

## MINIREVIEW

## Primary Effusional Lymphoma: A New Non-Hodgkin's Lymphoma Entity

András MATOLCSY

Department of Pathology, University Medical School of Pécs, Pécs, Hungary

**A distinct non-Hodgkin's lymphoma (NHL) entity that grow in the body cavities as lymphomatous effusions in the absence of clinically identifiable tumor masses has been defined as primary effusional lymphoma (PEL). This lymphoma characterized by distinctive morphology, immunopheno-**

*Keywords:* lymphoma, effusional

**type, genotype and association with Kaposi's sarcoma-associated herpesvirus (KHSV)/human herpesvirus-8 (HHV-8) infection. In this minireview, the clinico-pathological and biological characteristics of PELs are summarized. (Pathology Oncology Research Vol 5, No 2, 87–89, 1999)**

### Introduction

A novel non-Hodgkin's lymphoma (NHL) entity that grow exclusively in the pleural, pericardial and abdominal cavities as lymphomatous effusions in the absence of an identifiable tumor mass has been described as body cavity based lymphoma first,<sup>1,2</sup> and later as primary effusional lymphoma (PEL).<sup>3</sup> This lymphoma represents a new clinico-pathological entity based on their unique constellation of clinical morphologic, immunophenotypic and molecular characteristics and consistent infection of the tumor cells by the Kaposi's sarcoma-associated herpesvirus (KHSV)/human herpesvirus-8 (HHV-8).<sup>4</sup> This new lymphoma entity has been incorporated recently into the lymphoma classification proposed by the World Health Organization (WHO) as a subtype of diffuse large cell lymphoma.<sup>5</sup> In this minireview, the clinical, morphologic, phenotypic and genotypic characteristics of PELs are summarized.

### Clinical features of PEL

PEL occurs preferentially among human immunodeficiency virus-1 (HIV) seropositive patients and represents about 3% of all AIDS-related NHLs.<sup>3,6</sup> Among HIV-seronegative patients PEL may also occurs, however less frequently.<sup>6,7</sup> The clinical, morphologic and molecular features of AIDS-related and AIDS unrelated PELs are mainly similar, but PELs appears to develops at a substantially older age in immunocompetent hosts than in HIV-infected individuals.<sup>3,6</sup>

PELs tend to present in the pleural, pericardial or abdominal cavities and grow in liquid phase as lymphomatous effusions. In sporadic cases, PEL may also occur outside of the body cavities and forms solid tumor masses, it involves lymph nodes or bone marrow indicating that not every PEL remains localized to the body cavities.<sup>3</sup>

### Morphology, immunophenotype and genotype of PEL

PEL displays a pleomorphic cytomorphology which bridges the features of large-cell immunoblastic and anaplastic large-cell lymphoma.<sup>3</sup> The majority of tumor cells are multinucleated or multilobated large cells with prominent nucleoli. The cytoplasm of the PEL cells is abundant, deep basophilic and frequently contains small clear vacuoles. Some cells are highly similar to those of Reed-Sternberg or Hodgkin's cells. The number of mitoses is usually high (*Figure 1*).

*Received:* May 10, 1999; *accepted:* May 31, 1999

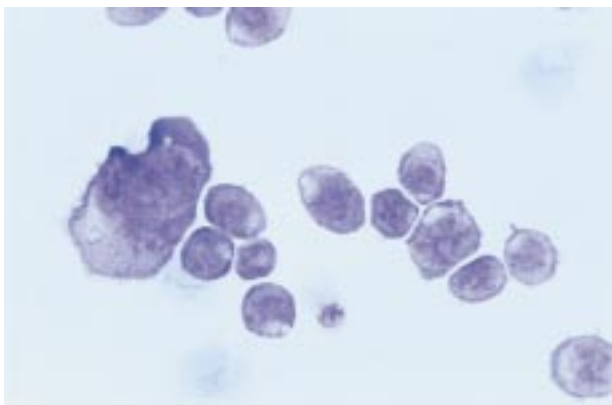
*Correspondence:* András MATOLCSY M.D., Ph.D., Department of Pathology, University Medical School of Pécs, H-7624 Pécs, Szigetesi út 12, Hungary; Tel: +36-72-324-122/ext.:1843; fax: +36-72-336-621; E-mail: [amatolc@pathology.pote.hu](mailto:amatolc@pathology.pote.hu)

Supported by grants from the Hungarian Ministry of Culture and Education FKFP 0931/97, the Hungarian National Science Foundation OTKA T023588 and T023588 and the Ministry of Welfare ETT 365/96.

