

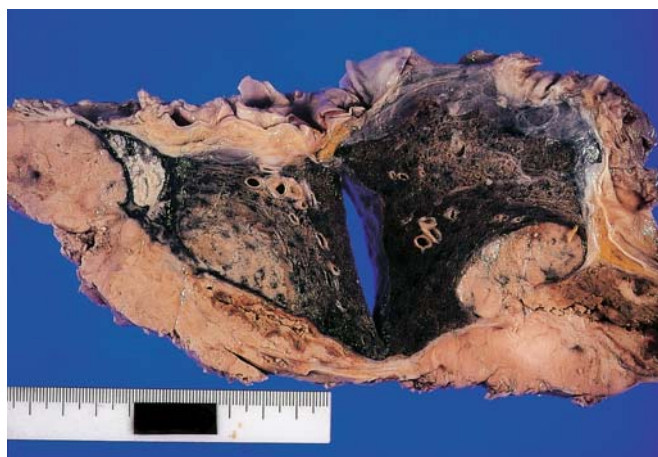
# Pyothorax-associated Lymphoma

Katsuyuki Aozasa

In Japan, EBV positive rate in immunocompetent patients with nodal lymphomas is less than 10% in B-cell and 20 - 50% in T cell lymphoma. Among extranodal lymphomas, EBV positive rate is higher in pyothorax-associated lymphoma (PAL), nasal NK/T-cell lymphoma, and adrenal lymphoma. PAL is non-Hodgkin's lymphoma that develops from chronic pyothorax resulted from artificial pneumothorax for the treatment of lung tuberculosis or tuberculous pleuritis. This disease was originally described by Dr. Aozasa as a distinctive clinicopathologic entity in 1987, and now listed as the disease entity in the WHO classification of Tumours, Pathology & Genetics, Tumours of the Lung, Pleura, Thymus and Heart (2004).

## INTRODUCTION

In 1987, Aozasa and colleagues reported three patients with pleural lymphoma, which developed after long-standing pyothorax resulting from artificial pneumothorax for the treatment of pulmonary tuberculosis or tuberculous pleuritis<sup>1</sup> (Fig. 1). Pleural lymphoma developed in these three patients (2.2%) from a total of 134 patients with chronic pyothorax (CP) at one of the hospitals specializing in chest diseases in Osaka, Japan, during the period from 1971-85. They regarded the CP to be etiologically important in the develop-



**Fig. 1.** There is a massive proliferation of lymphoma surrounding whole lung.

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ment of pleural lymphoma because (1) pleural lymphomas were never found in over 1,000 cases of malignant lymphoma in general hospitals in Osaka during the same period<sup>2</sup>; (2) review of the "Annual of Pathological Autopsy Cases in Japan (1974-85)" revealed six cases of pleural lymphoma, all of which were associated with CP; (3) review of pleural lymphoma cases reported in Japanese journals on chest diseases revealed that all were associated with CP<sup>3</sup>. Subsequent clinicopathological examination on 37 cases revealed that all patients had a more than 20-year history of CP, and histologically all had non-Hodgkin's lymphoma (NHL) with diffuse large B-cell lymphoma (DLBL) being most common<sup>4</sup>. From these findings, Aozasa concluded that this is a distinctive type of lymphoma and proposed the term "pyothorax-associated lymphoma (PAL)", defined as NHL of exclusively B-cell phenotype developing in the pleural cavity of patients with more than 20-year history of CP. PAL is now listed as a distinct disease entity together with primary effusion lymphoma (PEL) in the recent World Health Organization (WHO) classification for "Tumours of the Lung, Pleura, Thymus and Heart."<sup>5</sup>

Malignant lymphoma has been reported to be associated with antecedent autoimmune diseases such as Sjögren's syndrome, rheumatoid arthritis (RA), and Hashimoto's thyroiditis<sup>6,7</sup>. Irrespective of the nature of the antecedent autoimmune diseases, the lymphomas arising in such conditions are exclusively of B-cell type. The formation and continuation of the pyothorax is not thought to involve an autoimmune mechanism. Taken together, it is suggested that chronic inflammatory stimulation of a nonautoimmune nature could also be an etiological factor in the development of PAL. Malignant lymphomas developing in these conditions could be referred to generically as "malignant lymphomas developing in chronic inflammation." Malignant lymphomas of mucosa-associated lymphoid tissue (MALT) are included in this category, because they occur in the tissues normally

devoid of lymphoid tissue but are preceded by chronic inflammation that results in formation of MALT.

