EDITORIAL

Angiocentric Lymphoproliferative Disorders of the Respiratory System: Incrimination of Epstein-Barr Virus in Pathogenesis

By Stephen C. Peiper

LETHAL MIDLINE granuloma and lymphomatoid granulomatosis are related angiocentric, angiodestructive lymphoproliferative disorders that involve the upper and lower respiratory tracts, respectively. They are both characterized by a heterogeneous infiltrate composed of small lymphocytes, mononuclear phagocytes, plasma cells, occasional eosinophils, and variable numbers of large, atypical lymphoid cells, not unlike the reactive infiltrate observed in Hodgkin’s disease. Because of the lack of a predominant, clearly malignant population identifiable on histopathologic examination, these two clinicopathologic entities were assigned to a pathologic purgatory of descriptive diagnostic designations instead of classification as a non-Hodgkin’s lymphoma, despite a malignant clinical course in the absence of therapy.

A historical perspective shows that current technologies have provided profound molecular insights into the nature of this spectrum of lymphoproliferative disorders, although many questions remain. The report by Borisch et al in this issue of Blood demonstrates that a subtype of Epstein-Barr virus (EBV) commonly isolated from immunocompromised individuals is frequently associated with midline granuloma.

Typically, reports of lethal midline granuloma describe a prodromal phase with nasal symptoms of months to years duration, followed by the onset of ulcers that efface midline nasopharyngeal structures, resulting in fatal complications related to cachexia, hemorrhage, or infection. Originally, Edgerton and DesPrez questioned the nature of lethal midline granuloma: “It is still an unsolved question whether lethal midline granuloma represents a tumour unlike all other tumours, an infection unlike other infections, or a defect in the immune mechanism.” Similarly, Liebow et al speculated that there would be controversy as to whether or not lymphomatoid granulomatosis should be classified as a malignant lymphoma.

Subsequently, a critical review of nasal lymphoproliferative lesions seen at the Mayo Clinic resolved a group constituting approximately 27% of cases, which were composed of a heterogeneous infiltrate that included varying numbers of atypical lymphoid cells associated with necrosis and invasion of blood vessels, as well as chronic changes such as fibrosis, epithelial metaplasia, and hyperplasia, and glandular atrophy, perhaps sequelae of a chronic infection.

This group, designated polymorphic reticulosis, had a favorable prognosis and a mean symptomatic interval that was tenfold longer (55 months vs 5 months) than was observed in patients with histopathologically proved lymphomas. These lesions were presumed to represent the histologic manifestation of lethal midline granuloma. Although less conspicuous, blood vessel invasion and thrombosis were also observed in 62% of obvious lymphomas, raising the possibility that these lesions evolve into a spectrum, in which high-grade histopathologic features are associated with an aggressive clinical course.

Diagnostic criteria were established to separate lymphomatoid granulomatosis into three categories based on the content of atypical lymphoid cells: pure, focal lymphoma, and diffuse lymphoma. Moreover, both nasal and pulmonary lesions were shown to progress from low-grade to high-grade histopathology over time. Both lethal midline granuloma and lymphomatoid granulomatosis may extend to involve tissues outside the respiratory tract, including lymph nodes, skin, and the central nervous system.

In this context, the term angiocentric immunoproliferative lesion (AIL) was proposed to include both lethal midline granuloma/polymorphic reticulosis and lymphomatoid granulomatosis and guidelines for grading were set forth (grade I: polymorphic infiltrate with minimal necrosis, few large atypical lymphoid cells, and small lymphocytes lacking nuclear irregularities; grade II: cytologic atypia of small lymphocytes, scattered large atypical lymphoid cells, and intermediate amounts of necrosis; and grade III: lymphoma, either diffuse mixed, large cell, or immunoblastic, with prominent necrosis). Immunologic characterization of AIL shows that the large atypical cells consistently express CD2, frequently CD3 and HLA-DR antigens, and variably CD4, CD5, CD7, and CD25, but not B-lineage differentiation antigens.

