Clinicopathologic Characteristics of Post-Transplant Lymphoproliferative Disorders

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Abstract

Post-transplant lymphoproliferative disorder (PTLD) is a syndrome of uncontrolled lymphoid growth in the immunosuppressed transplant patient. Known risk factors include Epstein-Barr virus (EBV) seronegativity at the time of transplant, pediatric age and allograft type. Newer studies suggest that constitutional factors such as cytokine gene polymorphisms may also predispose to PTLD. Although PTLD may occur at any time, the majority of cases arise within the first two post-transplant years. Clinical presentation is heterogeneous and dependent upon the location and extent of disease. Allograft involvement is common, particularly in cases of lung, intestine, or pancreas transplantation. Most PTLD are of B lymphocyte origin. A histopathologic classification system has been proposed and it is important to understand the histology of these lesions, since the term PTLD incorporates both hyperplastic and neoplastic growths. Histologic subclassification also has prognostic value, although this remains imperfect at present. Clinical evaluation should include staging as for lymphomas, since PTLD stage is an important determinant of outcome. In EBV-associated PTLD, quantitative evaluation of EB viral genomic load has a role in guiding prophylaxis, diagnosis, and monitoring of therapy. The presence of EBV is not an absolute requirement for the diagnosis of PTLD, and it has been suggested that there has been a recent increase in the number of EBV-negative cases. Such lesions have a median onset time around 50–60 months post-transplant. Therapy of PTLD must be tailored to the individual patient. Newer modalities such as anti-CD20 antibodies are being evaluated and may complement the standard stepwise approach that begins...
with a reduction of immunosuppression. The role of chemotherapy continues to be defined, and in some cases early recourse to this approach may be desirable. Survival varies by age and extent of disease, with pediatric patients and those with localized disease tending to fare better. A finer understanding of the molecular cellular and virologic underpinnings of PTLD remains essential in order to define optimal treatment regimens. The emergence of EBV-negative PTLD is a problem and the relationship of this to standard lymphomas arising in nonimmunosuppressed patients remains to be defined. Continued individual and multi-institutional studies are essential for progress in these areas.

Introduction

Post-transplant lymphoproliferative disorders (PTLDs) represent a complication of the immunosuppressed state and are associated with significant morbidity and mortality in the transplant population. Much has been learned since the first description of these lesions over 30 years ago [1]. Much doubtless remains to be learned. In this essay, we briefly review selected clinicopathologic features of PTLD.

Frequency, Risk Factors, and Onset

A recent study from our institution showed a 2.8% frequency of PTLD in a series of 834 liver transplant patients (A. Jain, unpublished data). Overall 1-year actuarial PTLD frequency at our institution sampled during the 1990s was 2.3%, with adults having a 1.4% and pediatric patients a 6.7% frequency (unpublished data). The relationship between age and PTLD frequency has also been highlighted in individual series such as the recent report by Shapiro et al. [2] of PTLD in 1316 renal transplant patients over a 9-year period. In this study the PTLD frequency was 10.1% in the pediatric and 1.2% in the adult population.

Seronegative Epstein-Barr virus (EBV) status at time of transplant is a well-known risk factor for PTLD and to some extent explains the difference seen between pediatric and adult populations [3]. In addition, Manez and colleagues [4] showed that concomitant cytomegalovirus (CMV) infection in EBV-seronegative patients leads to a 7.3-fold increase in relative risk for development of PTLD.

An increased risk of PTLD has also been documented with increased immunosuppression [5], although the extent to which high