Dr. Aboulafia provides an accurate overview of the relationship between immunodeficiency and malignant lymphoma, the lymphoproliferative disorders that occur following solid organ transplantation, and the epidemiology and pathogenetic mechanisms possibly involved in acquired immunodeficiency syndrome (AIDS)-related lymphomagenesis.

The lymphoproliferative disorders that arise in immunodeficient individuals share several features, including frequent origination in extranodal sites, diffuse aggressive histopathology, B-cell lineage derivation, and association with the Epstein-Barr virus (EBV). However, immunodeficiency-associated lymphoproliferative disorders exhibit clinical, pathologic, clonal, and molecular heterogeneity that varies according to the immunodeficiency syndrome with which they are associated. For example, lymphoproliferative disorders arising in solid organ transplant recipients generally differ significantly from those arising in HIV-infected individuals who have AIDS.[1,2]

Initially, the lymphoid proliferations seen in solid organ transplant recipients were believed to be EBV-associated malignant lymphomas. The malignant status of these lesions was questioned, however, when Starzl and colleagues demonstrated that many regress spontaneously following withdrawal of immunosuppressive therapy.[3] These lesions are now known to represent a clinically and histopathologically diverse group of lymphoid proliferations of variable clonal composition and are collectively referred to as post-transplantation lymphoproliferative disorders.[1]

**Post-Transplantation Lymphoproliferative Disorders**

Most post-transplantation lymphoproliferative disorders are comprised of a polymorphic cell population, which often causes difficulty in determining with certainty their benign or malignant nature by histopathologic evaluation alone. Furthermore, post-transplantation lymphoproliferative disorders that fulfill the histopathologic criteria for malignancy lack morphologic features that allow precise categorization by the major lymphoma classifications. This has led to their subclassification by some investigators as polymorphic B-cell hyperplasia, polymorphic B-cell lymphoma, and immunoblastic lymphoma, and by other investigators as simply polymorphic or monomorphic. However, the latter histopathologic categories do not consistently predict clonality, and neither these histopathologic categories nor clonality has proven reliable in forecasting clinical behavior.[1]

Approximately 90% of post-transplantation lymphoproliferative disorders contain EBV. The presence of EBV usually is the result of a single infectious event, suggesting that EBV infection occurs prior to clonal expansion of the B-cell population.[1] This supports a pathogenetic role for EBV infection in the development of monoclonal post-transplantation lymphoproliferative disorders. We have shown that this is nearly always type A EBV infection.[4]

Our correlative morphologic and comprehensive molecular genetic analyses suggest that post-transplantation lymphoproliferative disorders can be classified into three groups[5]:

1. Plasmacytic hyperplasias are nearly always polyclonal; usually contain EBV, which may be multiclonal, oligoclonal, or monoclonal; and lack genetic alterations. These disorders regress spontaneously following withdrawal of immunosuppressive therapy.

2. Polymorphic lymphoproliferative disorders are monoclonal B-cell proliferations, usually contain clonal EBV, lack genetic alterations, and exhibit variable clinical behavior.

3. Malignant lymphoma/multiple myelomas are monoclonal B-cell proliferations, usually contain clonal EBV, and have alterations of ras, c-myc, and/or TP53 genes. These disorders usually
Epidemiology and Pathogenesis of AIDS-Related Lymphomas
Published on Cancer Network (http://www.cancernetwork.com)

Thus, the plasmacytic hyperplasias and the malignant lymphomas/multiple myelomas represent the benign and malignant poles of the spectrum, respectively. The explanation for the diverse clinical behavior of the polymorphic lymphoproliferative disorders remains unclear. However, we have recently shown that bcl-6 gene mutations predict the failure of post-transplantation lymphoproliferative disorders to regress following a reduction in immunosuppression, as well as shortened patient survival.[6] Thus, the bcl-6 gene appears to be an excellent marker for the subclassification of post-transplantation lymphoproliferative disorders into hyperplasia and malignant lymphoma. Whether these mutations are causally related to the development of post-transplantation lymphoproliferative disorders or simply represent a marker of genetic instability related to malignant transformation is still unclear.

