Evidence of Chronic Allograft Injury in Liver Biopsies From Long-term Pediatric Recipients of Liver Transplants.


Abstract

BACKGROUND AND AIM: A substantial proportion of pediatric liver transplant recipients develop subclinical chronic allograft injury. We studied whether there are distinct patterns of injury based on histopathology features and identified associated immunological profiles.

METHODS: We conducted a cross-sectional study of 157 stable, long-term pediatric recipients of transplanted livers (70 boys; less than 6 years old; mean 8.9±3.46 years after liver transplant) who underwent liver biopsy analysis from August 13, 2012 through May 1, 2014. Subjects received livers from a living or deceased donor and had normal results from liver tests for more than 4 years after receiving transplant. Liver biopsies were scored by a central pathologist; an unsupervised hierarchical cluster analysis of histologic features was used to sort biopsies into 3 clusters. We conducted transcriptional and cytometric analyses of liver tissue samples and performed a systems biology analysis that incorporated clinical, serologic, histologic, and transcriptional data.

RESULTS: The mean level of alanine aminotransferase in subjects was 27.6±14.57 U/L and the mean level of gamma-glutamyl transferase was 17.4±7.93 U/L. Cluster 1 was characterized by interface activity (n=34), cluster 2 was characterized by periportal or perivenular fibrosis without interface activity (n=45), and cluster 3 had neither feature (n=78). We identified a module of genes whose expression correlated with levels of alanine aminotransferase, class II donor-specific antibody, portal inflammation, interface activity, perivenular inflammation, portal and perivenular fibrosis, and cluster assignment. The module was enriched in genes that regulate T-cell mediated rejection (TCMR) of liver and other transplanted organs. Functional pathway analysis revealed over-representation of TCMR gene sets for cluster 1 but not clusters 2 or 3.

CONCLUSION: In an analysis of biopsies from an apparently homogeneous group of stable, long-term pediatric liver transplant recipients with consistently normal results from liver tests, we found evidence of chronic graft injury (inflammation and/or fibrosis). Biopsies with interface activity had a gene expression pattern associated with TCMR.