Case Study

The Challenges of Monitoring PTLD with Focus on Renal Transplantation: A Case Report

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Key Learning Points
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Post-transplant lymphoproliferative disorder (PTLD) is a serious complication occurring after solid organ or haematopoietic stem cell transplants and traditionally carries significant mortality. The relative risk of developing this disease following solid organ transplant is substantial, up to 20-fold greater than the general population, making this an important post-transplant pathology.

The pathophysiology is incompletely understood; however, the majority of cases involve EBV infection of circulating B cells causing lymphoproliferation and this has been the dominant conceptual framework until recently. It is increasingly apparent that a significant minority (up to 40% of cases) are EBV negative, with the mechanisms underlying these cases being unclear. There are multiple risk factors for PTLD, with one of the strongest being high levels of immunosuppressive medication. Therefore the mainstay of initial treatment involves reduction of immunosuppression, requiring a delicate balance to be struck in transplant patients.

The presentation of PTLD is varied and determined by the anatomical location of disease but, as highlighted in this case, can often present with acute abdominal symptoms to generalist clinicians. Classical B symptoms are also reported and may be the dominant features.

The management of PTLD has evolved significantly over the last two decades and aside from reduction of immunosuppression, now involves a combination of local (surgical/radiation) treatment and systemic treatment with R-CHOP chemotherapy. Although the changes in the management have a role to play in the improved outcomes, there have been significant advances in staging, supportive management, earlier diagnoses and greater clinical suspicion that have all contributed to improved outcomes.

This complex post-transplant pathology requires a multidisciplinary approach to achieve the optimal outcomes as it intersects a number specialist disciplines, all of which are required to manage this appropriately.

Introduction

The debilitating nature of organ failure is such that successful organ transplantation can gift patients with a freeing new lease of life; take renal transplants, which can liberate their recipients from the highly restrictive diet, dialysis and lifestyle of kidney failure. Yet every transplant must be accepted with its risks, perhaps one of the most severe being post-transplant lymphoproliferative disorder (PTLD)[1]. Although fairly uncommon, PTLD can have devastating effects[2], raising challenges in how to improve its prevention, monitoring and treatment whilst maintaining transplant function. The case of X, an adult renal transplant patient who developed a gastrointestinal localising PTLD, provides an interesting platform to discuss some of these challenges

in the context of kidney transplantation, highlighting complicating factors such as the heterogeneity of PTLD presentation, rejection risk and tailoring treatments, particularly in an area where conducting comprehensive research can be limited.

Patient X Case History

X is a 36 year old gentleman who underwent a living relative donor kidney transplant in April 2016. This was subsequent to a diagnosis of membranous glomerulonephropathy in July 2012; despite various treatment attempts, including enrolment in clinical trials and two courses of the Ponticelli regimen, his renal disease progressed, such that he required peritoneal dialysis from January 2016, precipitating the donation of

Category		Clonal Status	Architecture	EBV Associated	Early or Late PTLD
Early Lesions	- Plasmacytic hyperplasia - Infectious mononucleosis like lesion - Florid follicular hyperplasia (or other non-infectious mononucleosis like hyperplasia)	Polyclonal	Non-destructive Small lymphocytes, plasma cells, +/- immunoblasts, +/- hyperplastic follicles	Usually EBV + (almost 100%)	Mostly early
Polymorphic PTLD		Variable	Destructive Full spectrum of lymphoid maturation seen	Usually EBV + (>90%)	Variable
Monomorphic PTLD	**B-cell lymphomas** - Diffuse large B cell lymphoma (DLBCL) - Burkitt's lymphoma - Plasma cell myeloma - Plasmacytoma-like lesion **T-cell and NK cell lymphomas** - Peripheral T cell lymphoma - Hepatosplenic T cell lymphoma - Other	Monoclonal	Destructive Fulfils criteria for a NHL (other than one of the indolent B cell neoplasms) or plasma cell neoplasm	Both EBV + and − B- cell lymphomas usually EBV + T cell lymphomas usually EBV -	Both early and late
Classic Hodgkin Lymphoma (CHL) like PTLD		Monoclonal	Destructive Fulfils criteria for CHL	Usually EBV + (>90%)	Increase in late onset after allogenic HSCT?

