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Mini-review

Post-transplant lymphoproliferative disorders: From epidemiology to pathogenesis-driven treatment

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ABSTRACT

Post-transplant lymphoproliferative disorders (PTLDs) represent the most severe complication of both solid organ and hematopoietic stem cell transplantation. The Epstein–Barr Virus (EBV) is the main driver of PTLD, particularly those occurring early after transplantation. EBV-driven malignancies are associated with selective expression of latent viral proteins, but uncontrolled lytic replication may favor early phases of cell transformation. Besides immunodepression, persistent immune activation and chronic inflammation play an important role in both virus reactivation and expansion of EBV-infected B cells. EBV-induced immortalization requires the expression of telomerase. TERT, the rate-limiting component of the telomerase complex, is central in the switch from the lytic to the latent viral program, and TERT inhibition induces the EBV lytic cycle and cell death. Immunotherapy and combination of EBV lytic cycle inducers with antiviral drugs are promising strategies to improve the treatment of PTLD patients. This review is aimed at providing an update on the intriguing association between EBV and PTLD, mainly focusing on cases arising after kidney and liver transplantation, which account for the vast majority of transplants.

Introduction

The term 'post-transplant lymphoproliferative disorder' (PTLD) was first introduced in 1984 by Starzl [1]. PTLD represents the most severe complication of both solid organ (SOT) and hematopoietic stem cell transplantation (HSCT) and occurs in 1–20% of post-transplant patients [2]. SOT is an increasingly used medical procedure for treating otherwise fatal end-stage organ diseases. According to the WHO, more than 114,690 transplants were performed worldwide in 2012, 1.8% more than in 2011, but still less than 10% of the global need. The two most frequently transplanted organs were kidney (68%) and liver (21%) and most transplants were from deceased donors (58% kidney and 82% liver) [3]. Continuing improvements in the efficacy of anti-rejection drugs have greatly contributed toward prolonging the long-term survival of transplant recipients; however, life-long use of immunosuppressive drugs increases the risk of opportunistic diseases and malignancies. The frequency of cancer increases during immunosuppression; after 10 years of continued immunosuppressive therapies, approximately 20% of transplanted patients have a diagnosis of cancer, a risk 2- to 5-fold higher than in the general population [4,5].

Among malignancies occurring in transplanted persons, the incidence of PTLD varies according to several risk factors, such as type of transplant, age of recipient, and duration and type of immunosuppression treatment [6–8]. The entire PTLD spectrum includes lymphoproliferative entities varying from reactive hyperplasia to malignant lymphoma. According to the latest WHO classification in 2008, PTLD is classified into four basic histological types: (1) early lesions; (2) polymorphic (P-PTLD); (3) monomorphic (M-PTLD); and (4) classical Hodgkin lymphoma (HL) [6]. Early lesions consist of benign polyclonal lymphoproliferations, which mostly regress with reduction of the immunosuppressive regimen. P-PTLD is composed of a mixed population of immunoblasts, plasma cells and intermediate-sized lymphoid cells. Most P-PTLDs are Epstein–Barr Virus (EBV)-positive and arise within one year of transplantation. M-PTLD are mainly of B-cell origin. Most M-PTLDs are Non-Hodgkin Lymphomas (NHL), mainly Diffuse Large B-cell lymphoma (DLBCL), although sporadic cases of Burkitt's lymphoma (BL) do occur. Almost all cases display a clonal pattern of *IGH* gene rearrangement. M-PTLD is thought to arise from early lesions and P-PTLD. Moreover, within

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the M-PTLD group, EBV-positive lymphomas arise earlier after transplantation than EBV-negative ones [2,6–8]. Regardless of their histological type, PTLDs can also be defined as early- or late-onset if the diagnosis is made within or after 12 months from transplantation, respectively [2,9].

PTLD development following SOT is estimated from 1% to 20%, with the highest incidence for intestinal and multivisceral transplants (5%–20%), followed by lung and heart transplants (2–10%) and the lowest for renal and liver transplants (1%–5%) [2]. However, since the vast majority of transplanted organs are kidney (68%) followed by liver (21%), we focused our attention on the role of EBV in the onset of PTLD after kidney and liver transplantation. Increasing knowledge about the pathogenesis of PTLD will open the door to new therapeutic strategies.