In this paper, pathologic findings in PAL are described with emphasis on the association with EBV.

## HISTORY OF PYOTHORAX

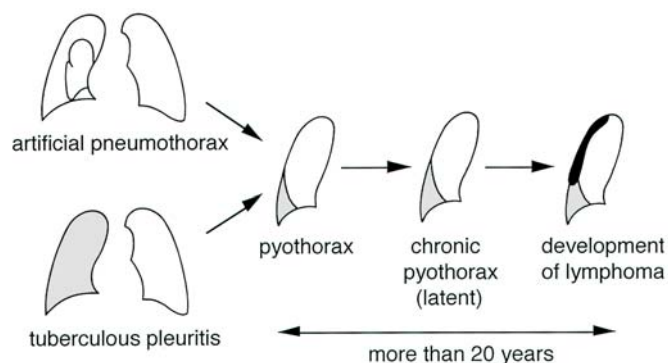
PAL patients are usually admitted to hospitals after a 20 to 64 (mean 37.4) -year history of pyothorax resulting from artificial pneumothorax for treatment of pulmonary tuberculosis or tuberculous pleuritis<sup>8</sup> (Fig. 2). Whereas a rare case in whom PAL developed shortly after the diagnosis and surgical drainage of CP was reported. PAL occasionally develops in patients with chronic pyothorax not complicated with lung tuberculosis. The artificial pneumothorax, originally established in Western countries as a form of surgical therapy for lung tuberculosis, had been more widely performed in Japan than in Western countries, especially in the 1930s to 50s. In the literature from Western countries, malignant lymphoma has been relative rarely described as a complication of CP. The higher frequency of PAL among CP patients in Japan might be related to frequent employment of artificial pneumothorax or to some genetic factors.

## PATHOLOGICAL FINDINGS

### *Histological and immunohistological findings*

Histologically pleural tissues adjoining the tumors generally show a marked fibrous thickening, with relatively sparse nonneoplastic inflammatory cells mainly consisting of small lymphocytes and plasma cells. Formation of lymphoid follicles is occasionally observed. All cases are NHL, among which diffuse large cell type is the most common often showing immunoblastic morphology<sup>8</sup> (Fig. 3). Marked angiocentricity with focal destruction of vessel walls was reported in a case of PAL of immunoblastic type. In general, however, this is not a common finding in PAL.

Immunohistochemical studies reveal that the majority of



**Fig. 2.** Schema for the development of pyothorax-associated lymphoma.

the cases are CD20<sup>+</sup> and/or MB1<sup>+</sup>, CD45RO<sup>-</sup>, CD3<sup>-</sup>, and thus are of the B-cell lineage, i.e., diffuse large B-cell lymphoma (DLBL). Petitjean *et al.*<sup>9</sup> described 12 European cases of PAL with diffuse large cell morphology and frequent plasmacytoid differentiation. Tumor cells in these cases showed CD20<sup>+</sup>, CD79a<sup>+</sup> and CD10<sup>-</sup>, BCL-6<sup>-</sup>, MUM-1<sup>+</sup>, CD138<sup>+</sup> phenotype consistent with derivation from late germinal center/post germinal center B cells. Androulaki *et al.*<sup>10</sup> reported the similar results in one case of PAL. Analysis of DNA sequences of the immunoglobulin heavy chain variable region gene also suggests that PAL is composed of B-lymphocytes at the differentiation stage of the postgerminal center. Whereas aberrant expression of T-cell markers (CD2, CD3, CD4) is relative frequently found in PAL with B-cell type<sup>10</sup>.

