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Epstein-Barr virus lymphoproliferative disease after solid organ transplantation

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Abstract

Epstein-Barr virus (EBV) was the first identified human oncovirus and is also one of the most ubiquitous viral infections known with established infections in more than 90% of individuals by early adulthood. EBV establishes latency by controlling expression of the viral genome making it silent to immune surveillance. In immunocompetent individuals, up to 1% of circulating T cells are directed at maintaining control over EBV replication. In addition to being involved in oncogenesis of lymphoid and epithelial tumors in immune-competent individuals, loss of immune surveillance over EBV predisposes individuals to EBV malignancies. Lymphoid proliferations from EBV-infected B cells arise in up to 20% of recipients of solid organ transplants (SOTs). One question not answered is why, when EBV requires such active immune surveillance, EBV malignancies are not even more prevalent in severely immune-compromised individuals. A better understanding of who develops complications related to EBV and what the immunologic risks are will ultimately make it feasible to perform prophylactic trials in those at highest risk. This review summarizes our current understanding of factors in SOT recipients that predispose them to the development of an EBV malignancy and that predict response to initial therapy. We then review the current landscape of those therapies, focusing on the goal of restoring long-term EBV-directed immunity to patients at risk.

Key Words: *EBV LPD, solid organ transplant, immune therapy, Adoptive therapy*

Introduction

Post-transplantation lymphoproliferative disorders (PTLDs) encompass a range of abnormal lymphoid proliferations that occur in the context of immune suppression imposed during and after allogeneic hematopoietic stem cell transplantation (HCT) and solid organ transplantation (SOT). PTLD occurring after HCT is not as variable as that arising after SOT and is usually an Epstein-Barr virus–positive (EBV+) high-grade monomorphic non-Hodgkin's lymphoma (NHL) in the form of diffuse large B-cell lymphoma (DLBCL). The presentation after SOT is more varied with both EBV+ and EBV- PTLD that can range from benign hypertrophy to aggressive DLBCL. Given these important differences this review will focus on the entity of EBV-related PTLD arising after SOT. Although the incidence of EBV-PTLD is relatively low, it caries significant risk of mortality and survival after EBV-PTLD arising after SOT is as low as 50% in some patient populations [1] and historically mortality has been as high as 90% after failure to respond to initial therapy [2]. The requirement for active immune surveillance to EBV is evidenced by the high frequency of EBV-directed cytotoxic T cells in normal EBV immune individuals [3] and restoration of the immune response to EBV in patients with post-SOT EBV-PTLD should remain one of the goals of treatment.

EBV and lymphoproliferative disease

EBV is a gamma human herpesvirus with a seroprevalence of 90–95% in adults. EBV, discovered in 1964 [4], is best known as the cause of infectious mononucleosis. Patients at risk for EBV-driven lymphoproliferative disorders (EBV-LPD) include those who are immune compromised due to congenital or acquired immune deficiency syndromes and recipients of HCT or SOT. These EBV + PTLDs are characterized by EBV-driven immortalization of B cells (and rarely T cells). In immune-competent individuals development of such PTLDs is countered by a strong immune response by cytotoxic T cell lines (CTLs) [5].

