Viruses Other than HIV and Non-Hodgkin’s Lymphoma

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Abstract

There are several viral infections which are known to cause lymphoma among animals; all establish latency in lymphoid cells. The human T-lymphotropic virus type I is a human virus which causes lymphomas among a subset of carriers. However, this virus is very restricted in its distribution and as such, is unlikely to play a role in the increase of non-Hodgkin’s lymphoma (NHL). A highly prevalent infection, the Epstein-Barr virus (EBV) is known to play a role in the etiology of NHL among persons with acquired or inherited immune suppression. However, whether it is involved with “spontaneous” NHL is unknown. We have found evidence that among a group of 104 NHL patients with blood samples taken several years before diagnosis, there was an alteration in the antibody profile against the EBV which is quite similar to that seen for immune-suppressed patients prior to their diagnosis. This pattern is most evident in the oldest patients. This suggests that there may be an age-related subclinical immune suppression leading to chronic activation of EBV. If a viral infection is a major factor in the recent increase in NHL in the world, then we should consider the role of immune-suppressive exposures which have become widespread in recent decades.

It has long been known that certain kinds of viruses play a causative role in the etiology of some cancers of the hematopoietic system. This has been well demonstrated in several of the naturally occurring lymphomas and leukemias of animals. In addition, there are a few clear examples in humans. Two characteristics of these viruses appear to be essential for oncogenesis to occur. First, the virus must be able to establish latency following primary infection, and second, it must be lymphotropic.

The mechanisms by which these viruses exert their oncogenic action may involve a direct genetic effect, such as insertion into the genome, leading to an alteration of expression of a host oncogene or suppressor gene. Alternatively, the virus may play a promotional role by inducing proliferation of target cells. Either mechanism can be triggered under conditions in which there is an enhanced level of virus reactivation. This could result from an early, severe infection as in Burkitt’s lymphoma, for example, or under conditions of immune suppression.

An example of a human virus which has been clearly shown to cause NHL is the HTLV-I (2). As all retroviruses, HTLV-I establishes a latent infection via reverse transcription in its target cells, activated T-helper cells, and can induce an ATL. It is estimated that the cumulative lifetime risk among HTLV-I carriers to develop ATL is about 5%. The evidence that HTLV-I plays a causative role in ATL is compelling, as the malignant cells in essentially all antibody-positive cases have monoclonally integrated provirus.

The mechanism by which this occurs does not appear to involve a genotoxic effect, since no common site of integration or oncogene has been identified. Rather, what has been proposed as a model of pathogenesis involves what we traditionally think of as a promotional effect. This model, as proposed by Yosida et al. (3) involves a process characterized by repeated rounds of virus replication, regulated by the transactivation of the virus by the regulatory protein, tax. This leads to a polyclonal expansion of HTLV-I-infected activated T-helper cells. In healthy carriers, the expansion of these cells is normally controlled by antibodies or cellular immunity against viral proteins. As a chance event, an infected cell with the acquired capacity for repeated replication loses the expression of viral proteins. Such cells can then expand monoclonally. With continuing rounds of viral expression and the likely presence of an additional factor or event, these cells can progress to malignancy.

In terms of risk factors, the epidemiology of ATL suggest that the carriers who are most likely to develop ATL are those who are infected perinatally, especially males (4). This hypothesis is based on two observations. First, the sex ratio of ATL cases in endemic populations shows a moderate male predominance; this is much closer to that seen among infected children reflecting perinatal transmission (an equal sex ratio), than that seen among adults reflecting sexual transmission (a female predominance). Second, the shape of the age-specific incidence curve (Fig. 1), is characteristic of a virus-associated malignancy, and suggests the role of an early, age-related exposure (5).

However, if we look at the epidemiology of the HTLV-I as a possible explanation of the current “epidemic” of lymphoma, it is clearly not related. All the evidence suggests that HTLV-I is a stable ancient infection, with a very low level of transmissibility, that is uniquely geographically restricted in its distribution (2). Although other variants of this virus are being identified, their behavior appears to be generally consistent with that of HTLV-I. Thus, a major role of a HTLV retrovirus for the recent increase of NHL in the world seems highly unlikely.

A second example of a human virus associated with the occurrence of NHL is the EBV. The EBV as a member of the herpesvirus family also establishes latency; in this case, the latent virus is carried in infected B-cells. Although there is very strong evidence that the EBV is causally associated with the occurrence of NHL under conditions of acquired or inherited immune suppression, the evidence is much less clear in relation to the risk of NHL in apparently non-immunosuppressed individuals.