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687
Based on a morphologic resemblance to polymorphic peripheral T-cell lymphomas and the expression of T-lineage antigens (with an immunophenotype that reflects either activation or an unscheduled repertoire), AIL has frequently been considered to be a T-cell lymphoma. Unexpectedly, however, the majority of cases tested express cell surface antigens associated with natural killer (NK) cell differentiation (CD16/FcyRII, CD56/N-CAM, and/or CD57), a rare finding in T-cell lymphomas. Rare cases have been shown to express the lymphocyte activation antigen CD30, a feature of large cell anaplastic lymphomas, been considered to be a T-cell lymphoma. Unexpectedly, however, the majority of cases tested express cell surface antigens associated with natural killer (NK) cell differentiation (CD16/FcyRII, CD56/N-CAM, and/or CD57), a rare finding in T-cell lymphomas. Rare cases have been shown to express the lymphocyte activation antigen CD30, also a feature of large cell anaplastic lymphomas, which may have either B- or T-lineage differentiation and occur in the nasopharynx.

Surprisingly, molecular biologic analysis of cases of AIL for clonal rearrangements of genes encoding immune receptors, as would be predicted in a non-Hodgkin’s lymphoma, have not supported this designation. Several reports, studying at least 19 cases in total, have failed to find evidence for clonal rearrangements of genes for the β chain of the γδ T-cell receptor (TCR) or the α chain of the αβ T-cell receptor (TCR) in AIL. At least three cases with clonal rearrangements of this gene have been reported. Parallel analysis of genes encoding chains of the γδ T-cell receptor (γδ TcR) have shown 1 of 8 cases to have a clonal rearrangement of the γ chain (CD2) and 1 of 8 to have a clonally rearranged β chain gene. Weiss et al. reported that among seven T-cell lymphomas that lacked clonal rearrangements of the TcRβ and TcRγ genes, five that consistently expressed only the CD2 antigen also involved the upper respiratory tract. Immunocytochemical analysis of expression of TcR poly peptides confirmed the lack of (productive) αβ rearrangements in seven cases, but suggested that there was expression of chains encoded by productive rearrangements of γδTcR genes in two of them. Genes encoding Ig heavy chains and light chains have been universally reported to be in the germline configuration.

Despite this, both clinical and histopathologic features of AIL point to its being a malignant lymphoma. Alternative interpretations to reconcile the immunophenotypic and genotypic findings include the possibilities that AIL is a T-cell lymphoma derived from a primitive cell type that has not yet undergone activation of the recombinase system for rearrangement of TcR genes or that it is derived from NK cells, which do not rearrange these genes. However, the infiltrate in AIL lacks cells that express CD antigens associated with early T-lineage differentiation, and the expression of cell surface CD3 molecules in the absence of T-cell receptor molecules, an apparent molecular heresy, is unexplained. On the other hand, expression of CD3 and/or CD4, albeit variable in AIL, is not characteristic of NK cells.

In the original description of lymphomatoid granulomatosis, Liebow et al. proposed that “…studies analogous to those that have led to the identification of a virus associated with Burkitt’s lymphoma should be performed in lymphomatoid granulomatosis. As a first step a search should be made for antibodies to this virus and for the Epstein-Barr virus itself.” Vetrì et al. described a case of lymphomatoid granulomatosis in which EBV-encoded antigens were expressed by lymphoid cells and the patient had serologic evidence of EBV infection. Subsequently, EBV genomes were detected by molecular hybridization in tissues from a patient with lethal midline granuloma and lymph nodes involved by a process morphologically resembling lymphomatoid granulomatosis in a child with Wiskott-Aldrich syndrome. Harabechi et al. used in situ hybridization and Southern blotting to demonstrate EBV genomes in 5 of 5 cases of lethal midline granuloma, and Katzenstein and Peiper applied the polymerase chain reaction to amplify EBV templates from 21 of 29 cases of lymphomatoid granulomatosis. Several studies have confirmed these original findings in AIL, as well as extending them to subsets of sporadic T-cell lymphomas apparently unrelated to AIL.

Analysis of EBV genomic termini has shown that viral episomes have a uniform configuration consistent with infection at an early stage, before clonal expansion of the neoplasm. Dual-parameter analysis confirmed that EBV-encoded RNA transcripts were indeed localized to T-lineage cells (CD43-positive, CD20-negative) in cases of high-grade AIL with numerous lymphomatous cells.

