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REVIEW ARTICLE

Recent advances in the risk factors, diagnosis and management of Epstein-Barr virus post-transplant lymphoproliferative disease

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Abstract Fifty years after the first reports of Epstein-Barr virus (EBV)-associated endemic Burkitt's lymphoma, EBV has emerged as the third most prevalent oncogenic virus worldwide. EBV infection is associated with various malignancies including Hodgkin and non-Hodgkin lymphoma, NK/T-cell lymphoma and nasopharyngeal carcinoma. Despite the highly specific immunologic control in the immunocompetent host, EBV can cause severe complications in the immunocompromised host (namely, post-transplant lymphoproliferative disease). This is particularly a problem in patients with delayed immune reconstitution post-hematopoietic stem cell transplant or solid organ transplant. Despite advances in diagnostic techniques and treatment algorithms allowing earlier identification and treatment of patients at highest risk, mortality rates remain as high as 90% if not treated early. The cornerstones of treatment include reduction in immunosuppression and *in vivo* B cell depletion with an anti-CD20 monoclonal antibody. However, these treatment modalities are not always feasible due to graft rejection, emergence of graft vs. host disease, and toxicity. Newer treatment modalities include the use of adoptive T cell therapy, which has shown promising results in various EBV-related malignancies. In this article we will review recent advances in risk factors, diagnosis and management of EBV-associated malignancies, particularly post-transplant lymphoproliferative disease. We will also discuss new and innovative treatment options including adoptive T cell therapy as well as management of special situations such as chronic active EBV and EBV-associated hemophagocytic lymphohistiocytosis.

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PALABRAS CLAVE
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Trasplante de órgano sólido

Avances recientes en los factores de riesgo, diagnóstico y tratamiento de la enfermedad linfoproliferativa post trasplante con infección por virus de Epstein-Barr

Resumen A cincuenta años de los primeros reportes de asociación del linfoma de Burkitt con el virus de Epstein-Barr (VEB), el VEB ha emergido como el tercer virus de tipo oncogénico con mayor prevalencia a escala mundial. La infección por VEB se asocia con diversas neoplasias, incluyendo el linfoma de Hodgkin y el no Hodgkin, linfoma de células T/NK y carcinoma nasofaríngeo. A pesar del control inmunológico altamente específico en el huésped inmunocompetente, el VEB puede ocasionar complicaciones severas en el huésped inmunocomprometido (es decir, la enfermedad linfoproliferativa post-trasplante). Esto es un problema particularmente en pacientes en quienes se retrasa la reconstitución de la inmunidad después de un trasplante de células madre hematopoyéticas o un trasplante de órganos sólidos. A pesar de los avances en las técnicas de diagnóstico y los algoritmos de tratamiento que permiten la identificación temprana y el tratamiento de pacientes de alto riesgo, las tasas mortalidad siguen siendo muy altas (del 90%) si no se recibe tratamiento temprano. La piedra angular del tratamiento incluye la disminución de la inmunosupresión y la depleción de células B in vivo con un anticuerpo monoclonal anti-CD20. Sin embargo, estas modalidades de tratamiento no son siempre posibles debido al rechazo del injerto, la enfermedad de injerto contra huésped y la toxicidad. Nuevas modalidades de tratamiento incluyen el uso de la terapia adoptiva de células T, que ha mostrado resultados promisorios en diversas neoplasias relacionadas con el VEB. En este artículo se revisan los avances más recientes en cuanto a los factores de riesgo, diagnóstico y tratamiento de las neoplasias asociadas con VEB, particularmente la enfermedad linfoproliferativa post-trasplante. También se discuten los tratamientos más recientes e innovadores, que incluyen la terapia adoptiva de células T así como el manejo de situaciones especiales, como la infección crónica activa de VEB y la linfohistiocitosis hemafagocítica asociada con VEB.

1. Introduction

Epstein Barr Virus (EBV) is a highly immunogenic γ-herpes virus with a >90% worldwide seroconversion rate by young adulthood.[1,2] Whereas infections in childhood are usually asymptomatic, in adolescence and early adulthood, EBV infection can manifest as acute mononucleosis, a typically self-limiting infection. During a primary infection, the normal host mounts a vigorous cellular immune response consisting of both CD4+ and CD8+ cytotoxic T lymphocytes (CTLs). These CTLs effectively control both primary EBV infection and periodic reactivations by targeting both lytic and latent cycle antigens.[3] Despite the highly specific immunologic control in the immunocompetent host, EBV can cause severe complications in the immunocompromised host, particularly patients with delayed immune reconstitution post-hematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT). In addition to being the primary virus associated with post-transplant lymphoproliferative disease (PTLD), endemic Burkitt's lymphoma, and up to 40% of Hodgkin (HL) and non-Hodgkin lymphoma (NHL), uncontrolled EBV infection is the cause of many HIV- or AIDS-associated lymphomas.[1,4] Whereas the causative relationship between EBV and the aforementioned disorders is well established, more recently EBV viremia has been linked to hemophagocytic lymphohistiocytosis (HLH) with associated chronic active EBV infection (CAEBV).[5] The common denominator in all of these scenarios appears to be the lack of EBV-specific T cells able to successfully control the infection. Whether this is due to pre-transplant conditioning regimens, the prolonged immunosuppression necessary following transplant, or anergic T cells incapable of recognizing and controlling EBV infection, all of these patients possess the perfect immunosuppressed environment for unchecked EBV reactivation and its sequelae.[6]

In this article we will review recent advances in risk factors, diagnosis and management of EBV-associated malignancies, particularly PTLD. We will also discuss new and innovative treatment options including adoptive T cell therapy as well as management of special situations such as CAEBV and EBV-associated HLH.

2. Post-transplant lymphoproliferative disease: pathogenesis and risk factors

PTLD is a heterogeneous group of malignant diseases ranging from the classic polyclonal subtype to more aggressive, monoclonal forms. Nearly 85% of cases are of B-cell lineage, with the remaining 15% of cases of T or NK cell lineage. The majority of PTLD cases are associated with EBV infection, whereas only ~30% of reported cases are EBV negative.[7,8] EBV-negative PTLD tends to occur later in life and be monomorphic in origin (T- or NK-cell neoplasms), although the etiology of the vast majority of EBV-negative PTLD remains unknown.[9]