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Pathologic Analysis of Recurrent Posttransplant Lymphoproliferative Disorders

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POSTTRANSPLANT lymphoproliferative disorders (PTLDs) are a family of lesions that may become clinically manifest at different stages of progression.[1-4] The histopathology of this disorder ranges from a polyclonal lymphoproliferation resembling infectious mononucleosis to a monoclonal disorder most frequently resembling non-Hodgkin's lymphoma. The Epstein-Barr virus (EBV) is detectable in the overwhelming majority of PTLDs and current theories invoke the virus as an important factor in the development of these lesions. However, even with successful treatment of PTLD, the natural history of the underlying EBV infection, that is, lifelong persistence of latent virus, remains unchanged. Thus, these patients remain at risk for the development of complications associated with EBV infection.

We reviewed the Pittsburgh transplant patient series to determine the number of patients who developed clinical recurrence of PTLD and evaluated histologic, clonal, and viral features to determine the relationship between primary and recurrent lesions.

MATERIALS AND METHODS

Surgical Pathology files at the University of Pittsburgh Medical Center Hospitals (Presbyterian University Hospital, Children's Hospital of Pittsburgh, and Montefiore University Hospital) were reviewed to detect patients who had evidence of two or more episodes of PTLD. Only patients who had documented clinical remission were included. Those with incomplete regression of mass lesions or persistent clinical symptoms were excluded. Pathologic slides were reviewed. PTLDs were categorized as polymorphic or monomorphic based on previously defined criteria.[3] In addition, those cases with a picture of infectious mononucleosis were distinguished from these categories. Immunoglobulin gene rearrangement studies and evaluations of T cell receptor beta chain rearrangements and of EBV presence and clonality were performed as previously described.[4]

RESULTS

Eleven patients with clinical recurrence of PTLD were identified. Three patients had a histologically similar recurrence (IM-like, polymorphic and monomorphic PTLD). In two cases identical clones of B cells were identified in the primary and second lesions. Three patients evolved from IM-like lesions to polymorphic PTLDs. One of these patients developed a clonal B-cell population that was not present in the first specimen. Five patients who initially had a polymorphic PTLD developed morphologically dissimilar EBV-associated lesions that had widely divergent histologic appearances.

DISCUSSION

This series underscores the diversity of lesions that fall under the general heading of PTLD. Clinical recurrence of this syndrome may occur and may be due to relapse of the original lesion or to the development of a tumor that is distinguishable on both histologic and clonal levels from the primary lesion. This latter category is of particular interest from a pathogenetic standpoint. In one case, the original and second lesions contained different clonal populations of EBV in addition to different immunoglobulin gene rear-

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rangement patterns. This suggests that these two clones were unrelated. The possibility that the second lesion arose from a cryptic clone in the first tumor cannot be ruled out by the present studies.

The diversity of EBV-positive tumors in this series also points out the limitations of designating all such complications of EBV infection as PTLD or, worse, as transplant lymphomas. Patients with PTLD recurrence may provide unique insights into the evolution of this disease. Infectious mononucleosis and polymorphic PTLD are likely to be closely related processes that may differ in the extent of architectural destruction, degree of clonal outgrowth, and possibly other factors undefined at present. In some cases the distinction between these two complications of EBV infection may be difficult if not impossible to make on a morphologic basis alone. Monomorphic EBV-positive neoplasms indistinguishable from high-grade lymphomas represent a less common and more advanced form of disease and should be distinguished from the preceding categories. Efforts to establish a classification system incorporating our current understanding of the evolution of this disease will provide a rational foundation on which to study frequency data and to evaluate the efficacies of different therapeutic strategies.

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