PTLD incidence after kidney or liver transplant

The PTLD incidence in kidney and liver transplant reported in the last 5 years (2010–2015) is shown in Table 1. In an Italian cohort of 7217 kidney transplant recipients, 52 patients developed PTLD, with a cumulative incidence of 0.7% [10]. A slightly higher cumulative incidence of 2.9% was reported in a Spanish cohort [11]. Similarly, the PTLD frequency described by Yoon et al. [12] was 1.9%. In a larger US cohort of 156,740 kidney transplant recipients, 762 (0.5%) cases of PTLD were identified during a 20-year follow-up (1987–2007). The incidence rates of PTLD at 5 and 10 years post-transplant were 0.7% and 1.4%, respectively [13]. Taking into account the timing of PTLD onset, most early-PTLD (n = 361, within the first 2 years after transplantation) were monomorphic (48% vs. 42% polymorphic and 10% of unknown pathology) and of B-cell origin (72% vs. 4% T-cell, 24% unknown). Late-PTLD (n = 401, more than 2 years after transplant) was even more likely to be of monomorphic pathology (56% vs. 31% polymorphic and 13% unknown) and predominantly of B-cell, but with a higher proportion of T-cell origin (64% B-cell vs. 10% T-cell, 26% unknown) [13]. Data obtained from this large cohort, including cases from the Scientific Registry of Transplant Recipients, are of particular importance since they identified a more reliable incidence of PTLD onset (in general and also in particular, looking at both early- and late-onset) than other smaller cohorts, confirming that PTLD remains an important source of morbidity associated with solid organ transplantation. In a cohort of 137,939 primary kidney transplants, 913 (0.7%) patients developed PTLD, with an incidence of 0.4% at 1 year (early-onset) and 0.5%, 0.9% and 1.9% at 3, 5 and 10 years (late-onset), respectively [14].

In one study, the incidence of PTLD was 0.8% (17/2192) for kidney transplant recipients and 0.8% (16/2067) for liver transplant recipients; 93% (14/15) of PTLDs in the former were of late-onset, while 50% (8/16) of PTLDs in the latter were of early-onset and 50% (8/16) of late-onset [15]. As regards liver transplant, Marino et al. [16] described the experience of a single center in which a total of 826 transplants in 766 recipients was performed over a period of 20 years. Of these, 10 patients developed PTLD with a cumulative incidence of 1.2%, with two cases (20%) of early-onset. A 1.3% of PTLD incidence was found by Ettorre et al. [17] in a cohort of 1675 liver transplants from various Italian centers. Similarly, in an Argentinean cohort of 1621 liver transplant recipients, 27 patients developed PTLD (1.7%); early-onset disease was identified in 7 patients (27%) and late-onset in 19 (73%) [18], and yet another study reported a 2.3% (15/658) incidence of PTLD, of which 33% occurred during the first year after liver transplantation [19]. In a recent study of a total of 444 liver transplants, PTLD occurred in 16 (3.6%) patients, most being of early-onset (11/16, 69%) [20]. Three patients (0.9%) developed PTLD out of 323 adult patients who underwent liver transplant and all 3 were cases of late-onset [21]. Overall, as already reported in the literature [2,7,8], the incidence rates of PTLD reported in our review were quite broad (0.5–2.9 in kidney and 0.8–3.6 in liver), probably due to the different sizes of the examined cohorts (Table 1).

EBV-related PTLD

EBV is a member of the γ-herpesvirus family which usually establishes a lifelong asymptomatic infection in immunocompetent hosts. Most individuals contract EBV infection in early adulthood [22] and primary EBV infection may sometimes result in a self-limiting disease, known as infectious mononucleosis, due to an abnormal EBV-specific immune response. Host immunity plays a crucial role in controlling EBV infection and the virus has evolved an elegant strategy which allows EBV to exploit B-cell differentiation to finally establish an asymptomatic latency in resting memory B lymphocytes [22]. In post-transplant patients, impaired immunosurveillance against EBV may favor the onset of EBV-associated diseases, such as PTLD [23]. PTLD is commonly of B-cell origin [2,7,22,24]. Overall, 60–80% of total PTLD cases are found to be EBV-positive [15,25] and the incidence of EBV positivity changes slightly according to PTLD type, being higher in early than in late cases. The EBV genome is found in more than 90% of PTLD during the first year after transplantation [26]. A comprehensive search for cases of liver transplantation disclosed EBV infection in 80% of PTLD

Table 1
PTLD incidence after kidney or liver transplantation.

Organ	Reference	Country	Population no.	PTLD no. (%)[a]	Early-onset no. (%)	Late-onset no. (%)
Kidney	[10]	Italy	7217	52 (0.7)	–	–
	[11]	Spain	2011	60 (2.9)	–	–
	[12]	Korea	1489	28 (1.9)	5 (18)	23 (82)
	[13]	USA	156,740	762 (0.5)	361 (47)[b]	401 (53)
	[14]	USA	137,939	913 (0.7)	–	–
	[15]	Korea	2192	17 (0.8)	8 (50)	8 (50)
Liver	[12]	Korea	2067	16 (0.8)	1 (7)	14 (93)
	[16]	Italy	766	10 (1.2)	2 (20)	8 (80)
	[17]	Italy	1675	22 (1.3)	–	–
	[18]	Argentina	1621	27 (1.7)	7 (27)	19 (73)
	[19]	Hong Kong	658	15 (2.3)	5 (33)	10 (67)
	[20]	Taiwan	444	16 (3.6)	11 (69)	5 (31)
	[21]	Japan	323	3 (0.9)	0 (0)	3 (100)

Search strategy was: Post-transplant lymphoproliferative disorder [All Fields] OR PTLD [All Fields] AND incidence [All Fields] AND (kidney [All Fields] OR liver [All Fields]) AND (early-onset [All Fields] OR late-onset [All Fields]) AND ("2010/01/01"[PDAT] : "2015/03/31"[PDAT]) AND English [lang].

[a] Cumulative incidence for PTLD onset.

[b] Within two years after transplantation.

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