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Human herpesvirus 8-associated primary effusion lymphoma in human immunodeficiency virus-negative patients: a clinico-epidemiologic variant resembling classic Kaposi's sarcoma

The term primary effusion lymphoma (PEL) defines an extranodal non-Hodgkin's lymphoma, usually classified as a B-cell lymphoma, that grows in liquid-phase within body cavities. A mandatory requisite for the diagnosis is the demonstration of human herpesvirus 8 (HHV-8) genome within tumor cells. HHV8 was first identified in late 1994 within acquired immunodeficiency syndrome (AIDS)-Kaposi's sarcoma (KS) lesions,[1] subsequently in classic, iatrogenic, and endemic (African) KS variants[2,3] and finally, in 1995, within large-cell type, AIDS-related intracavitary lymphomas.[4] HHV-8 infection is also associated with multicentric Castleman's disease[5] and a range of post-transplantation hematologic conditions, such as bone marrow failure[6] and lymphoproliferative disorders.[7,8] In 1996, body cavity based lymphomas harboring HHV-8 were proposed as a new entity with the name of PEL, to be distinguished from other primary and secondary lymphomatous effusions.[9]

PEL typically presents with recurrent effusions but without a solid component. The most common sites of involvement are the pleural, peritoneal and pericardial cavities delimited by mesothelium. Tumor cells may be co-infected by Epstein-Barr virus (EBV) and show large-cell morphology, with plasmablastic or immunoblastic features. Immunophenotypic features include positive staining for CD45, CD45R0, CD138, and activation-associated antigens, and negative staining for B-/T-cell-associated antigens. PEL cases exhibiting aberrant expression of B-, T- and NK-markers have also been reported. The B-cell lineage derivation of PEL cells is established on the basis of clonal rearrangements of the heavy immunoglobulin (Ig) genes and recent polymerase chain reaction (PCR)-based findings of a preferential expression of certain lambda light chain genes, suggesting clonal proliferation by an antigen selection process.[10] In contrast to other non-Hodgkin's B-cell lymphoma types, neither c-MYC nor other proto-oncogene rearrangements are detected in PEL. Likewise, a wild type of the tumor suppressor gene p53 is expressed, while mutations of the BCL6 5' non-coding regions have been recently documented in most of the analyzed cases.[11] PEL cells show complex karyotypes, the most frequent chromosomal abnormalities being trisomy 7, 12 and aberrations of chromosomal bands 1q21-q25.[11] The postulated normal cell(s) counterpart is unknown, but the expression of CD138/syndecan-1 and CD45R0 antigens, together with frequent BCL6 mutations reflect a late stage of B-cell differentiation.[12] Recently, the expression status of MUM1/IRF4 (multiple myeloma 1/interferon regulatory factor 4) protein, which is involved in physiologic B-cell maturation, has been shown to cluster selectively with PEL among lymphomatous effusions, corroborating the notion that PEL originates from post-germinal center, preterminally differentiated B-cells.[13]

As to disease pathogenesis, the role of HHV-8 in PEL development is widely accepted, whereas more controversy exists on possible co-factors that may trigger the transformation of HHV-8-infected lymphoid cells and their tropism for body cavities.

Over the last few years, PEL has been mainly described in human immunodeficiency virus (HIV)-positive patients.[4,9,14] In the non-HIV setting, this entity remains almost unreported but it may be hypothesized that its epidemiology correlates with the distribution of HHV-8 infection, which is known to have a peculiar ethnic/geographic pattern, being higher in the ethnic groups at risk for classic KS, namely those of Jewish descent or those living in the Mediterranean basin (i.e. Israel, Greece, Spain and Italy)[15-17] and sub-Saharan Africa.[18] So far, two examples of PEL have been reported in HIV-negative transplant recipients, one from Haiti[19] and one from Italy,[20] but none from sub-Saharan Africa where KS accounts for a high proportion of all malignancies. However, one case of a black man from South Africa with KS and unexplained pleural effusions containing bizarre cells was reported prior to the discovery of HHV-8.[21] To date, there are 20 well-documented cases developing in elderly subjects[9, 22,23,34] or even in centenarians[35] of Eastern European/Mediterranean or Jewish ancestry, supporting the existence of a distinct clinico-epidemiologic variant of PEL paralleling classic KS, i.e. *classic PEL*, as recently suggested also by Klepfish *et al*.[34]

Table 1. Summary of 20 HIV-negative patients with the classic variant of intracavitary HHV8-positive PEL.