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As reviewed by Thorley-Lawson et al [6] during primary infection, the EBV infects naïve B cells typically in Waldeyer's ring and expresses the entire Type III latency gene program. This antigen-independent process leads to the same developmental steps that cognate antigen recognition leads to in uninfected B cells: activation and differentiation. These activated B cells enter a primary follicle in a lymph node and form a germinal center (GC). The activated B cells down-regulate expression of immunoglobulin (Ig)M and IgD to allow class switch recombination (CSR) to IgG, IgA or IgE and somatic hypermutation (SHM) to increase the antibody's affinity and specificity. In the GC the B cells infected with EBV express the latency II program and presumably undergo SHM and CSR similarly to an activated uninfected counterpart. After leaving the GC, these EBV-infected B cells mainly differentiate into memory B cells expressing the latency I or latency 0 programs, but also to a minor extent into plasma cells (activating the lytic cycle). The virus survives in B cells by down-regulating its highly immunogenic proteins, thus becoming invisible to the host immune system. When circulating EBV-infected B cells divide they transiently express Epstein–Barr nuclear antigen 1 (EBNA I type I latency) ensuring that the viral genome is replicated. When infected plasma cells transit through the oropharynx they transfer the virus to epithelial cells where it is replicated and secreted in the saliva at which time it can infect both uninfected memory B cells and new hosts. Multiple stages of this process can give rise to malignancy, resulting in different lymphoma subtypes that have features of their normal counterpart. EBV-encoded RNA (EBER) 1 and 2 are the only gene products that are expressed throughout all latency and lytic phases of the viral cycle and represent the most reliable markers to determine EBV infection [7]. EBV is able to escape immune evasion both by control of the latency viral program as well as by controlling components of the immune response to the initial infection [8] and is thus able to establish long-term latent infection requiring control by immune surveillance.

EBV-PTLD develops in up to 20% of SOT recipients [9] The first cases were described in renal transplantation patients, shortly after the introduction of chronic immunosuppressive drugs in the 1960s [10]. Despite the strong association between EBV and PTLD (about 80% of PTLDs are EBV-positive [EBV+]), disease biology is not fully understood. Overall PTLD has a bimodal presentation with "early" PTLD developing within a year of transplantation and being nearly uniformly EBV-positive while "late" PTLD typically develops 2–5 years after transplantation and is less uniformly EBV-positive. Since the 1990s, the incidence of PTLD has increased in conjunction with an increase in the number of patients undergoing SOT and the duration of survival post-transplantation. The pathological presentation of EBV-PTLD is variable, ranging from low-grade lymphoid proliferation to aggressive monomorphic and clonal lesions that are most commonly classified as DLBCL. These aggressive lesions typically express a Latency III program. In addition, EBV-PTLD can present with characteristics of Hodgkins, Burkitt or plasmablastic lymphomas. In these instances the lymphoma type is associated with different latency programs (Figure 1) and memory B cells have undergone a mutational event.

DLBCL is the most common of the aggressive EBV + PTLDs. In immune-competent individuals DLBCL has recently been categorized as GC-derived and non-GC–derived or activated B cell (ABC)–derived DLBCL with GC subtypes having a better prognosis [11]. Both subtypes have been reported in the transplant setting, although the majority are of ABC

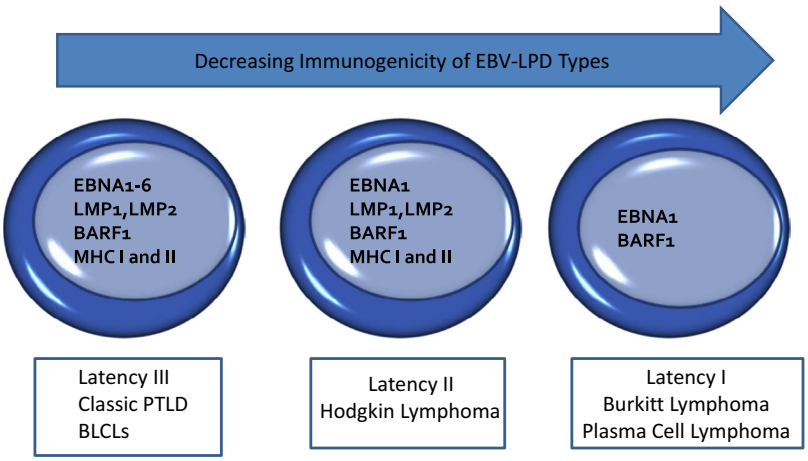

Figure 1. EBV latency program expressed by different lymphoid populations. Different EBV-associated lymphoid malignancies expressed antigens consistent with broader verus more limited immunogenicity.

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