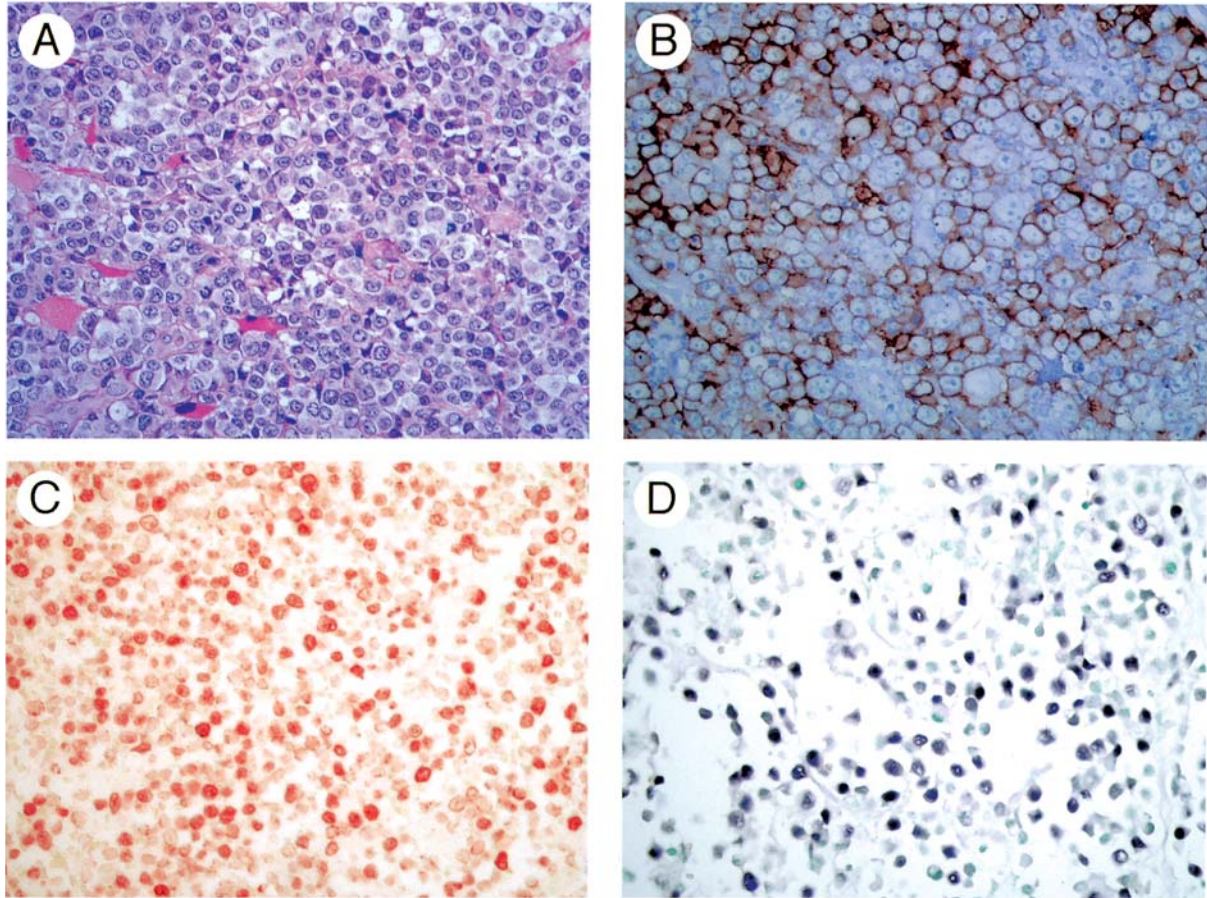
The tumor cells in a limited number of cases were CD20<sup>-</sup>, MB1<sup>-</sup> but positive for at least one monoclonal antibody reactive with T lymphocytes on immunohistochemistry or flow cytometry. These cases were conventionally determined to be peripheral T-cell lymphoma<sup>8</sup>. Strictly speaking, however, it is possible that these cases might be B-cell PAL with aberrant T-cell markers.

### *Autopsy findings*

Tumors usually show a contiguous pattern of invasion into adjacent structures, such as the lung, diaphragm, pericardium, mediastinum, and liver. Characteristically tumors remain to be localized in the thoracic cavity even at the time of autopsy in about a half of PAL patients<sup>8</sup>. Non-contiguous metastatic lesions are found in the adrenal glands, intrathoracic and extrathoracic lymph nodes. Central nervous system involvement is occasional.

## ASSOCIATION OF EBV WITH PAL

In 1993, two Japanese groups simultaneously suggested the association of EBV with PAL development based on a study of a total of nine cases of PAL<sup>11,12</sup>. They reported that (1) all patients had elevated serum values of anti-EBV antibodies; (2) the presence of EBV genomes in the nucleus of tumor cells as revealed by *in situ* hybridization using an EBER-1 probe; and (3) expression of latent infection genes such as EB nuclear antigen (EBNA)-2 and latent membrane protein (LMP)-1 in the tumor cells. Our subsequent studies on EBV in histological samples and cell lines established from PAL cases also showed the etiological importance of EBV for the development of PAL<sup>13</sup>. EBV DNA is detected in various kinds of malignant lymphomas, and latent infection gene of EBV, especially LMP-1 and EBNA-2, show a transforming activity in infected cells. LMP-1 in EBV-infected cells plays a central role in B-lymphomagenesis by mimicking members of the tumor necrosis factor (TNF) receptor family to the nucleus through cytoplasmic TNF-associated factor<sup>14</sup>.



