ACQUIRED IMMUNODEFICIENCY SYNDROME ASSOCIATED LYMPHOMA

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1. ABSTRACT

A prior diagnosis of HIV increases the risk of lymphoma between 150 to 250-fold, depending on the subtype, as compared with the risk observed in the general population. The advent of highly active anti-retroviral therapy (HAART) has seen a dramatic reduction in AIDS morbidity and a modest reduction in the incidence of opportunistic infections along with a corresponding reduction in Kaposi’s sarcoma. There has not, however, been a clear reduction in the incidence of lymphoma. As HAART therapy continues to improve in the Western world, the morbidity of HIV infection is beginning to shift from AIDS to other associated illness such as lymphoma. The treatment and etiology of lymphoma is a burgeoning issue in the care of HIV positive populations. This review will provide a basic overview of the association between HIV and lymphoma.

2. INTRODUCTION

The introduction of HAART in 1996 has seen a dramatic reduction in the morbidity of AIDS patients (1-6). As HAART has slowed the progression of AIDS in HIV-infected Western populations, there has been a corresponding decrease in opportunistic infections, such as Mycobacterium, Pneumocystis and cytomegalovirus (4-6). In addition, a modest decrease in the incidence of Kaposi’s sarcoma (HHV-8) has been reported among AIDS patients for post-HAART periods (7). However for AIDS defining lymphoma, that has no apparent infectious cause, the incidence has largely remained the same or even increased slightly, since the introduction of HAART (4-6). Thus, lymphoma is increasing as a major cause of morbidity and mortality among HIV-infected individuals.
Table 1. AIDS-defining Illnesses

<table>
<thead>
<tr>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cervical Cancer</td>
</tr>
<tr>
<td>• Kaposi Sarcoma</td>
</tr>
<tr>
<td>• Lymphoma, Burkitt</td>
</tr>
<tr>
<td>• Lymphoma, immunoblastic</td>
</tr>
<tr>
<td>• Lymphoma, primary in CNS</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Infectious disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Candidiasis, Respiratory system or esophagus</td>
</tr>
<tr>
<td>• Coccidiodomycosis</td>
</tr>
<tr>
<td>• Cryptosporidiosis, chronic</td>
</tr>
<tr>
<td>• Cytomegalovirus disease, excluding liver, spleen &amp; lymph nodes</td>
</tr>
<tr>
<td>• Herpes Simplex: chronic ulcers, bronchitis, pneumonitis, esophageal</td>
</tr>
<tr>
<td>• Histoplasmosis (disseminated)</td>
</tr>
<tr>
<td>• Kaposis Sarcoma (HHV-8)</td>
</tr>
<tr>
<td>• Mycobacterium avium,</td>
</tr>
<tr>
<td>• Mycobacterium kansasii</td>
</tr>
<tr>
<td>• Mycobacterium tuberculosis</td>
</tr>
<tr>
<td>• Pneumocystis carinii pneumonia</td>
</tr>
<tr>
<td>• Progressive Multifocal Lekoencephalopathy</td>
</tr>
<tr>
<td>• Recurrent pneumonia</td>
</tr>
<tr>
<td>• Recurrent Salmonella</td>
</tr>
<tr>
<td>• Toxoplasmosis of brain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Encephalopathy, HIV-related</td>
</tr>
<tr>
<td>• Wasting syndrome</td>
</tr>
<tr>
<td>• Isosporiasis of intestine</td>
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</tbody>
</table>

This review will provide an introduction into AIDS-defining Non-Hodgkin lymphoma (NHL) and will also discuss AIDS associates Hodgkin disease (HD). Kaposis sarcoma is reviewed elsewhere in this issue (8).

3. B-CELL DEFECTS ASSOCIATED WITH HIV INFECTION

A variety of abnormalities in the B-lineage have been described in HIV patients. Spontaneous proliferation of B-cells in patients with advanced disease has been reported; as has a general polyclonal activation of B-cells in HIV infected individuals (9-10). This often results in polyclonal hypergammaglobulinemia. This observed non-specific activation of B-cells and lack of antigen-specific B-cell proliferation and antibody production is, of course, most likely the result of reduced CD4+ T-cell help. There is a loose association between non-specific B-cell activation and proliferation and the eventual onset of lymphoma (9).

B-cells from HIV infected patients have been reported to express tumor necrosis factor alpha (TNF-alpha) and interleukin-6 (IL-6), contributing to their general polyclonal activated state (10). In addition, high levels of IL-6 are associated with multiple myeloma and other cancers such as chronic lymphocytic leukemia (CLL) and lymphomas (9,10).

