CT-scans and/or MRI are usually done for staging of the disease. The range of appearances is large due to the number of possible sites. If the disease affect solid organs (liver, spleen, kidney) it can be showed as nodules with characteristic such as hypoechoic, low density on CT or as a diffuse infiltration. When the disease affects bowel, it can appear as a circumferential wall thickening, an aneurysmal dilatation, an ulceration or perforation, and even bowel obstruction. In the lung, it can appear as nodules usually homogeneous, may centrally cavitate, or as diffuse infiltration. When the object of study is the brain, must be considered characteristics similar to lymphoma in the setting of HIV infection and also necrosis and hemorrhage. Overall, nodes can appear as non-specific nodal enlargement, similar to other lymphomas. (Pickhardt et al., 2000)

The single most frequent imaging finding is lymphadenopathy within the abdomen, as expected, being the most common region involved. Previous studies have reported lymphadenopathy between 55% and 74%. (Steiber et al., 1991) Pickhardt & Siegel, 2000, reported a lower incidence of 34%, but only concentrated on intra-abdominal abnormalities.

11. Differential diagnoses

The differential diagnosis depends on the location of PTLD and is therefore broad. If the disease locates at the small bowel the differential diagnosis can be inflammatory bowel disease - especially Crohn's disease - or acute rejection. If the disease locates at the lung, metastases, infection, lymphoid interstitial pneumonia (LIP) must be considered. When located in the head and neck, infections mononucleosis or reactive nodal enlargements are diagnostic possibilities.

12. PCR monitoring for EBV DNA

EBV titers have been shown to be sensitive to adjustments of immunosuppressive therapy, and it has been suggested that immunosuppressive therapy could be reduced when a rising titer is observed, thus preempting the development of PTLD. Studies examining this have concentrated on the pediatric population where it is thought that EBV exposure occurs at

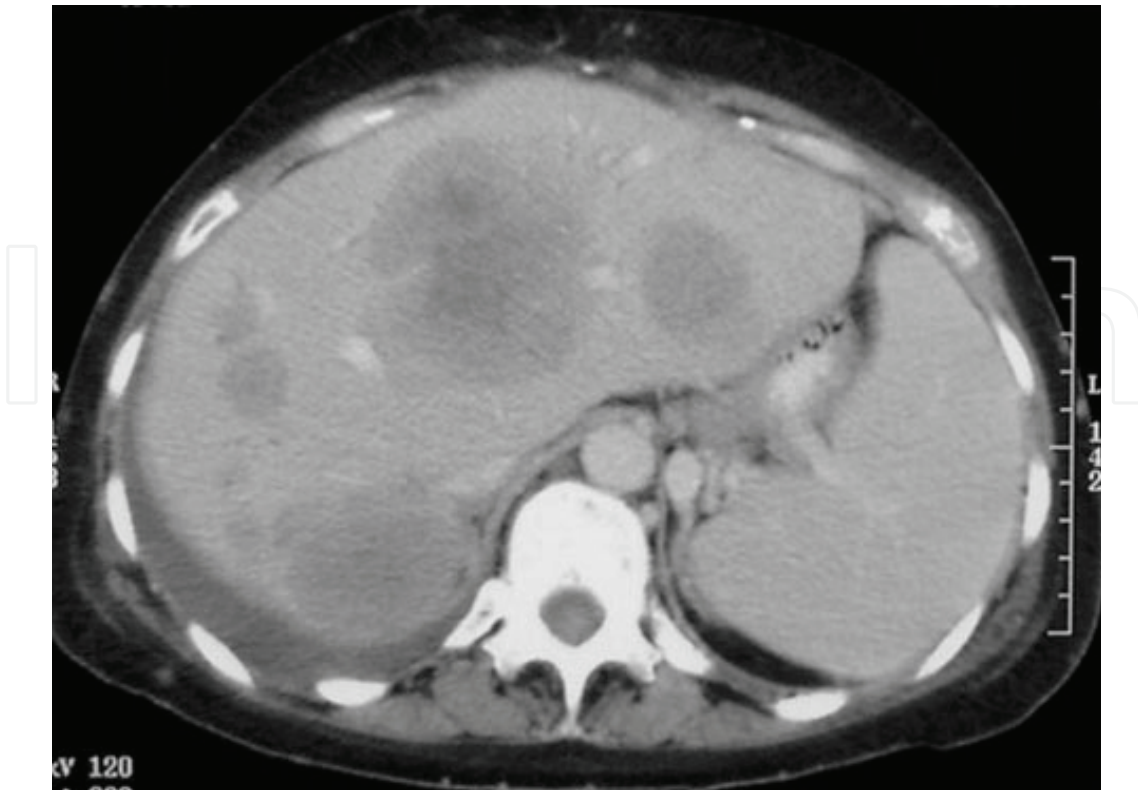


Fig. 1. CT confirmed multiple low attenuation lesions within the liver and the presence of ascites. (Dhillon et al., 2007)