EBV – Epstein Barr Virus, NHL – Non-Hodgkin Lymphoma, HSCT - Haematopoietic Stem Cell Transplantation

TABLE 1: WHO CLASSIFICATION OF PTLD [2,3]

Risk Factor	Additional Information
Infectious Aetiology	- 50-65% of PTLD is associated with EBV infection - CMV mismatch between donors and recipients - Hepatitis C and Human Herpes Virus 8 also associated with increased PTLD
Immunosuppression	- Both intensity and duration of immunosuppression increase PTLD risk. - Certain drugs implicated as possible risk factors (e.g. ATG, OKT3, calcineurin inhibitors, azathioprine)
Transplant type	*Relative Risk per transplant type:* multi-organ and intestinal 239.5; lung 58.6; pancreas 34.9; liver 29.9; liver 27.6; kidney 12.6
Race	Caucasians are more likely to develop PTLD
Age	Patients <10 years and >60 years are at increased risk
Genetics	Certain cytokine polymorphisms and recipient HLA haplotypes are associated with increased PTLD risk

TABLE 2 – PTLD RISK FACTORS[1,3,6,7]

a kidney for transplant from his mother. Aside from his renal disease course, X has no other significant medical history.

X initially reported no significant complications in relation to his transplant, attending regular renal clinic appointments for monitoring. However, from October 2018 he began to notice symptoms of intermittent abdomen pain that worsened on eating. By April 2019 his symptoms had progressed, accompanied by a 14kg unintentional weight loss over 4 months, difficulty eating solid foods and a 6 week history of diarrhoea; the persistence and progression of his symptoms raised the suspicion of PTLD, precipitating further investigation. On examination, X showed signs of clinical pallor with a distended abdomen and tender right flank. Otherwise, X's abdomen was soft and non-tender with no palpable masses, although the spleen tip could be felt on inspiration. Abdominal pain presented every few minutes, with bowel sounds being audible from the end of the bed, accompanied by palpable contractions that were non-responsive to tramadol. Stool analysis supported a possible GI cause with raised faecal calprotectin; this was confirmed with CT-PET imaging, demonstrating a large intussuscepting mass in the ascending colon and distal colon collapse, although there were no distant lesions excepting a 2cm lymph node in the adjacent mesentery. Subsequent colonoscopy also identified the malignant 10cm caecal mass, which was seen to be bleeding spontaneously and obstructing the colon lumen. Biopsies confirmed the mass to be EBV positive monomorphic PTLD (diffuse large B cell lymphoma, germinal centre type).

It was planned for X to undergo an urgent elective colonic resection to remove the mass. However in May 2019, he was hospitalised after several episodes of heavy PR bleeding, eventually being transferred to the Surgical Emergency Unit. On arrival to ward, he passed 120ml fresh blood with clots, requiring transfusion of 2 units of RBCs before an emergency laparotomy and right hemicolectomy to remove the tumour. This was followed by a relook the next day to anastomose X's ileum to his terminal colon.

X experienced a largely uncomplicated recovery. On examination post operatively, X appeared well and comfortable walking, with a soft and non-tender abdomen, a good appetite and observations all within normal range. He was started on a course of hydrocortisone (to minimise transplant rejection, following the halting of his tacrolimus and azathioprine over the course of his investigation for PTLD), although this was replaced by prednisolone for a slow wean after discharge. He was subsequently discharged 10 days post operatively, with arrangements to return to clinic for further discussions about his PTLD treatment and transplant management to minimise rejection risk.

PTLD – An Overview

PTLD refers to a heterogeneous spectrum of lymphoid disorders – from indolent proliferation to lymphoma – that can occur as a complication of either solid organ or haematopoietic stem cell transplants[3]. Whilst the first cases were reported in 1968 by Doak, the term PTLD was not officially coined until the mid-1980s[1]. Incidence varies depending on transplant type; based on US registry data cumulative PTLD incidence is estimated at 0.7-9% in the transplant population[4]. Adjusted for time under immunosuppression other studies have suggested

that, for kidney transplants, incidence density is 1.58 cases per 1000 patient years under immunosuppression[5]. It has also been noted that PTLD incidence tends to peak in the first year after transplant with a second peak occurring over 10 years post–transplant[2]. Regardless of metric employed, data suggests that the incidence of new PTLD diagnoses has been rising in recent decades, perhaps reflecting better awareness and therefore recognition of the disease, as well as the rising number of transplant operations undertaken[3].

The WHO classification divides PTLD into 4 main subtypes based on histopathological characterisation[2,3], as seen Table 1. As alluded previously, PTLD can be further categorised based on time of onset; "early onset PTLD" refers to that presenting within a year of transplantation, whilst PTLD presenting after this point is "late onset"[2].