PEL displays an intermediate immunophenotype. In most of the cases, tumor cells express CD45, consistent with the haemopoietic cell derivation, but lack surface immunoglobulin (Ig) and B- or T-cell associated antigens. Tumor cells also may express CD30, CD38, CD71 and epithelial membrane antigen (EMA). However, in the majority of PELs the tumor cells do not express B-cell associated antigens, the Southern blot analysis usually display a unique band of Ig gene rearrangement suggesting a B-cell origin of tumor cells.<sup>3,6,8</sup>

#### **Normal counterpart and cellular origin of PEL**

In most of the NHLs the cellular origin and lineage of neoplastic cells have been determined, but the normal counterpart of PEL is highly debated. The expression of antigens specific for late stage of B-cell differentiation, and the absence of surface Ig expression suggest a plasma cell origin of PEL.<sup>3</sup> In contrast, the combination of the pleomorphic morphology, null cell immunophenotype, and CD30 antigen expression have led some authors to link PEL to anaplastic large cell lymphoma.<sup>8</sup> Finally, some of the PELs display Ig heavy chain but not light chain gene rearrangement, which suggest that PELs may arise early in B cell development, following heavy chain gene but prior to light chain gene rearrangement.<sup>9</sup> The mutational analysis of Ig heavy chain (H) genes expressed by PELs showed that tumor cells of PEL may express unmutated, highly mutated and intraclonal divergent Ig V<sub>H</sub> gene sequences. Since unmutated IgH genes are characteristic for virgin B cells, and highly mutated IgH genes are expressed by mature B-cells that have reached the germinal (GC)/post-GC stage of B cell maturation, the heterogeneous pattern



**Figure 1.** Wright-Giemsa-stained cytocentrifuge preparation of a primary effusion lymphoma. The cells exhibit cytological features that appear to bridge large-cell immunoblastic and anaplastic large-cell lymphoma. The cells are polymorphous and possess basophilic cytoplasm which frequently contains small cytoplasmic vacuoles. The nuclei vary in shape from round to irregular and multilobated (x600).

of IgH gene mutation suggest that development of PELs is not restricted to one stage of B cell maturation.<sup>10</sup> The GC/post-GC origin of PELs has also been demonstrated to constitute a fraction of the cases. Gaidano et al<sup>11</sup> found mutations in the 5' noncoding region of BCL-6 gene in eight of 13 PEL cases. Because BCL-6 mutations are genetic marker of B-cell transition through the GC, these data are consistent with histogenetic derivation of PEL from GC/post-GC B-cells.

#### **Molecular pathology of PEL**

PELs are associated with infection of Kaposi's sarcoma-associated herpes virus (KSHV), also called human herpesvirus 8 (HHV8).<sup>4</sup> KSHV is a  $\gamma$ -2 herpesvirus and is the first member of this species known to infect humans.<sup>12,13</sup> The virus infect B-cells, and a latent infection of KSHV precedes the malignant transformation. However, the factors and mechanisms that lead to malignant transformation of B-cells are unclear, several lines of evidence suggest that KSHV infection may play a central role in the development of PELs. KSHV carries different genes which may behave as oncogenes, including a gene homologous to BCL-2 (ORF16), a gene homologous to the cellular D-type cyclins (ORF72/cyclin D), and a G-protein coupled receptor displaying constitutive activation (ORF74/GPCR).<sup>14,15</sup>

In the majority of PELs, tumor cells are coinfecting by both the KSHV and the Epstein-Barr virus (EBV). The EBV infection is monoclonal in PELs suggesting that EBV infection has preceded clonal expansion of tumor cells. The analysis of the pattern of EBV latent gene expression revealed a restricted latency with expression of EBNA1.<sup>16</sup> Since EBNA1 may induce B cell lymphomas when expressed in B cells as a transgene in mice, it is possible that EBNA1 may contribute to neoplastic transformation in the PEL cells.<sup>17</sup>

