Tertiary lymphoid tissues predict progressive graft dysfunction in kidney transplant recipients

Yu Ho Lee¹, Yuki Sato², Mitsuru Saito⁴, Shingo Fukuma³, Tomonori Habuchi⁴, Shigeru Satoh⁶, Sang-Ho Lee⁵, Motoko Yanagita²
¹Department of Internal Medicine-Nephrology, Bundang CHA General Hospital, Korea, Republic of
²Department of Department of Nephrology, Graduate School of Medicine, Kyoto University, Japan
³Department of Human Health Sciences, Graduate School of Medicine, Kyoto University, Japan
⁴Department of Department of Urology, Graduate School of Medicine, Akita University, Japan
⁵Department of Internal Medicine-Nephrology, Kyung Hee University Hospital at Gangdong, Korea, Republic of
⁶Department of Center for Kidney Disease and Transplantation, Akita University, Japan

Objectives: Tertiary lymphoid tissues (TLTs) are inducible ectopic lymphoid tissues found in chronic inflammatory organs. Although previous studies have demonstrated that TLTs develop in chronically rejected renal allografts, the evidences regarding TLTs in transplanted kidney without rejection are limited and their clinical relevance remains undefined. In this study, we examined the frequency of TLTs and their association with renal function in kidney transplant recipients without apparent risk factors for poor allograft outcome.

Methods: We analyzed serial protocol biopsy samples (0-hour, 1-month, 6-month, and 12-month) obtained from 181 patients who underwent living-donor kidney transplantation and assessed TLTs utilizing the staging methods we had recently established. TLTs were defined as organized lymphocyte aggregates (CD3ε+, CD20+) with signs of proliferation (Ki67+), and their stages were classified as follows; stage I, TLTs containing neither follicular dendritic cells (FDCs) nor germinal centers; stage II, TLTs containing FDCs but lacking germinal centers; and stage III, TLTs exhibiting both FDCs and germinal centers.

Results: Upon microscopic examination, we identified the presence of stage I and stage II TLTs, but no stage III TLTs. Although 5.1% of patients exhibited TLTs at 0-hour biopsy, the prevalence increased to almost 50% at one month after transplant and maintained similar levels for one year. The proportion of stage II TLTs increased over time, up to 18.0% in 12-month biopsy. Patients with no TLT or stage I TLTs had stable graft function over 5 years, whereas those with stage II TLTs in 6-month and/or 12-month biopsies exhibited progressive decline in graft function. Additionally, rituximab treatment before transplantation significantly reduced the incidence of stage II TLTs.

Conclusions: TLTs were commonly found in transplanted kidney without rejection, and stage II TLTs predicted progressive renal function decline in kidney transplant recipients.

Figure 1. The prevalence of tertiary lymphoid tissues in transplanted kidney
Figure 2. Longitudinal trends of renal allograft function in kidney transplant recipients according to the presence and the staging of tertiary lymphoid tissues.