	Case identification			Patient				PEL			
No.	*Institution/Ref.*	*Country*	*Year*	*Sex*	*Age*	*Origin*	*Diseases prior to PEL*	*Body cavity*	*EBV*	*Treatment*	*Outcome*
1	New York Hospital, Cornell Medical Center, New York/[9]	USA	1996	M	85	NR	Ischemic cardiomyopathy, CHF	Pleural-bilateral	Neg	None*	Died 6 mos.
2	idem			M	79	NR	Unknown	Peritoneal	Pos	Unknown	Died 6 mos.
3	CRO, Aviano/[23]	Italy	1996	F	69	Italy	Cirrhosis	Peritoneal	Pos	Chemotherapy	Died 1 mos. (unrelated cause)
4	Cedars Sinai Medical Center, UCLA, Los Angeles/[22]	USA	1996	F	85	Russia	KS	Pleural-bilateral	Neg	None*	Died 4 mos.
5	Mount Sinai School of Medicine, New York/[24]	USA	1996	M	94	NR	Colon cancer, KS	Pleural/pericardial/peritoneal	Neg	None*	Died 6 y
6	NIH, Bethesda/[25]	USA	1998	M	73	Portugal	MCD, CHF	Pleural-bilateral[#]	Neg	Chemotherapy	Died ? mos.
7	Metropolitan Geriatric Hospital, Tokyo/[35]	Japan	1998	M	101	NR	Ischemic cardiomyopathy, CHF	Pleural-bilateral	Pos	Chemotherapy	Died 8 mos. (hemopericardium)
8	Hospital Universitario Ramon y Cajal, Madrid/[26]	Spain	1999	M	83	NR	Ischemic cardiomyopathy, CHF	Pleural	Neg	None*	Died 3 d
9	IDIBAPS, Barcelona/[27]	Spain	1999	M	58	Morocco	Cirrhosis	Peritoneal	Neg	Chemotherapy	Died 3 mos. (sepsis)
10	La Sapienza University, Rome/[28]	Italy	1999	M	89	Italy/Foggia	Malaria, hypertension, colon cancer	Pleural	Neg	Unknown	Lost to follow up
11	idem			M	75	Italy/Frosinone	hypertension, dilatative cardiomyopathy, CHF	Pleural	Neg	None*	Alive 4 y (remission)
12	Soroka Medical Center & Ben Gurion University of the Negev, Beer Sheva/[29,30]	Israel	2000	M	68	Morocco/Jewish	Ischemic cardiomyopathy	Pleural/Peritoneal	Neg	Chemotherapy	Died 8 mos.
13	idem			F	73	Russia/Jewish	hypoglicemia, KS, MCD	Peritoneal	Neg	Chemotherapy	Died 16 mos.
14	St.Louis University School of Medicine, St.Louis/[31]	USA	2000	M	80	NR	Hypertension, ischemic cardiomyopathy, CVA	Pleural-bilateral	NR	Chemotherapy	Alive, 8 mos.
15	Instituto National de Enfermedade Infecciosas, Buenos Aires/[32]	Argentina	2001	M	72	NR	NR	Pleural-bilateral/Peritoneal	Neg	Rituximab	Alive 13 mos. (remission)
16	Hôpital Henri Mondor, Créteil/[33]	France	2001	M	87	Algeria	NR	Pleural	Neg	NR	NR
17	Kaplan Medical Center & Hebrew University-Hadassah School of Medicine, Jerusalem/[34]	Israel	2001	M	78	Eastern Europe/Jewish	Hypertension, CVA	Pleural	Neg	Chemotherapy & G-CSF	Died 18 mos. (unrelated cause)
18	University of Modena,	Italy		M	92	Italy/Cremona	CHF	Pleural-bilateral	Pos	None*	Died 12 mos (unrelated cause)
19	idem			M	87	Italy/Piacenza	CHF	Pleural	Pos	IC-cidofovir¶	Died 8 mos (unrelated cause)
20	idem			M	70	Italy/Modena	KS	Peritoneal/Pleural	Neg	IC-cidofovir¶	Alive 6 mos.

**In addition to thoracentesis or paracentesis. [#]This patient also had large B-cell lymphoma of the stomach. ¶Luppi et al. (submitted). Abbreviations: CHF, congestive heart failure; MCD, multicentric Castleman's disease; KS, Kaposi's sarcoma; NR, not reported; IC, intracavitary; CVA, cerebral vascular accident. Minor clinical findings: pruritus, (cases #9, 11, 12); anemia, (cases #7, 9, 12, 18). Elevated β_2-microglobulin values (case #9). Clonality: 16 cases are monoclonal of B-cell origin (IgH rearrangements), 1 case (case #16) is monoclonal of T-cell origin (T-cell receptor γ chain gene rearrangement), and 2 cases are polyclonal (cases #6 and 20). Aberrant phenotype: B markers positive (case #1, 7, 15 and 17); T & natural killer markers positive (case #14); T-markers positive (case #16 and 20). Cytogenetics: 52, XY, +del (3p), del (7p), +8, +12, +2 mar, der (8) (case #18; 49, XY, t(4; 14), +8, +12, +19 (case #19).*

Table 1 summarizes the available data concerning classic PEL. The major distinguishing features of this variant in comparison to the more common AIDS-related PEL are an older age at presentation, apparent host immunocompetence except for functional immune senescence, a less aggressive clinical course in a subset of patients, and infrequent EBV co-infection of the tumor clone. The almost exclusive EBV negativity (26% of the cases in contrast to 70-80% of AIDS-PEL) points out an EBV-independent role for HHV-8 in the pathogenesis of PEL. Overall, these studies show several epidemiologic and clinical features that this form of PEL shares with classic KS.[36] Nevertheless, it is notable that synchronous or metachronous KS is rare in PEL.

