Immunosurveillance, Immunodeficiency and Lymphoproliferations

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Abstract

The incidence of malignant lymphomas is significantly higher in patients who have congenital or acquired immunodeficiencies. Although there are some differences between these immunodeficiency-associated lymphoproliferative disorders (IALD), they share several features: a tendency to present in extranodal sites, particularly the central nervous system and gastrointestinal tract, rapid clinical progression when untreated, diffuse large cell histology, B-cell origin and association with the Epstein-Barr virus (EBV). In the presence of disturbed T-cell function EBV may induce not only prolonged proliferation but also transformation of B-cells. In patients with primary, congenital immunodeficiency the incidence of IALD ranges from 0.7% for patients with X-linked agammaglobulinemia to 12–15% in patients with ataxia telangiectasia. In patients with post-transplant lymphoproliferative disorders (PT-LPD) the incidence varies from 0.5% after bone marrow transplantation to 10% after heart-lung transplantation. PT-LPD are often characterized by a polymorphic cell population. Recent studies identified three categories: plasmacytic hyperplasia, polymorphic lymphoproliferation and B-cell non-Hodgkin’s lymphoma (NHL). The plasmacytic hyperplasias are of polyclonal composition, while polymorphic lymphoproliferations and NHL are monoclonal. The precise risk of lymphoma development in HIV infection is not defined, but estimates suggest a prevalence of 3–4%. HIV-related NHLs are divisible by site of manifestation into systemic, primary central nervous system and body-cavity lymphomas, and by pathology into Burkitt’s and Burkitt’s-like lymphoma, and diffuse large cell lymphoma (DLCL). In about 90% of cases these lymphomas are of
monoclonal B-cell composition. Recent experiences suggest a link between therapy with immunosuppressive drugs (methotrexate, azathioprine, cyclophosphamide, etc.) and development of IALD, best supported by the increased rate of IALD in patients with rheumatoid arthritis who receive methotrexate therapy. The occurrence of IALD demonstrates the importance of competent immunosurveillance in the development of lymphoid neoplasias, which may have therapeutic relevance too.

**Introduction**

The concept of immunosurveillance against neoplasms was developed by Ehrlich in 1957 [1]. It is proposed that a major function of the immune system is to control the development of malignancies. In individuals with primary or acquired immunodeficiencies, a malignant cell may have a better chance of escaping immunosurveillance and giving rise to a neoplastic cell clone. Immunodeficient patients are at an increased risk for development of a narrow range of tumors, including lymphomas, skin carcinomas, carcinomas of the vulva, and Kaposi’s sarcoma, while the incidence of malignancies that are common in the normal population are the same. The distribution of these malignancies is different between patients with primary immunodeficiency, HIV infection, or those on immunosuppressant drugs in the post-transplant or non-transplant setting, but lymphoproliferative disorders are common and frequent in all these different types of immunodeficiency. Immunodeficiency-associated lymphoproliferative disorders (IALD) exhibit some degree of heterogeneity but a variety of relatively common features, notably a high degree of clinical aggressiveness and a tendency to present in extranodal sites, particularly the central nervous system (CNS) and gastrointestinal tract. These lymphoproliferations are typically of B-cell origin and the majority are diffuse large cell lymphoma (DLCL).

A particular aspect in the understanding of IALD is their association with Epstein-Barr virus (EBV). Experimental and clinical evidence supports the notion that EBV can become oncogenic in immunodeficient hosts. Following the primary infection with EBV the virus establishes latency in resting B-lymphocytes of the peripheral blood. During latency the virus exists as a circular plasmid with only restricted expression of viral genes, but a restricted pattern of lytic virus infection is also detectable in healthy seropositive blood donors [2]. In healthy individuals an equilibrium exists between EBV and the