**Fig. 3.**

- A. Diffuse proliferation of large lymphoid cells.  
 B. Tumor cells show positive immunoreactivity for CD20 by ABC method.  
 C. Tumor cells express LMP-1 by ABC.  
 D. *In situ* hybridization using EBER-1 probe reveals positive signals in the nucleus of numerous tumor cells.

Expression patterns of EBV latent genes among EBV-associated neoplasias are categorized as latency (Lat) I, II or III according to expression of EBNA-1, -2, and LMP-1<sup>15</sup>. Burkitt's lymphoma expresses only EBNA-1 (Lat I)<sup>16,17</sup>. Nasopharyngeal carcinoma and Hodgkin's lymphoma express EBNA-1 and LMP-1, but not EBNA-2 (Lat II)<sup>18,19</sup>. Malignant lymphomas arising in patients with AIDS and receiving organ transplantation, i.e., immunocompromised hosts, express EBNA-1, EBNA-2, and LMP-1 (Lat III).

Previous immunohistochemical study reported that the PAL cells showed the Lat III pattern of EBV infection at protein level, i.e., EBNA-1<sup>+</sup>, EBNA-2<sup>+</sup>, and LMP-1<sup>11,12</sup>. Whereas recent immunohistochemical study on the large number of PAL cases revealed that 67% and 70% of PAL were positive for EBNA-2 and LMP-1, respectively<sup>8</sup>. Immunohistochemical results might be influenced by fixation condition and tissue condition such as occurrence of degeneration, necrosis, and degree of inflammatory change. Alter-

natively latency pattern could be more accurately defined based on the pattern of promoter usage of EBNA-1 gene, i.e., CpWp for Lat III and Qp for Lat I/II. Analysis of the promoter usage of EBNA-1 gene revealed that less than 60% of cell lines and clinical samples from PAL tissues showed usage of CpWp promoter, i.e., Lat III<sup>20</sup>.

EBNA-2 and LMP-1 serve as target antigens for the elimination of infected cells by host cytotoxic T-lymphocytes (CTL)<sup>16,21</sup>. In immunocompromised hosts, proliferating cells expressing EBNA-2 and LMP-1 can escape from immune surveillance by the host CTL, which might result in development of malignant lymphoma<sup>22</sup>. However, systemic immunosuppression is not noted in CP or PAL cases<sup>8</sup>, thus suggesting an unknown underlying mechanism for escape of these latent antigen-expressing tumor cells from the CTL. EBV can be categorized as type A or type B based on differences in the sequences of EBNA-2<sup>23</sup>. Our previous study showed that type B genome was detected in approximately 40% of PAL

patients<sup>13</sup>. Type A EBV was detected in about 90% of gargle solution from control individuals in Japan<sup>24</sup>, indicating the relative predominance of type B EBV in patients with PAL. Several studies indicated the occurrence of type B EBV in lymphoma of immunocompromised patients<sup>25</sup>. Type B EBV is less immunogenic than type A EBV<sup>26</sup>, and thus the predominance of type B EBV might contribute in part to the escape of PAL cells from host CTL. Another mechanisms for escape included production of immunosuppressive cytokine, IL-10, by tumor cells. This is discussed later.

EBV latent antigens can induce efficient CTL response in combination with HLA class I molecules<sup>27</sup>. Down-regulation of HLA class I expression was observed in PAL cell line<sup>28</sup>. EBNA-3A, -3B and -3C are immunodominant antigens for CTL responses<sup>29</sup>, and among them, the CTL epitopes in EBNA-3B are well characterized<sup>30</sup>. Mutations and strain differences in these sequences is known to reduce CTL responses to latently infected B cells<sup>31</sup>. Most EBV strains in PAL tissue that expressed EBNA-3B exhibited mutations and strain differences compared to the prototype A sequence and were different from strain detected in peripheral blood leukocytes<sup>32</sup>. This might also contribute to the escape of PAL cells from host CTL.