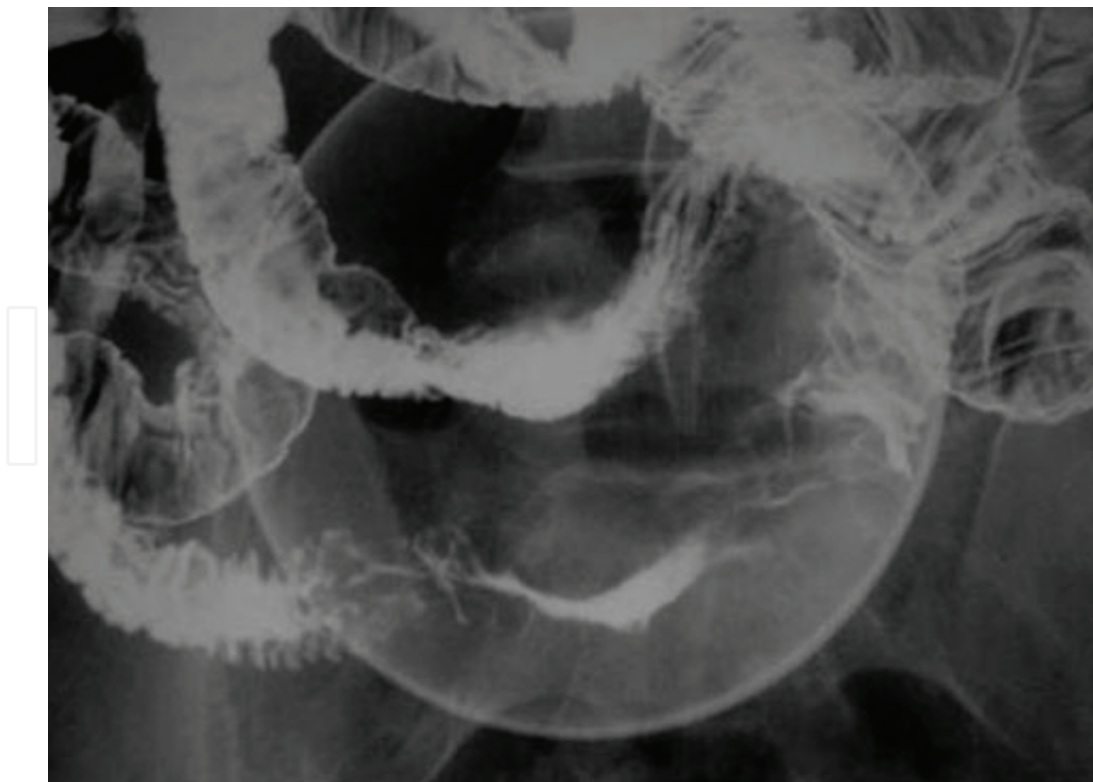


Fig. 2. Small bowel involvement: barium follow-through presenting a small bowel obstruction with an extensive stricture within the terminal ileum. (Dhillon et al., 2007)

the time of transplantation so that PTLD is most frequently observed during the first post-transplant year. (McDiarmid et al., 1998) However, in adults, there is often pre-transplant EBV immunity and this is reflected in the later development of PTLD.

In high-risk patients, such as children who are seronegative at transplant, determination of viral load throughout the post-transplant period may be useful. Increases in viral DNA can be detected months before clinical onset of PTLD. Viral load determination can also be used to monitor response to the treatment. The problem of this approach is that not all patients with PTLD will have an increase in the viral load, and only a minority of patients with high viral load will develop PTLD. Although there is no consensus on the threshold value, as well as standard methodology and compartment measured, some reports indicate 200 copies/ 10^5 PBMC correlates with symptomatic disease in children. (Martinez, 2010)

It has been revealed that there are subsets of patients who are chronic high load carriers, with no symptomatic or clinical disease. This is typically of patients who have undergone a primary infection and were seronegative at the time of transplant. It can also occur after asymptomatic primary infection or after EBV disease, including PTLD. (Martinez, 2010)

13. Prevention

Prophylactic treatment with antivirals, acyclovir and gancyclovir, is used in many high-risk patients. Those drugs are not effective in the context of PTLD because at that stage the virus is in a latent infection and the antivirals depend upon viral replication. One way to overcome such problem is to use arginine butyrate to re-initiate a lytic infection and combined that with antiviral drugs.

The reports that prophylactic antiviral drugs minimize PTLD risk have been somewhat unconvincing, involving very small number of patients in observational studies. Each investigator defined 'high-risk' differently: some included only patients with elevated EBV viral loads, while others included EBV-negative patients receiving organs from EBV-positive donors, or patients receiving high-dose immunosuppression or specific anti-lymphocyte therapy.