Defects in B-lineage activation and the eventual loss of T-lineage cells in HIV infected patients is complicated by a reduction in general hematopoiesis (4,11,12). This is typically associated with later stage disease and is a result of macrophage uptake of HIV particles. This results in the subsequent release of transforming growth factor-beta (TGF-beta), TNF-alpha and interleukin-1 (IL-1) that can act to suppress bone marrow hematopoiesis.

4. AIDS AND LYMPHOMA

4.1. AIDS Defining – Non-Hodgkin’s Lymphoma

Table 1, AIDS-defining Illnesses, lists AIDS defining diseases, of which there are three cancers (13): cervical cancer (reviewed in 14), Kaposis’s sarcoma (reviewed in 8) and NHL. HIV-associated NHL typically consists of a diffuse growth pattern with a high growth rate and primarily a B-lineage phenotype (13). Cases that present with a T-lineage phenotype or an undetermined phenotype are relatively rare: less than 1.4% for T-cell lymphomas (15). Analysis of Ig gene segments in HIV-associated NHL has confirmed the clonal nature of the disease (16).

The estimated risk of NHL among HIV-positive individuals is between 10 and 29% since the introduction of HAART (17-19). There is some discussion that the incidence of HIV related NHL might be underestimated, in part due to some patients presenting with NHL prior to HIV diagnosis (19). NHL has been reported to be responsible for up to 16% of deaths in HIV-positive patients (20). The major risk factor for NHL (and Hodgkin disease (see below)) among HIV-infected individuals is a low CD4+ T-cell count (9,13,18,20,21). Below 350 cells/microliter the incidence of NHL rises nearly 10-fold (20,21). Length of time since HIV diagnosis and chronic B-cell stimulation (see above) have also been implicated as risk factor for AIDS associated NHL (9).

4.2. Non-AIDS Defining Lymphoma – Hodgkin Disease

While not considered an AIDS defining cancer, Hodgkin disease (HD) has been associated with HIV (1,2,22). Compared with non-HIV infected individuals, AIDS associated HD exhibits a higher frequency of mixed cellularity and lymphocytic depletion subtypes and is typically a more systemic disease (1,2,22). Involvement of the bone marrow has been reported for up to 60% of HIV-positive HD patients (22). In addition HD in HIV-infected patients has a much poorer prognosis than those without HIV (2). The incidence of HD increases nearly 8-fold in HIV populations as compared to the general population (5). Major risks factors in HD are similar to those discussed above for NHL.
Table 2. EBV Latency Types and Cancer

<table>
<thead>
<tr>
<th>Latency Type</th>
<th>Expressed Viral Genes</th>
<th>Associated Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency I</td>
<td>EBNA-1, EBERs, BARF0</td>
<td>Burkitt Lymphoma, Hodgkin Disease</td>
</tr>
<tr>
<td>Latency II</td>
<td>LMP-1, LMP-2</td>
<td>Nasopharyngeal Lymphoma, T/NK peripheral Lymphoma</td>
</tr>
<tr>
<td>Latency III</td>
<td>All EBNA genes, BARF0</td>
<td>HIV associated lymphoma, Post-transplant lymphoproliferative disorders</td>
</tr>
<tr>
<td></td>
<td>LMP-1</td>
<td></td>
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EBNA-1 is non-transforming, so Burkitt Lymphoma with EBV Latency I bear additional alterations (e.g.: translocations involving c-myc) that are transforming.

4.3. Lymphoma in Other Immunocompromised Settings

A high incidence of lymphoma, NHL in particular, is a hallmark of all immunodeficiency and is not limited solely to HIV settings. Similar to HIV, the risk of NHL in other immunodeficient settings parallels the severity of the immunodeficiency and the amount of immune stimulation (11,13). For example, kidney transplant patients have a very high risk of NHL during their first year post transplant, when anti-rejection therapy with immunosuppressive drugs is the most intense (11). Bone-marrow transplant recipients have a similar risk as a result of acute graft versus host disease suppression in the first year post-transplant (11). These experiences indicate that HIV infection is not itself a requisite for the development of leukemia, but rather it is the broader setting of immunodeficiency (11).

