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INVITED COMMENTARY

Post-transplantation lymphoproliferative disease in pediatric kidney transplant recipients—early success does not mean the battle is over!

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Post-transplantation lymphoproliferative disease (PTLD) is one of the most serious complications of kidney transplant (KT) and entails the vast majority (86%) of malignancies of pediatric KT recipients. The estimated 5-year incidence in this population is 1–2% [1–3]. PTLD results from the necessary post-transplantation immunosuppression (IS) protocol that targets prevention of graft rejection but impairs defense against certain infectious triggers, specifically EBV, for which pediatric KT recipients are mostly immunologically naïve [2–4]. Significantly malignancy is responsible for 11.5–15% of all mortality cases in this young population [1,2,4,5].

Kanzelmeyer *et al.* [6] described their center's experience with pediatric KT recipients followed for 3 years after PTLD diagnosis. Their goal was to evaluate their structured PTLD protocol: Ped-PTLD-2005, which was previously described [2]. In the current report, PTLD therapy, consisted mainly of CNI withdrawal (in 10/12 patients), mTOR introduction (in 9/12) and rituximab administration (9/12). Chemotherapy was administered to only two of 12 patients of their cohort: one with non-EBV-PTLD and another with Hodgkin lymphoma. The main outcomes examined were PTLD course and graft survival during at least 3 years follow-up.

The results reported are remarkable, with 100% patient survival. This exceeds the considerably lower survival rates of 64–83% [2–5,7], and even the recently reported 87.4% survival rate after PTLD diagnosis [8]. The high rate of patient survival in Kanzelmeyer *et al.*'s cohort [6] is even more noteworthy in light of the diagnosis of the high grade monomorphic PTLD, which was detected in more than half of their patients (7/12). This PTLD type is less frequently reported in pediatric patients and has a worse prognosis [4,7,9]. However, the EBV-driven PTLD type (found in 11/12 of the presented cohort) and the early onset of malignancy (first post-transplantation year in 7/12) are known to associate with better prognosis [3,4,10], as is the timely introduction of Rituximab. The latter likely has an important role in modulation of this mainly B-cell dysregulation-induced tumor [2–4]. Also of note is the high rate of PTLD remission achieved with the adopted protocol in Kanzelmeyer *et al.*'s cohort.

The high rate of graft preservation observed in 10 of the 12 patients in the described cohort, during at least 3 years post-PTLD diagnosis and treatment [6], is also of note. The rate was actually 100%, as during this period, the three graft losses were due to the basal disease: two aHUS at a time when eculizumab was not available and

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one due to FSGS recurrence. The depressed renal function, GFR 29–40 ml/min/1.73 m^2, in all these patients at the time of PTLD diagnosis, probably attests to the same etiology that eventually caused graft loss. The single graft loss caused by chronic antibody-mediated rejection (cAMR), the most common cause of graft failure in KT recipients, was associated with *de novo* DSA (donor-specific antibodies), which appeared 7 years after PTLD diagnosis and which induced graft loss 13 years post-transplantation and more than 11 years after PTLD diagnosis, treatment, and complete remission. This timeline might occur in any KT recipient, as the present graft half-life is estimated at 12.5–15.3 years [11].

Overall, PTLD accounts for 20% of graft failures [1,2,4,5,9], due to the necessary reduction in IS, and also due to graft dysfunction induced by the malignancy itself or by chemotherapy-induced nephrotoxicity. Graft survival rates in PTLD patients have been reported to reach 81.8% at 1 year, with a progressive decrease to 65% at 5 years, and further to 57% at 10 years [2,3,7–9,12]. Greater rates of graft loss for PTLD generally occur during the first post-transplantation year [7]. Of note, the CNI withdrawal policy used in the present cohort was reported to incur a worse prognosis for both graft and patient survival by others [12].

The occurrence of *de novo* DSA after successful PTLD treatment and remission, even at a late time: 3–7 years, raises important questions regarding a possible link between these conditions. PTLD management entails first of all, IS reduction including CNI withdrawal or dose reduction [2,4]. Several studies have shown an increased rate of *de novo* DSA formation mostly when these changes must be applied during the first post-transplantation years—the period during which most cases of PTLD actually occur [13]. Although Rituximab as part of the PTLD treatment protocol might partly counter, and mostly defer, this sequence of events through B-cell modulation, such effect is not endless and DSA might eventually occur, especially with the low-grade IS maintained in post-PTLD patients. On the other hand, *de novo* DSA are recognized to associate with cAMR(chronic antibody-mediated rejection), which is the main cause of graft loss in adults and pediatric KT recipients[14,15].

An intriguing matter is the reported association of HLA mismatches—the target of *de novo* DSA—with PTLD risk [3,16,17]. This common denominator—HLA mismatches—might predispose KT recipients after PTLD to an increased risk of *de novo* DSA formation with consequent graft damage and possibly reduced graft survival. While consensus guidelines for DSA monitoring and intervention have been issued for low- and high-risk patients, they apply only to the early post-transplantation period (first post-transplantation year), and not long-term [18]. A future option is to better assess the risk for excessive IS (developing PTLD), as well as alloimmunization (developing DSA). The latter may be achieved by analysis of a genetically determined immune response [19].