More recently it has been demonstrated that PEL cells synthesize IL-6 and IL-6 receptors, and the application of IL-6 antisense oligonucleotides inhibited the clonal proliferation of PEL cells, which suggest that IL-6 is an autocrine growth factor for these cells.<sup>18</sup>

#### **References**

1. Knowles DM, Inghirami G, Ubriaco A, et al: Molecular genetic analysis of three AIDS-associated neoplasms of uncertain lineage demonstrates their B-cell derivation and the possible pathogenetic role of the Epstein-Barr virus. *Blood* 73:792-799, 1989.
2. Wals AE, Shintaku IP, Said JW: Diagnosis of malignant lymphoma in effusions from patients with AIDS by gene rearrangement. *Am J Clin Pathol* 94:170-175, 1990.
3. Nador RG, Cesarman E, Chadburn A, et al: Primary effusion lymphoma: a distinct clinicopathologic entity associated with the Kaposi's sarcoma-associated herpes virus. *Blood* 88:645-656, 1996.

4. Cesarman E, Chang Y, Moore PS, et al: Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. *N Engl J Med* 332:1186-1191, 1995.
5. Jaffe ES, Harris NL, Diebold J, et al: World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues. A progress report. *Am J Clin Pathol* 111(suppl. 1):8-12, 1999.
6. Carbone A, Ghoghini A, Vaccher E, et al: Kaposi's sarcoma-associated herpesvirus DNA sequences in AIDS-related and AIDS-unrelated lymphomatous effusions. *Br J Haematol* 94:533-543, 1996.
7. Nador RG, Cesarman E, Knowles DM, et al: Herpes-like DNA sequences in a body-cavity-based lymphoma in an HIV-negative patient. *N Engl J Med* 333:943, 1996.
8. Ansari MQ, Dawson DB, Nador R, et al: Primary body cavity-based AIDS-related lymphomas. *Am J Clin Pathol* 105:221-229, 1996.
9. Green I, Espiritu E, Ladanyi M, et al: Primary lymphomatous effusions in AIDS: a morphological, immunophenotypic, and molecular study. *Modern Pathol* 8:39-45, 1995.
10. Matolcsy A, Nador RG, Cesarman E, et al: Immunoglobulin V<sub>H</sub> gene mutational analysis suggest that primary effusion lymphomas derive from different stages of B cell maturation. *Am J Pathol* 153:1609-1614, 1998.
11. Gaidan G, Capello D, Cilia AM, et al: Genetic characterization of HHV-8/KSHV-positive primary effusion lymphoma reveals frequent mutations of BCL6: implications for disease pathogenesis and histogenesis. *Genes Chromosomes Cancer* 24:16-23, 1999.
12. Moor PS, Gao S-J, Dominguez G, et al: Primary characterization of a herpesvirus agent associated with Kaposi's sarcoma. *J Virol* 70:549-558, 1996.
13. Ambroziak JA, Herndier BG, Glogau RG, et al: Herpes-like sequences in HIV-infected and uninfected Kaposi's sarcoma patients. *Science* 268:582-583, 1995.
14. Cesarman E, Nador RG, Bai F, et al: Kaposi's sarcoma associated herpesvirus contains G protein-coupled receptor and cyclin D homologs which are expressed in Kaposi's sarcoma and malignant lymphoma. *J Virology* 70:8218-8223, 1996.
15. Chang Y, Moore PS, Talbot SJ, et al: Cyclin encoded by KS herpesvirus. *Nature* 382:410, 1996.
16. Horenstein MG, Nador RG, Chadburn A, et al: Epstein-Barr virus latent gene expression in primary effusion lymphomas containing Kaposi's sarcoma-associated herpesvirus/human herpesvirus-8. *Blood* 90:1186-1191, 1997.
17. Wilson JB, Bell JL, Levine AJ: Expression of Epstein-Barr virus nuclear antigen-1 induces B cell neoplasia in transgenic mice. *EMBO J* 15:3117-3122, 1996.
18. Asou HA, Said JW, Yang R, et al: Mechanisms of growth control of Kaposi's sarcoma-associated herpes virus-associated primary effusional lymphoma cells. *Blood* 91:2475-2481, 1998.