The origin/descent of patients is from countries where high rates of the incidence of both classic KS and HHV8 seropositivity are observed. One third of classic PEL are of Italian origin. The first case of non-AIDS PEL was reported in 1996.[23] The other five cases were collected in two institutions during a 6-year period (1995-2001; University of Rome La Sapienza[28], and University of Modena) and consist of HIV–, HBsAg–, and HCV-negative males who were born in Italy and have lived in this country all their life. Other reports include a number of cases among Jews in Israel or immigrants in North African countries.

Clinical features similar to those of classic KS are the overwhelming male predominance, seventh decade of life at diagnosis (mean, 79.9; range 58-101 years), minor immunosuppression (low leukocyte and CD4 lymphocytes counts) and/or immunoactivation (elevated β_2-microglobulin values),[37] moderate anemia (hematocrit <30%, hypoglycemia and, less commonly, pruritus or erythematous skin rash). Also, the 2-fold increase in risk of KS for birthplace in area endemic for malaria in the past[38] and history of malaria found in classic KS seems to be reproducible in classic PEL. PEL occurring as a second primary neoplasm in 2 patients with colon cancer is an intriguing – but difficult to explain – finding. Cancer-related immune dysfunction might be a relevant risk factor.

Two special forms of edema causing body cavity effusions appear to be frequently associated with classic PEL: congestive heart failure (with pleural PEL, often bilateral) that is also found in patients with classic KS more often than expected, and cirrhosis (for peritoneal PEL). Although there are no clinical data confirming the presence of pleural or peritoneal effusion prior to the diagnosis of PEL in a given patient, water retention in the form of hydrothorax and ascites is a common finding in chronic heart failure and cirrhosis, respectively. These edematous states could facilitate the process of lymphomagenesis by continuous accumulation of excess fluid (ultrafiltrate of plasma with low protein content) and cells (mesothelial cells, macrophages, polymorphonuclear cells and lymphocytes, and lymphomatous precursors) within body cavities. Herein, there might be favorable conditions for the growth of HHV-8-infected cells via release of various cytokines and inflammatory mediators[39] similarly to the situation in KS, in which inflammatory cytokines co-operate to induce angiogenesis, edema, and lesion formation.[40] Human interleukin-6 secreted by mesothelium induces vascular endothelial growth factor, which in turn can increase vascular permeability, critical to the pathogenesis of PEL.[41] This hypothesis is supported by the occurrence of lymphomatous effusions other than PEL complicating ascites due to cirrhosis.[42-44]

The pathogenesis of PEL shares some aspects with that of KS, including the model according to which both diseases are cytokine-mediated diseases originating as polyclonal expansions with subsequent evolution to clonal proliferations.[45] It can be speculated that PEL-progenitors (circulating in the peripheral blood mononuclear cell fraction, like KS-progenitors) may undergo viral replication when exposed to inflammatory sites or cytokine-rich environments. Independent HHV-8-infected clones may outgrow following a premalignant/hyperplastic stage. Patients infected with HHV-8 may develop non-lymphomatous body cavity effusions containing HHV-8 DNA and mononuclear cells that are reminiscent of a reactive process (early inflammatory stage? pre-lymphomatous effusion?) similar to early, inflammatory KS.[46] In the tumoral stage of PEL, fluids show a peculiar appearance of scattered lymphomatous cells in a heavy inflammatory background. Consistent with this hypothesis, a few cases of full-blown PEL of polyclonal nature have been reported both in HIV-infected and HIV-uninfected patients.

PEL is usually highly aggressive.[4,17] However, the natural history of the *classic variant* is more heterogeneous. In the surveyed articles, only a minority of patients had a very aggressive course with death within 6 months. Others experienced prolonged survival, partial or complete regression and even remission after simple thoracentesis or thoracentesis plus local anti-viral therapy or chemotherapy. As occurs with classic KS, in which patients often die of other causes, the actual cause

of death is not well defined.

Given the steady increase of the elderly population and the decline in immune status associated with physiologic aging, classic PEL may represent an emerging disease in those areas that are endemic for HHV-8 infection. However, establishing a diagnosis of PEL is a challenge. PEL is not as easy to discover as KS, which is visually identified, since it is an out-of-sight disease. Patients are first seen by general physicians or internists more frequently than by hematologists, in view of the fact that the key complaints are shortness of breath, pleuritic chest pain, and fever because of the underlying pleural effusion or ascites. The diagnosis is first made from routine cytology plus immunophenotyping studies but requires, as an essential step, the molecular demonstration of HHV-8. In fact, failure to detect HHV-8 DNA sequences precludes a diagnosis of PEL. Immunohistochemistry, using commercially available monoclonal antibodies directed against the latent nuclear antigen (LNA-1) ORF-73, is also useful for detecting HHV-8. Knowledge of HHV-8 epidemiology and of the variety of risk indicators is needed to identify classic PEL. The therapeutic approach, which is far from being settled, should be aimed at both reducing viral activity and eradicating predisposing host-factors favoring edematous states.

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