### GENE EXPRESSION PROFILES IN PAL

PAL is a subtype of DLBCL. DLBCL is a major constituent of malignant lymphoma in the WHO classification<sup>33</sup>. At present, analysis of expression profiles of a large number of genes is an essential step toward understanding in detail the mechanism of lymphomagenesis and lymphoma progression. cDNA microarrays have been used for investigating gene expression profiles in human cancers<sup>34</sup>. Alizadeh *et al.* reported successful molecular classification of DLBCL, i.e., germinal center (GC) and activated signature with more favorable prognosis in the former than the latter<sup>35</sup>. cDNA microarray analysis was performed in six cases with PAL of DLBCL and 12 with nodal DLBCL<sup>36</sup>. Among 5,516 informative genes, 348 known to be involved in apoptosis, interferon response, and signal transduction displayed more than 2-fold (higher or lower) of expression level between PAL and nodal DLBCL. One of the most differentially expressed genes was interferon-inducible (IFI) protein 27. Overexpression of IFI27 was also found in cell lines derived from PAL, confirming the overexpression of IFI27 in PAL cells not bystander cells. IFI27 is known to be induced in B-lymphocytes by stimulation of interferon  $\alpha$ , but its function is not known as yet. Therefore exclusive expression of interferon inducible genes in PAL indicate a role of chronic inflammation for development of PAL. These findings show that PAL is a distinct form of DLBCL not only in its clinical presentation but also in its molecular profile.

### HUMAN HERPESVIRUS (HHV)-8 IN PAL

DNA sequences belonging to the recently discovered Kaposi's sarcoma-associated herpesvirus<sup>36</sup>, now known as human herpesvirus (HHV)-8, have been identified in a subset of NHL. Most HHV-8-containing lymphomas are body cavity-based lymphomas (BCBL) that occur in human immunodeficiency virus (HIV)-positive individuals<sup>37,38</sup>. They develop mainly in the pleural and peritoneal cavities as lymphomatous effusions, usually with no identifiable tumor mass. Although PAL presents as a solid tumor mass, it is otherwise similar to BCBL in that the lesions are exclusively B-cell lymphomas, usually exhibit immunoblastic morphology, and contain EBV. PCR analysis, however, revealed that PAL was devoid of HHV-8 sequences<sup>9,10,39</sup>. Thus, BCBL is EBV-associated and could be divided into two types; PAL showing mass formation in the pleural cavities and HHV-8<sup>-</sup>, and primary effusion lymphoma (PEL) showing pleural effusion without identifiable mass formation and HHV-8<sup>+</sup>.

### CONCLUSIONS

PAL is a distinctive type of malignant lymphoma of mostly B-cell nature and strongly associated with EBV infection. PAL develops in chronically inflamed tissues, and is thus defined as "malignant lymphoma developing in chronic inflammation." Employment of artificial pneumothorax, EBV infection, and cytokines and reactive oxygen species produced in CP lesions might be important factors for PAL development. Malignant lymphoma of MALT could also be included in the malignant lymphoma developing in the chronic inflammation because *Helicobacter pylori*-induced gastritis and Hashimoto's thyroiditis are known to have roles in predisposition to gastric lymphoma and thyroid lymphoma, respectively. These lymphomas might share common underlying factors for disease processes, such as inflammatory cytokines and genetic alterations induced by reactive oxygen species. However, there are several different aspects in these lymphomas. MALT lymphomas are usually EBV negative and show the proliferation of small lymphoid cells (centrocyte-like cells) at least at initial stage. Gastric lymphomas require tumor-infiltrating T-cells for growth by antigen triggering<sup>40</sup>. Thyroid lymphoma is thought to arise among activated lymphoid cells infiltrating in the thyroid gland of patients with Hashimoto's thyroiditis. DNA sequencing of immunoglobulin heavy chain variable region gene of the both lymphomas reveals the differentiation stage at the germinal center under antigen selection, i.e., on-going mutations<sup>41,42</sup>. Whereas PAL is composed of B-lymphocytes at the differentiation stage of the postgerminal center and antigen-dependent maturation is not usually involved in the development of lymphoma<sup>43</sup>.

There have been accumulating evidences linking chronic inflammation and development of lymphomas. Recently Jaf-

fe reviewed the role of chronic inflammation caused by bacteria including *Helicobacter pylori*, *Chlamydia psittaci*, *Borrelia burgdorferi*, and *Campylobacter jejuni* for development of gastric, ocular adnexal, cutaneous, and small intestinal MALT lymphoma<sup>44</sup>. These lymphomas usually respond to antibiotic therapy until chromosomal translocations occur in the proliferating cells. Reactive oxygen species associated inflammation might induce chromosomal translocation<sup>45</sup>. PAL develops in the long-standing inflammation of more than 20 years duration, which could cause very complicated numerical and structural abnormalities.

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