Antiviral agents (such as intravenous immunoglobulin containing neutralizing antibody or acyclovir, ganciclovir, and foscarnet) that target steps in the lytic virus cycle are sometimes used for PTLD prevention. The potential efficacy of these agents depends on the relative importance of EBV-driven lymphoproliferation (which is not influenced by these agents) and the lytic virus cycle (which is) on EBV-induced lymphomagenesis. (Preiksaiti, 2004)

However, historical comparisons of the incidence of PTLD among patients receiving and patients not receiving ganciclovir prophylaxis, either immediately after transplantation or during antilymphocyte antibody therapy, suggest that prophylactic antiviral therapy may be of some benefit (Preiksaiti, 2003). A multicenter, randomized controlled trial of CMV immunoglobulin prophylaxis in EBV-seronegative, pediatric SOT recipients was inconclusive with respect to PTLD prevention. This was likely the result of immunosuppression modification by clinicians in response to EBV load data, resulting in an overall reduction over time in the incidence of PTLD, irrespective of the prophylactic regimen used. (Green et al., 2003) Antiviral agents may have indirect benefit on PTLD risk by eliminating other viral infections, such as CMV infection, that act as cofactors in PTLD development. For this reason, the use of ganciclovir may be preferred over the use of

acyclovir. Antiviral agents may also influence global immunosuppression by preventing the expression of EBV immunomodulatory proteins expressed during the lytic cycle. There is an urgent need for additional multicenter controlled trials that evaluate the efficacy of agents used alone and together for prophylaxis. (Preiksaiti, 2004)

An alternative approach to prevention employs a preemptive strategy in which intervention (usually in the form of reduction in immunosuppression and/or the use of antiviral drugs, with or without immunoglobulin) is administered in response to “trigger points,” usually high EBV loads. This approach has been used in both intestinal transplant recipients and pediatric liver transplant recipients. (Green et al., 2001) Although the simultaneous use of multiple interventions makes it difficult to determine the efficacy of any single approach, the incidence of PTLD decreased in these populations, compared with historical controls, when preemptive strategies were applied. (Preiksaiti, 2004)

14. Treatment

Primary approach for of PTLD is to reduce immunosuppression in these patients. The response rate for this strategy varies from 23-100%, which in some cases places the allograft in danger for rejection, and occurs as a potential complication in 39% of the patients. It is not the ideal approach but it has been effective for some patients. Predictors of lack of response to reduction of immunosuppression include a serum LDH 42. 5 times the upper limit of normal, organ dysfunction, and multiple visceral sites of disease. (Tsai et al., 2001) In patients with life-sustaining organ transplants such as hearts, livers and lungs, reduction in immunosuppression should be more moderate and closely monitored as allograft rejection may be swift and fatal. (Loren et al., 2003)

Initial attempts to prevent PTLD in the solid-organ transplant population were focused primarily on using antiviral therapies, such as thymidine kinase inhibitors ganciclovir or acyclovir, to eradicate or control EBV for high-risk patients. These drugs inhibit the replication of other herpes viruses, such as herpes simplex and cytomegalovirus. In vivo, however, they are ineffective against EBV, because EBV survives as an episome outside of the lymphocyte’s genome. In addition, these drugs do not eradicate latently infected B cells. (Crumpacker et al., 1996)

The use of humanized antibody to CD20 (anti-CD20 mAbs, Rituxan) has been shown to be effective, although there are some issues with relapse and it is restricted to CD20 positive tumors. Chemotherapy, surgery and radiation can also be used in some patients with variable outcomes. (Muchak et al., 2010)

Chemotherapy has also been used to treat PTLD, generally after patients have failed to respond to surgical excision with or without reduction of immunosuppression. Regimens are similar to those used for non-Hodgkin’s lymphoma, such as CHOP and ProMACE-CytaBOM.

While chemotherapy may occasionally provide long-term relapse-free survival, it is accompanied by a high infection and mortality rate. (Mamzer-Bruneel et al., 2000)

When possible, complete surgical excision of localized disease is highly effective as well as local radiation. Localized disease treated with definitive local therapy (surgery or radiation), combined with reduction of immunosuppression, have an excellent prognosis, with PTLD-related mortality rates reported between 0 and 26%. (Davis et al., 1998)

Treatment	Response Rate (%)
Reduction immunosuppression	23-100
Anti-CD20mAbs (Rituxan)	44-68
Chemotherapy	24-65
Surgery and radiation	Variable

Table 4. Therapeutic strategies for PTLD and their efficacy

Two new strategies have been shown to be of some value in the treatment of PTLD patients. One is to improve the immune system response against the virus, and a second one is to try to lower the viral load or the number of infected cells. T cell lines - CTL, specifically directed against B cell can be obtained *in vitro*. (Haque, 2002)

Attempts to establish a competent immune to control EBV-related lymphoproliferations, with immune modulators such as cytokines with or without immunoglobulins have been made. Several case series and case reports have described responses to interferon-alpha and interferon-alpha combined with intravenous IgG. (Davis, 1998) Interleukin-6, a cytokine that promotes the growth and proliferation of B cells, provides another potential target. It is difficult to assess the effectiveness of cytokine therapy as most studies utilizing these agents have also incorporated concurrent reduction in immunosuppression or antiviral agents.