In conclusion, Kanzelmeyer *et al.* have raised an important point concerning the follow-up of KT recipients recovering from PTLD. While high grade of suspicion for early diagnosis and management of this serious malignancy continues to be implemented with optimal patient and graft outcome, continuous close follow-up is needed for detection of *de novo* DSA with potential evolution to graft damage. This risk is potentially higher in post-PTLD patients who are usually maintained on low-intensity IS after recovery from the malignancy. Evaluation of HLA mismatches should guide the intensity of DSA monitoring in post-PTLD patients who have overtly shown an intrinsically unbalanced immune response through their response to IS and infection.

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REFERENCES

1. NAPRTCS 2014 Annual Transplant Report. Accessed September 29th 2017.
2. Mynarek M, Hussein K, Keripe HH, Maecker-Kolhoff B. Malignancies after pediatric kidney transplantation: more than PTLD? *Pediatr Nephrol* 2014; **29**: 1517.
3. Caillard S, Dharnidharka V, Agodoa L, *et al.* Posttransplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. *Transplantation* 2005; **880**: 1233.
4. Gross TG, Savoldo B, Punnett A. Posttransplant lymphoproliferative diseases. *Pediatr Clin North Am* 2010; **57**: 481.
5. Farrrugia D, Cheshire J, Mahboob S, *et al.* Mortality after pediatric kidney transplantation in England – a population-based cohort study. *Pediatr Transplant* 2014; **18**: 16.
6. Kanzelmeyer N, Maecker-Kolhoff B, Zierhut H, *et al.* Graft outcomes following diagnosis of post-transplant

lymphoproliferative disease in pediatric kidney recipients: a retrospective study. *Transpl Int* 2018; **31**: 367.
7. Maksten EF, Vase MO, Kampmann J, *et al.* Post-transplant lymphoproliferative disorder following kidney transplantation: a population-based cohort study. *Transpl Int* 2016; **29**: 483.
8. Dharnidharka VR, Martz KL, Stablein DM, Befield MR. Improved survival with recent post-transplant lymphoproliferative disorder (PTLD) in children with kidney transplants. *Am J Transplant* 2011; **11**: 751.
9. Caillard S, Porcher R, Provot F, *et al.* Post-transplantation lymphoproliferative disorder after kidney transplantation: report of a nationwide French registry and the development of a new prognostic score. *J Clin Oncol* 2013; **31**: 1302.
10. Cleper R, Ben Shalom E, Landau D, *et al.* Post-transplantation lymphoproliferative disorder in pediatric kidney-transplant recipients – a national study. *Pediatr Transplant* 2012; **16**: 619.
11. Matas AJ, Smith JM, Skeans MA, *et al.* OPTN/SRTR 2013 annual data report: kidney. *Am J Transplant* 2015; **15** (Suppl. 2): 1.
12. Rabot N, Buchler M, Foucher Y, *et al.* CNI withdrawal for post-transplant lymphoproliferative disorders in kidney transplant is an independent risk factor for graft failure and mortality. *Transpl Int* 2014; **27**: 956.
13. O'Leary JG, Samaniego M, Crespo Barrio M, *et al.* The influence of immunosuppressive agents on the risk of de novo donor-specific HLA antibody production in solid organ transplant recipients. *Transplantation* 2016; **100**: 39.
14. Pape L, Becker JU, Immenschuh S, Ahlenstiel T. Acute and chronic antibody-mediated rejection in pediatric kidney transplantation. *Pediatr Nephrol* 2015; **30**: 417.
15. Aubert O, Loupy A, Hidalgo L, *et al.* Antibody-mediated rejection due to preexisting versus *de novo* donor-specific antibodies in kidney allograft recipients. *J Am Soc Nephrol* 2017; **28**: 1912.
16. Opelz G, Dohler B. Pediatric kidney transplantation: analysis of donor age, HLA match, and posttransplant non-Hodgkin lymphoma: a collaborative transplant study report. *Transplantation* 2010; **90**: 292.
17. Bakker NA, van Imhoff GW, Verschuuren EA, *et al.* HLA antigens and post renal transplant lymphoproliferative disease: HLA-B matching is critical. *Transplantation* 2005; **80**: 595.
18. Tait BD, Susal C, Gebel HM, *et al.* Consensus guidelines on testing and clinical management issues associated with HLA and non-HLA antibodies in transplantation. *Transplantation* 2013; **95**: 19.
19. Reindl-Schwaighofer R, Heinzel A, Signorini L, Thaunat O, Oberbauer R. Mechanisms underlying human genetic diversity: consequence for antigraft antibody responses. *Transpl Int* 2018; **31**: 239.