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Cardiac transplantation for congenital heart disease is associated with an increased risk of post-transplant lymphoproliferative disorder (PTLD) in children: a single centre experience

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Patients receiving lifelong immunosuppressant therapy following solid organ transplantation are at increased risk of malignancies. Post-transplant lymphoproliferative disorder (PTLD) is the commonest malignancy and represents a significant cause of morbidity and mortality in this patient group. Previous studies have commonly analysed factors associated with PTLD across paediatric recipients of any solid organ transplant. The current study aimed to determine risk factors for development of PTLD specific to paediatric recipients of a heart transplant.

We retrospectively analysed the clinical features and outcomes of 203 children (<18 years) who received a heart transplant in our institution between January 2000 and December 2015. Kaplan-Meier method and Cox proportional hazards were used to assess the impact of prognostic factors on survival and freedom from PTLD.

The study cohort consisted of 75 patients transplanted for congenital heart disease (CHD) and 128 patients for idiopathic cardiomyopathy (IC). The median follow up was 5.5 years. There was a significant difference in age at first invasive cardiac procedure via median sternotomy between children with CHD and IC (4 months vs 5 years, p < 0.001) but no difference in the median age at transplantation between both groups (5.5 years vs 5.6 years, p = 0.78). PTLD was diagnosed in 15 (7.4%) children transplanted for underlying CHD (10/15) and IC (5/15) with a median age at diagnosis of 10.4 years (range; 6.6–14.0) and 11.5 years (range; 4.8–13.5) respectively. The median time to PTLD was 24 months (range; 10–50 months) with no significant difference in time to PTLD between patients with CHD and IC (p = 0.09). All tumour samples were Epstein Barr Virus (EBV) positive and of B-cell lineage. The histological subtypes consisted of 10 (67%) monomorphic lesions, 3 (20%) polymorphic, and 2 (13%) classical Hodgkin lymphoma. Early stage disease (stage I- II) was observed in 5 (33%) patients while advanced tumours (stage III- IV)
were seen in the remaining 10 (67%) children. Overall freedom from PTLD was 96% at 1-year, 92% at 5-years and 90% at 10-years. On univariate analysis, risk of PTLD was not significantly associated with age at transplantation, gender, ethnicity or type and number of immunosuppressants used (p > 0.05). Recipient EBV seronegativity prior to transplantation was found to increase the risk of PTLD (p = 0.04) on multivariate Cox regression. Notably, children with CHD had a significantly higher risk of developing PTLD compared to those with IC (Hazard Ratio = 5.3; 95% Confidence Interval = 1.5–18.9) after adjusting for all study co-variates.

In conclusion, the identification of pre-transplant cardiac diagnosis as a significant risk factor for the development of PTLD in paediatric heart transplant recipients is a novel finding. We postulate that the increased risk of PTLD following transplantation for underlying CHD could be linked to early dysregulation of T cell mediated immunity as a result of early thymectomy during palliative surgery pre-transplantation. Impaired T cell development may further predispose to uncontrolled primary EBV infection and aberrant lymphoid proliferation. This hypothesis is supported by the significant age disparity at time of first median sternotomy between children with CHD and IC and warrants further investigation.

**Disclosure of Interest:** None Declared.

**Keywords:** Congenital heart disease, Paediatric heart transplant, Post transplant lymphoproliferative disorder, Risk factor.