Rapamycin and everolimus, mTOR inhibitors, that are antiproliferative agents may be effective in preventing PTLD. (Nepomuceno et al., 2003) Also, mTOR inhibitors provide an option of switching immunosuppression while providing some anti-tumor effect as an alternative to removal of immunosuppression. (Vaysberg et al., 2007 and Krams et al., 2008)

A promising therapeutic option to control B-cell proliferation is anti-B-cell antibody therapy. Expression of B-cell antigens is variable in PTLD, most likely because of the dysregulation by EBV infection. Nevertheless, results have been quite promising with many patients achieving longterm relapse-free survival.

15. Prognosis

Overall response and survival rates are difficult to compare because of the wide range of PTLD forms and therapies. Furthermore, crude rather than actuarial survival rates are often reported. Within these limitations, a review of relevant literature shows responses that tend to vary according to histology and stage. In two separate series, (Knowles et al., 1995 and Cohen et al., 1991) mortality from polymorphic and monomorphic PTLDs ranged from 0% to 20% and 67% to 87%, respectively. PTLDs with abnormalities of oncogenes or tumor suppressor genes would fit within the monomorphic category, and these abnormalities appear to augur a worse prognosis. (Knowles et al., 1995 and Locker et al., 1989) According to Cohen, 1991, it was observed that 44% of PTLD survivors had involvement of only one organ, and involvement of 3 or more organs occurred in 57% of fatal cases. Dror and colleagues considered thrombocytopenia and neutropenia to represent negative prognostic indicators and PTLD histology and stage to be marginally significant in their series. An absence of stage effect on survival was also reported in a retrospective review of 27 pediatric patients. (Donnelly et al., 1998) In this series, mortality was more closely related to the

underlying procedure, with BMT and heart transplant recipients having higher mortality rates than liver and kidney transplant recipients. Gross and colleagues reported 92% mortality in PTLD arising in recipients of allogeneic hematopoietic stem cell transplants. In their series, the only responders seen were among those patients treated with interferon alpha. In a separate pediatric liver transplant series, (Praghakaran, 1999) 4 patients with B-cell lymphoma and 1 with B-cell leukemia were successfully treated with reduced immunosuppression and high-dose acyclovir alone or with this treatment followed by chemotherapy. (Praghakaran, 1999) In our series of 7 liver transplants in small children with PTLD, median age at transplantation was 35.14 months, and the mortality was 57%. (Wiederkehr et al., 2010)

The heterogeneity of these reports exemplifies the variable results seen with different treatment regimens among different centers and argues for standardized multicenter therapeutic trials against this disease. According to Nalesnik's series of 256 patients with PTLD, the overall 2-year actuarial survival is 90%, and the overall actuarial 5-year survival is 77%. (Nalesnik et al., 2000)

According to a study made by Jain et al., 2002, the actuarial patient survival rates for entire population of PTLD patients at 1, 5, 10, 15 and 20 years were 85%, 69%, 55%, 47%, and 45% respectively. In the article there was a numerical difference in survival, with women having a better survival than men but this was only evident at 10 years after PTLD diagnosis and did not reach statistical significance. Long-term survival rates for pediatric patients with PTLD were better than for adults (60% pediatric at 15 years, compared to 39% for adults). Survival in the tacrolimus group was significantly better than for cyclosporin (60% vs. 40% by 12 years). Other factors that appeared to have a positive effect on survival included single site versus multiple site. Overall, mortality due to PTLD ranges from 22% to 70%. (Levi et al., 1993 and Newell et al., 1996)

16. References

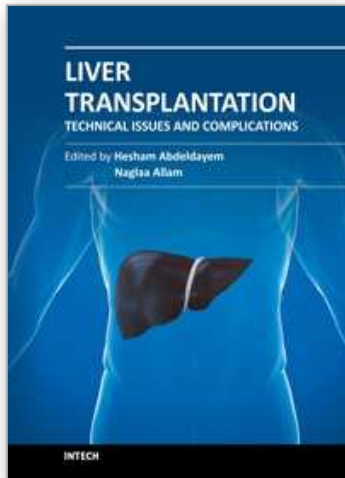
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