Although the strongest evidence for a causal role for a virus in a specific malignancy is the consistent demonstration of integrated viral genome in tumor cells, serological evidence has also been instructive. Specifically, in the case of EBV genome-positive NHL occurring in patients undergoing therapeutic immune suppression for organ transplantation, the collection of serial blood specimens during the intervening period has provided a picture of the oncogenic process. This process is reflected in the pattern of antibody response against the EBV.

2 The abbreviations used are: NHL, non-Hodgkin’s lymphoma; HTLV-I, human T-cell lymphotropic virus type I; ATL, adult T-cell leukemia or lymphoma; EBV, Epstein-Barr virus; VCA, viral capsid antigen; EA, early antigen; RR, relative risk; EBNA, Epstein-Barr nuclear antigen.
The antibodies which are commonly measured to assess the host response to the EBV include those against three antigens (or complexes of antigen). These include the VCA, the EBNA, and the EA. Under normal conditions, a person with an established infection would have IgG antibodies against the VCA and the EBNA; antibodies against EA are seen infrequently and likely reflect viral replication. However, following immune suppression, patients who subsequently develop NHL characteristically have elevated IgG titers against the VCA and sometimes IgM as well, detectable titers against the EA, but low or absent antibody titers against the EBNA. This pattern in consistent with virus activation (6).

In order to see if this alternation in antibody pattern to the EBV also precedes the occurrence of “spontaneous” NHL, we undertook a case-control study, based on a collaboration of institutions responsible for population-based serum banks with linkage to data for subsequent cancer incidence (7). From four serum banks containing specimens from about 240,000 persons, we identified 104 individuals for whom a blood specimen had been stored an average of 63 months before diagnosis of NHL. For comparison, 259 controls were identified, matched for age, sex, ethnic group, and date of serum collection. The specimens were analyzed for IgG, IgM, and IgA antibodies against the VCA; for both the diffuse and restricted form of antibody reaction to the EA; and for antibodies against EBNA.

The major findings of this study are summarized in Table 1. The data were analyzed by matched analysis, comparing cases and controls for elevated titers against each antigen. The level of antibody termed elevated was that which was equalled or exceeded by 85% of the controls. In this analysis, elevated titers of both IgG and IgM against the VCA were associated with a higher risk of subsequent development of NHL, the RR equals 2.5 and 3.2, respectively. Although elevated levels of both forms of antibody response to EA were associated with NHL, the RR associated with these were no longer increased with simultaneous control for the other antibody levels. The cases had an unusually constricted distribution of antibody titers against the EBNA with few very high or very low observations. Thus the point estimate of the RR associated with elevated titers against EBNA was low, 0.5, as was the estimate for having low titers, 0.5. Other than for the latter, the prediagnosis EBV antibody profile seen in these apparently normal persons who developed NHL fits that predicted by the immune suppressed patient prototype.

This observation suggests that EBV may play a role in a subset of spontaneous NHL. This is consistent with the finding of Herbst et al. (8), who found 18% of 151 biopsies from NHL patients positive for EBV gene products with the use of the polymerase chain reaction assay. In addition, when the data from our study were stratified by age at diagnosis (Table 1), the prototypic pattern is most evident in the oldest group. This observation suggests that EBV-associated NHL is more common in older persons and may be related to more chronic viral activation due to subclinical immune suppression. The age-incidence curve of NHL is also consistent with the effect of a chronic exposure.

Unlike HTLV-I, EBV is an extremely prevalent infection. Almost all adults throughout the world are carriers of latent EBV infection. This fact, however, has been true for generations. If the EBV is playing a role in the current epidemic of NHL, its effect would likely be mediated by an increase in the frequency of viral reaction, especially among older persons. Whether there has been an increase in the proportion of NHL which is EBV positive over the last decades among older persons could be evaluated if there are sufficient population-based archival tissue samples available for genome studies.

If the epidemic which we are discussing is due primarily to an increase in EBV-positive NHL in older people, this change in incidence would likely be mediated by changes in environmental factors which influence the immunological control of latent infection.
EBV. Since the increase in NHL has occurred apparently among all populations, the exposure(s) involved would have to be essentially universally experienced. Since none of the exposures discussed in this workshop affect a broad spectrum of the world’s population, we must consider other factors which are ubiquitous in their effect. As an example, we might consider whether the recent depletion of the ozone levels, which has been reported to be associated with a suppression of immunity (9), could account for an increase of EBV-associated NHL. Obviously, this hypothesis is highly speculative and the data concerning an effect on the immune system extremely tentative. Nonetheless, it represents an example of the type of environmental factors that we should consider.

References
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