Risk Factors

Multiple risk factors have been associated with the development of PTLD after solid organ transplantation (SOT)[6], as overviewed in Table 2. Whilst this report will not look at each risk factor in detail, it is worth highlighting the roles of EBV and immunosuppression in PTLD. Immunosuppression is required in transplant patients to minimise allograft rejection, however this comes at the cost of impaired immune surveillance, which can promote tumorigenesis[2]. Standardised incidence ratios reflect this, suggesting that the incidence of non-Hodgkin lymphoproliferative disorders can be 5-15 fold times greater in SOT patients compared to the general population[2]. Certain immunosuppressive agents are also thought to contribute to a favourable tumour forming environment – e.g. azathioprine reducing DNA damage repair, cyclosporins and calcineurin inhibitors promoting TGF-β production and tumour angiogenesis – however data regarding the impact of individual drugs on PTLD development has been conflicting[8]. The role of immunosuppression could also explain the increased risk seen with certain types of SOT; for example SOTs with more rigorous immunosuppression regimes (e.g. multi-organ transplants) have a greater PTLD risk than kidney or liver transplants (that typically warrant reduced immunosuppression doses and duration)[7].

Immunosuppression is also closely linked with oncogenic viral activation, particularly that of EBV. In B cell PTLD - the most common subcategory, as exhibited by Patient X - immunosuppression is thought to depress T cell activity, resulting in reactivation of latent EBV infection which drives B cell proliferation[2]. EBV recipient seronegativity (with donor EBV positivity) is a significant predisposing factor for PTLD, explaining the increased risk in children, for whom primary EBV infection is the most common PTLD trigger[7]. The driving mechanism for EBV negative PTLD - more likely late onset - remains unclear[3].

Clinical Presentation and Diagnosis

Table 1 has already highlighted the heterogeneous nature of PTLD with regards to histopathology; this is further reiterated in its clinical presentation. For both renal transplants and wider SOTs presentation can range from asymptomatic to fulminant[3]. Classic B symptoms of weight loss, sweats and pyrexia may be exhibited1. Extranodal involvement is common and symptoms can reflect the localisation of a mass, from the GI tract (as in Patient X) to liver, lung, bone skin and the CNS[3]. Once the suspicion of PTLD has been raised, the gold standard for diagnosis is histopathological analysis,

followed by CT or PET imaging to determine staging[3]. Staging is crucial, since extranodal and CNS PTLD tend to have a worse prognosis, which may inform treatment strategy[2].

Screening and Monitoring for PTLD

Considering PTLD's fairly high mortality rate, preventative strategies and screening for the disease would seem attractive if possible. However, the breadth of possible presentations, with varied organ involvement, can make PTLD challenging to identify; differentials are broad, from allograft rejection to sepsis[3]; take patient X, whose PTLD bowel obstruction pain was initially ascribed to an ulcer. Similarly, the variety of risk factors and our limited understanding of their interplay complicate identifying transplant patient populations at high risk of PTLD.

Focusing on EBV's role in PTLD, several studies have looked at monitoring viral load or treatment with anti-viral medication post-transplant, to assess any correlation with subsequent PTLD development or progression[1,9]. Whilst evidence is mixed regarding the predictive value of viremia in relation to PTLD progression, some studies reported a reduction in PTLD risk with post-transplant acyclovir and ganciclovir administration[1]. Nevertheless a 2016 systematic review suggested that the overall data was inadequate to support the use of routine anti-viral prophylaxis[9]. It must also be considered that EBV is not the sole risk factor for PTLD, so such screening attempts would be rather limited. Ultimately, this perhaps highlights our need to develop an improved understanding of the disease mechanisms and aetiological triggers behind PTLD if we wish to develop better prognostic indicators of PTLD.

Treatment Strategies and Outcomes

Multiple treatment strategies have been employed to treat PTLD, including reduction of immunosuppression (RI), chemotherapy, immunotherapy and other novel approaches, with a curative aim[1]. Success is variable; studies of cohorts of renal transplant patients suggest that 10 year survival after PTLD diagnosis is anywhere between 30-70%[2].

The first line treatment for PTLD is RI, employed since the initial characterisation of the disease. Strategies include the reduction of calcineurin inhibitors by at least 50% and the halting of anti-metabolic agents (for severely ill patients, all immunosuppressive agents, excepting glucocorticoids should be stopped)[3]. PTLD regression can be seen in 20-80% of patients – the variety in results is thought to be multi-factorial, reflecting heterogeneity amongst patient populations, treatment algorithms and study designs[1,10]. To date there has only been one prospective study focusing on RI; conversely to other clinical reports, its results suggest that RI alone is not sufficient to achieve complete remission in PTLD, although in conjunction with chemotherapy, remission was facilitated in 57% of patients[10]. On the other hand, it should be noted that the cohort of 16 patients was small and that the study predated rituximab, which is one of the mainstays of current PTLD treatment.