Together, these findings provide the first direct evidence that AIL is a clonal process and implicates EBV as a “smoking gun” in the pathogenesis of this disorder. Recognized targets for EBV infection include B lymphocytes and epithelial cells of the nasopharynx. However, it also has been shown that human thymocytes and subsets of blood T lymphocytes express the cell surface receptor for EBV (CD21) and can be infected by EBV. Because AIL cells have not been found to bind CD21 antibodies it is presumed that an alternative receptor is used or that CD21 is temporally expressed at the time of infection.

Further evidence for the involvement of EBV as an etiologic agent is derived from the demonstration that lethal midline granulomas express mRNA transcripts encoding the latent membrane protein (LMP1) encoded by EBV, as well as the polypeptide itself. Transfection of a cDNA encoding LMP1 into rodent fibroblasts results in morphologic transformation, anchorage-independent growth, and tumorigenicity in immunocompromised mice. When similarly expressed in B-lymphoblastoid cells, LMP1 enhances cytoadhesion through induction of expression of adhesion molecules such as LFA-1, LFA-3, and ICAM-1. Analogous effects on cognate molecules in the cellular target in AIL could augment cytoadhesion to extracellular matrix proteins resulting in the angiocentricity that is observed in this disorder. LMP1 expression protects B cells from programmed cell death through induction of bcl-2 expression, which should be explored in AIL. Finally, an EBV-encoded polypeptide highly homologous to interleukin-10 has been shown to be secreted by infected B cells, which could contribute to the heterogeneous inflammatory infiltrate in the background.

Two common biotypes of EBV have been characterized. In addition to the common type (designated A), a second type (designated B) has been described that differs genetically in the sequences encoding EBNA-2, EBNA-3, and small-RNAs (EBER), geographically in its concentration in equatorial Africa, and biologically in its attenuated transforming ability. Sculley et al. found a higher incidence of antibodies to type B EBNA-2 in human immunodeficiency...
virus (HIV)-infected individuals and acquired immunodeficiency syndrome (AIDS) patients than in healthy controls, and Sixbey et al.\(^3\) isolated type B virus more frequently from AIDS patients than in healthy controls, virus (HIV)-infected individuals and acquired immunodeficiency syndrome (AIDS) patients than in healthy controls.

Thus, the current finding of increased frequency of type B EBV in AIL by Borisch et al.\(^1\) raises the possibility that these patients may have an occult immunodeficiency, not unlike the B-lineage posttransplant lymphoproliferative disorder induced by EBV in patients immunosuppressed with cyclosporin A (and anti-T-lymphocyte antibodies). Immune surveillance of EBV in latently infected individuals is largely dependent on reactivation of cytotoxic T lymphocytes that recognize epitopes on latent viral gene products, such as the nuclear antigens and latent membrane proteins. Epitope drift or variation in primary structure of products encoded by viral genes may result in subtle flaws in the T-lymphocyte repertoire that may be related to the HLA-class I haplotype.\(^3\) Such subclinical deficiencies in immune surveillance could lead to chronic infection with EBV, which has been implicated as a prodomme to the development of T-cell lymphomas\(^5\) and AIL (J.B. Parkhurst and S.C. Peiper).\(^4\)

Thus, AIL is a clinicopathologic entity with an aggressive clinical course, commensurate with a designation of lymphoma, and a pathologic signature of angiotropism. The immunologic features of this lymphoproliferative disorder are indeterminate: the immunophenotype shows expression of CD antigens associated with T-lineage differentiation and others with NK cell differentiation in a repertoire that does not characterize a recognized normal population. Although there is not convincing evidence of clonal rearrangements of genes encoding polypeptide subunits of immune receptors, there is clear evidence for EBV infection and expression of the EBV latent membrane protein 1, which can confer the transformed phenotype in transfectants. EBV episomes have a uniform configuration, suggesting that this is a clonal process. The disproportionate association of type B EBV raises the possibility of a predisposing immunodeficiency, perhaps focal or related to chronic EBV infection. Returning to the rhetorical insight expressed by Edgerton and DesPree in 1956,\(^2\) our current understanding of AIL in 1993, based on characterization at the molecular level, reflects features of "... a tumour unlike all other tumours, an infection unlike other infections, or (and) a defect in the immune mechanism."  

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