AIDS-Related Lymphomas
In contrast with post-transplantation lymphoproliferative disorders, virtually all AIDS-related lymphomas are monomorphic and can be categorized according to the major lymphoma classifications. Approximately 40% are Burkitt’s or Burkitt’s-like lymphomas, and most of the remainder are large-cell and immunoblastic lymphomas.[2] Other investigators have described occasional cases of AIDS-related, anaplastic large-cell lymphomas and plasmablastic lymphomas, and we have described the primary effusion lymphomas, which contain the Kaposi’s sarcoma-associated herpesvirus.[7]

Like the post-transplantation lymphoproliferative disorders, the vast majority of AIDS-related lymphomas are B-cell lineage neoplasms. More than 90% express monotypic surface immunoglobulin and/or B-cell lineage-associated antigens. Their immunophenotypes are similar to those expressed by lymphomas of comparable morphology occurring in non-HIV-infected immunocompetent persons.[2]

One group of West Coast investigators have claimed that one-third of all AIDS-related lymphomas originating in the San Francisco area are polyclonal, and that many of these cases also lack EBV and c-myc gene rearrangements.[8] However, we have found that a comprehensive approach, which includes immunoglobulin heavy- and light-chain gene rearrangement and EBV terminal repeat analysis, demonstrates monoclonality in more than 95% of AIDS-related lymphomas from both the East and West Coasts of the United States.[9] Therefore, AIDS-related lymphomas exhibiting a germ-line immunoglobulin gene configuration appear to be quite rare.

Also, the failure to detect monoclonality does not necessarily indicate polyclonality. A variety of scientific and technical explanations can be offered to account for this phenomenon.

Acquired immunodeficiency syndrome-related lymphomas are characterized by the accumulation of multiple distinct genetic lesions. In contrast with the post-transplantation lymphoproliferative disorders, however, only approximately 50% of AIDS-related lymphomas contain clonal EBV infection, and as many as 50% or more contain c-myc gene rearrangements. Many AIDS-related lymphomas exhibit bcl-6 gene rearrangements and/or mutations, as well as TP53 gene mutations.[2]

These findings suggest that multiple alternative molecular genetic pathways operate in AIDS lymphomagenesis. Also, some of these pathways may be preferentially associated with certain histopathologic categories or anatomic sites of origin.[2]

Polymorphic B-Cell Lymphoproliferative Disorders in AIDS Patients
Finally, although the majority of AIDS-related lymphomas and post-transplantation lymphoproliferative disorders differ clinically, pathologically and molecularly, we have recently identified 10 HIV-infected men and women who have lymphoid proliferations that resemble the post-transplantation lymphoproliferative disorders.[10] The lesions develop in lymph nodes and extranodal sites. These patients generally have low-stage disease.[10]

The lesions grow diffusely and are comprised of a polymorphic lymphoid cell population similar to that found in the post-transplantation lymphoproliferative disorders. A clonal B-cell population representing only a small subset of the cells that comprise each lesion is detectable in the majority of cases. These lesions lack genetic alterations, except in those instances where there is morphologic transformation to large-cell lymphoma.[10] Thus, polymorphic B-cell lymphoproliferative disorders apparently occur in both HIV-infected individuals and solid organ transplant recipients, although they are infrequent in the former group.

Summary
Post-transplantation lymphoproliferative disorders and AIDS-related lymphomas represent two distinct categories of immunodeficiency-associated lymphoproliferative disease. These differences may be related to the level and type of immunosuppression and/or to other as yet unidentified...
aspects of the effects of immunosuppressive therapy and HIV infection on the immune system. Further investigation into the clinical and biological nature of each of these categories of immunodeficiency-associated lymphoproliferative disease should help us to better understand the development and progression of lymphoid neoplasia in the immunocompromised host.

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