Over the last 10 years, rituximab has become the standard treatment in patients with non-destructive, polymorphic and DLBCL PTLD who do not respond to RI alone[3]. Various clinical trials have demonstrated rituximab's value in treating CD20+ PTLD; administered as a monotherapy over 4 weeks following RI, response rates to rituximab are 44-79%, with complete remission of up to 55%11. Whilst rituximab appears a successful treatment option so far, reports have emerged of Progressive Multifocal Leukoencephalopathy development in patients after rituximab therapy for PTLD[12], highlighting the need for long term monitoring of patients for unexpected complications of newer treatments.

Systemic chemotherapy can also be employed if RI and rituximab do not induce a response, the commonest regimen being CHOP (cyclophosphamide, doxorubicin, oncovin, prednisone)[1]. Historically, chemotherapy for PTLD had been associated with increased graft rejection and high treatment related mortality, estimated at up to 50%[8]. This has improved somewhat in recent years, with better supportive care and the use of granulocyte colony stimulating factors (GCSF). The PTLD1 trial assessing rituximab treatment with CHOP (followed by GCSF support and recommended Pneumocystis jirovecii prophylaxis) demonstrated complete response rates of 70% with a TRM of only 8%[11]. Such studies suggest that risk stratified sequential treatment can be helpful in the treatment of PTLD, improving outcomes and also minimising the risk of unnecessary over-treatment.

Local treatment such as surgery and radiotherapy can also be used in PTLD management, where appropriate, although without RI this is often unlikely to be curative[1,2]. Patient X is an example of employing a surgical and RI strategy, to manage his gastrointestinal obstructive symptoms and underlying PTLD. In the context of renal transplantation, few studies have been undertaken looking at PTLD outcomes following surgery. Only one study to date has explored the outcomes of surgical management of gastrointestinal PTLD, although this is in liver transplant patients; mortality was 69%, although outcomes were better for patients where bowel obstruction was the main indication for surgery[13]. Although the study had its limitations, being retrospective so not allowing for controls in terms of additional treatments patients received, it did find that long term outcomes did not differ between gastrointestinal-PTLD patients who underwent surgery and those who did not.

More novel strategies have focused on immunomodulation or interfering with cellular proliferation, for example EBV specific cytotoxic lymphocytes (some of which have been engineered to be tacrolimus resistant), interferon α and antibodies against IL-6 and cell checkpoint proteins[1]. However, many of these treatments remain in the experimental stage and require further investigation.

Whilst curing PTLD is the primary objective regardless of therapy type employed, consideration should be made of how best to preserve graft organ function. At times this can be akin to balancing on a knife edge, in terms of best adjusting RI or chemotherapy doses to promote PTLD survival yet avoid transplant rejection; treatment must be individualised to meet the patient's most pressing clinical need at the time. For renal transplant patients, retrospective studies have reported varying rates of allograft survival after PTLD treatment, although the majority demonstrate impaired graft survival compared to non-PTLD populations[6]. A marked exception was noted in an Irish national observational study over 19 years, where 5 year allograft survival after PTLD diagnosis was 93% (comparable to non-PTLD patients)[14]. However, it may be that PTLD patients should be followed up for longer periods to assess true differences in allograft survival; a cohort analysis in British Columbia demonstrated a median graft survival of 9.5 years in PTLD

patients compared to 16 years in non-PTLD patients[15].

Discussion

Over the course of this discussion of PTLD, with focus on renal transplantation, disease heterogeneity has been a recurring theme, in terms of risk factors, disease mechanisms and presentation. Subsequently it can be seen there is no unifying best prognostic or treatment algorithm for PTLD, in part due to a limited understanding of cellular pathogenesis and risk factors, making it difficult for healthcare professionals to optimise individualised management for patients like X.

Good evidence-based management has partly been limited by the body of available research on PTLD. The relative rarity of the disease means that attempts at prospective studies or single centre analysis are often hindered by small sample sizes. This is further exacerbated when trying to recruit substantial cohorts of PTLD subgroups – e.g. of the same histopathological classification, age group, EBV classification, or transplant type – hence the fairly small number of studies focusing on very specific categories of PTLD presentation and the reliance on retrospective, observational studies. Of course, whilst these studies have been useful in gauging incidence and mortality, as well as identifying possible risk factors, the lack of adequate controls and the risk of confounding remains problematic; thus, statistics on risk and outcomes can vary significantly between populations, with many highlighted risk factors often only having been shown to be "associated with" rather than definitively impacting PTLD outcomes. This is a particular issue when assessing treatment interventions retrospectively, since the accepted standard of care can vary significantly over the single time period chosen by a study for data analysis.