5. FACTORS CONTRIBUTING TO AIDS ASSOCIATED LYMPHOMA

5.1. EBV Infection

Nearly half of systemic AIDS lymphoma cases exhibit detectable EBV and some studies place this number closer to 80% (3,23,24). While it is evident that EBV is abundantly present in AIDS-associated lymphoma, it is not clear if EBV is the root cause of oncogenesis or if it is merely contributing to a multi-step process (see below). EBV has a complex pattern of latent infection, of which there are three categories that can be distinguished by expression of different EBV gene products (see 23 for review). Table 2, EBV Latency Types and Cancer, lists EBV gene products expressed in latency types I through III and the associated malignancies. In healthy individuals, EBV is latent in resting memory B-cells and EBNA-1 is the major expressed viral protein (23). Because the virus is not replicating and because cytotoxic responses to EBNA-1 are rare, these EBV infected memory B-cells escape immune surveillance.

Cytotoxic responses are generated for all of the other EBV gene products, including the LMP-1 gene that is essential for EBV mediated oncogenesis (3,23). EBNA-2 has also been shown to play a role in transformation through activation of components of the Notch signaling pathway (25). Thus, in order for EBV to be oncogenic, it must first avoid immune surveillance. In addition, the EBV genome must be maintained in the cell without killing the cells (e.g.: latent infection) and the virus must activate pathways that regulate cell growth.

In HIV immunodeficiency, all EBV gene products are expressed (latency type III) establishing the potential for EBV for directly participate in mediating oncogenesis (23). While this has been difficult to formally establish, it is clear that EBV has a role in the pathogenesis of AIDS-associated lymphoma (3,23,24). Evidence of EBV infection is found in about 40% of classical HD cases in western countries (3). It is likely higher in HIV positive populations. For NHL, the frequency of EBV varies depending on the lymphoma subtype. EBV is found in nearly 80% of diffuse large cell lymphoma (DLCL) (3). This rate drops to 30% for AIDS-associated NHL that can be classified as Burkitt’s lymphoma and is often accompanied by genomic alterations such as c-myc activation or p53 mutations (3,23,24). These features make it difficult to determine if EBV infection is the primary cause of oncogenesis or if it is participating in establishing a setting in which oncogenic genomic alterations are permitted to accumulate in clonal populations of cells.

5.2 DNA Alterations

Leukemia and lymphoma are frequently associated with specific chromosomal alterations that are associated with specific disease subtypes and that are predictive of therapeutic outcome and prognosis (26). AIDS-associated lymphoma is no exception to this paradigm. Rearrangements resulting in activation of the c-myc oncogene are often observed in AIDS-associated lymphoma (16). These include t(8;14), t(8;22) and t(8;2) in which c-myc is rearranged into the antigen receptor loci (13,16). Other mechanisms of myc deregulation have also been described in AIDS-associated lymphoma, including evidence that HIV may directly affect c-myc expression (27,28).

Alterations in Bcl-6 are also often observed in HIV positive lymphoma (29). While large chromosomal alterations are not frequent, mutations in the 5' region of Bcl-6 are detectable in nearly 60% of HIV-associated lymphoma (30). Mutations in p53 have been reported to be in nearly 60% of some AIDS-related lymphomas and alterations in Ras have also been observed (31-33). Thus, genetic alteration of genes that control cell growth and survival is a contributing factor to AIDS-related lymphoma similar to that observed in the general population.

6. MULTISTEP PROGRESSION TO HIV ASSOCIATED LYMPHOMA

It has become generally accepted that oncogenesis, including leukemia and lymphoma, is a multi-
Figure 1. Multi-step progression to lymphoma in HIV-infected individuals. In most cases, AIDS associated lymphoma is unlikely to be the result of a single oncogenic event, but rather a continuous cascade of events that eventually establish B-lineage oncogenesis. The initiating event is HIV infection, which can result in non-specific polyclonal activation of B-cells. In some cases HIV may also result in the deregulation of pathways controlling B-cell growth such as c-myc. This activation and subsequent proliferation is reinforced by deregulated cytokine production, also a result of HIV infection, in particular over-expression of IL-6. Opportunistic infection such as EBV can also contribute to B-cell proliferation and activation. In a few cases, EBV infection itself may be transforming as a result type III latency that is typically found in immunosuppressed situations. Chronic B-cell activation and proliferation may result in an unusually high frequency of genomic alterations, some of which may transforming and/or oncogenic; such as translocations involving c-myc or mutations in the Bcl-6 or p53 genes. The eventual accumulation of genomic alterations in clonal populations of B-cells can then lead to the emergence of lymphoma.

As the effectiveness of HAART continues to rise, lymphoma is becoming an increasing problem in the care of HIV-positive populations. Understanding the factors contributing to AIDS associated lymphoma and how these compare and contrast with lymphoma in the general population will certainly lead to the development of better therapeutic strategies.

7. ACKNOWLEDGEMENTS

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8. REFERENCES


HIV Associated Lymphoma


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