Since PTLD is on the rise, it is important to try and improve current research quality, for example through attempting to coordinate international collaboration for prospective trials comparing PTLD monitoring and treatment strategies (this could perhaps facilitate better controlled studies with larger sample sizes). Long term follow-up of PTLD patients should also be attempted, which could help to identify risk factors and late onset PTLD.

Of course, data from such studies would take considerable time for collection and analysis. In the interim, we should stay vigilant about PTLD. In the absence of reliable prognostic markers and uncertain long-term PTLD outcomes, it is important to promote awareness of symptoms and risks of PTLD, not only among healthcare practiners but also transplant patients. Such a collective awareness could promote self-monitoring, in turn improving chances of earlier PTLD diagnosis for potentially better treatment outcomes.

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Consent
The patient has consented to the publication of this case study.

References

1.   Al-Mansour, Z., Nelson, B. P. & Evens, A. M. Post-Transplant Lymphoproliferative Disease (PTLD): Risk Factors, Diagnosis, and Current Treatment Strategies. Curr. Hematol. Malig. Rep. 8, 173 (2013).

2.   Dharnidharka, V. R. Comprehensive review of post-organ transplant hematologic cancers. Am. J. Transplant. 18, 537–549 (2018).

3.   Dierickx, D. & Habermann, T. M. Post-Transplantation Lymphoproliferative Disorders in Adults. N. Engl. J. Med. 378, 549–562 (2018).

4.   Kotton, C. N., Huprikar, S. & Kumar, D. Transplant Infectious Diseases: A Review of the Scientific Registry of Transplant Recipients Published Data. Am. J. Transplant. 17, 1439–1446 (2017).

5.   Sampaio, M. S. et al. Posttransplant Malignancies in Solid Organ Adult Recipients. Transplant. J. 94, 990–998 (2012).

6.   Gwon, J. G., Kim, Y. H. & Han, D. J. Different causes of early and late-onset post transplant lymphoproliferative disorder in kidney transplantation patients after 2000. Asian J. Surg. 42, 551–556 (2019).

7.   Opelz, G. & Döhler, B. Lymphomas After Solid Organ Transplantation: A Collaborative Transplant Study Report. Am. J. Transplant. 4, 222–230 (2004).

8.   Jagadeesh, D., Woda, B. A., Draper, J. & Evens, A. M. Post Transplant Lymphoproliferative Disorders: Risk, Classification, and Therapeutic Recommendations. Curr. Treat. Options Oncol. 13, 122–136 (2012).

9.   AlDabbagh, M. A. et al. The Role of Antiviral Prophylaxis for the Prevention of Epstein-Barr Virus-Associated Posttransplant Lymphoproliferative Disease in Solid Organ Transplant Recipients: A Systematic Review. Am. J. Transplant. 17, 770–781 (2017).

10.   Swinnen, L. J. et al. Prospective study of sequential reduction in immunosuppression, interferon alpha-2B, and chemotherapy for posttransplantation lymphoproliferative disorder. Transplantation 86, 215–22 (2008).

11.   Trappe, R. U. et al. Response to Rituximab Induction Is a Predictive Marker in B-Cell Post-Transplant Lymphoproliferative Disorder and Allows Successful Stratification Into Rituximab or R-CHOP Consolidation in an International, Prospective, Multicenter Phase II Trial. J. Clin. Oncol. 35, 536–543 (2017).

12.   Windpessl, M. et al. Progressive Multifocal Leukoencephalopathy Following Combined Rituximab-Based Immune-Chemotherapy for Post-transplant Lymphoproliferative Disorder in a Renal Transplant Recipient: A Case Report. Transplant. Proc. 50, 881–883 (2018).

13.   Cruz, R. J. et al. Surgical management of gastrointestinal posttransplant lymphoproliferative disorders in liver transplant recipients. Transplantation 94, 417–23 (2012).

14.   O'Regan, J. A. et al. Posttransplant Lymphoproliferative Disorders in Irish Renal Transplant Recipients. Transplantation 101, 657–663 (2017).

15.   Ready, E. et al. Posttransplant Lymphoproliferative Disorder in Adults Receiving Kidney Transplantation in British Columbia: A Retrospective Cohort Analysis. Can. J. kidney Heal. Dis. 5, 2054358118760831 (2018).