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Invited Paper

Malignant Lymphoma Developing from Long-standing Inflammation and MALT Lymphoma

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Introduction

We summarize here the findings of two types of extranodal lymphomas, which support our proposal for "maligant lymphoma developing in the long-standing inflammation". One type is thyroid lymphoma developing chronic lymphocytic thyroiditis (CLTH), an organ-specific autoimmune disease. Another is pleural lymphoma developing in the patients with over 20-years history of pyothorax. This kind of lymphoma mostly overlapped the lymphoma of mucosa-associated lymphoid tissue (MALT).

Thyroid lymphoma

Hashimoto's thyroiditis as a risk factor thyroid lymphoma

Follow-up studies carried out by Holm et al. in Sweden[1] and by us[2] in Japan have comfirmed the etiologically important role of CLTH in development of thyroid lymphoma. In our study, a total 5592 female patients over 25 years of age with CLTH, diagnosed between 1965 and 1982 at Kuma hospital, Japan, were followed up until 1985 (Table 1). Eight new cases of primary thyroid lymphoma were observed (O). Since the expected numbers of patients with malignant lymphoma (E1) and thyroid lymphoma (E2) were 2.25 and 0.1, respectively, the O/E1 and O/E2 ratios were 3.3($p<0.01$) and 80($p<0.001$), respectively. In the reference group including cases of hyperthyroidism, no increased risk of thyroid lymphoma was observed. These findings suggest that the autoimmune reaction present in CLTH may play an important role in the etiology of thyroid lymphomas. We also reported a close relationship between CLTH and thyroid lymphoma on the basis of histology, and all these were lymphocytic lymphomas[3]. Histological findings indicative of CLTH included the presence of lymphocytic infiltration usually with the formation of lymphoid follicles containing germinal centers, varing degrees of fibrosis, and oxyphilic changes or squamous metaplasia in the epithelial cells of the thyroid follicles. Histological evidence of CLTH in the thyroid tissue apart from lymphomas was confirmed in approximately 80% of patients with or without antibodies against thyroglobulin and/or microsomes.

Table 1. O/E1 and O/E2 ratios in patients with chronic thyroiditis and patients with Basedow's disease

Group	No. of patients	No. of person-years	Observed No. of cases (O)	Expected* No. of cases 1 (E1)	O/E1	Expected** No. of cases 2 (E2)	O/E2
Chronic thyroiditis	5592	45623	8	2.45	3.3****	0.10	80.0***
Basedow's disease	3856	32886	0	0.97	0.0	0.04	0.0

*expected number of cases with malignant lymphoma; **expected number of cases with thyroid lymphoma; ***$p<0.0001$; ****$p<0.001$

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Histopathology and immunophenotype of thyroid lymphomas

Follicular center cell tumors were the most common among thyroid lymphomas: 66% in our series[3]. In our 10% of cases of thyroid lymphoma, there was diffuse proliferation of atypical small lymphoid cells with a slightly irregular nuclear contour. Immunological marker studies showed that these atypical small lymphoid cells expressed surface properties intermediately between mantle-zone lymphocytes and follicular center cells. Immunological and immunohistochemical studies revealed that thyroid lymphomas were almost exclusively B-cell derived[4].

Pyothorx-associated lymphoma (PAL)

In 1987, we reported development of PAL in three patients suffering from long-standing pyothorax, resulting from an artificial pneumothorax for the control of pulmonary tuberculosis, or from tuberculous pleuritis[5]. PAL developed in three (2.2%) of 134 patients with chronic pyothorax at one of the hospitals specializing in chest diseases (Kinki Chuo Hospital for Chest Diseases) in Osaka, Japan, during the period 1971-85 (Photo. 1). Meanwhile, our study on malignant lymphomas in the general hospitals of the same district showed that there were no cases of PAL in over 2000 cases of malignant lymphoma. These findings suggested an etiologically important role for chronic pyothorax (CP) in the development of lymphoma in the pleura cavity.

To obtain more precise information, we carried out a nation-wide study of PAL[6]. The clinical findings are summarized in Table 2. The patients were admitted to hospitals with the histories of CP ranging from 22 to years (mean 33 years), resulting from artificial pneumothorax for the treatment of pulmonary tuberculosis or tuberculous pleuritis. Histologically, all tumors were lymphocytic lymphoma with the diffuse large cell type being the most common: approximately 80% of all cases. Immunologically, almost all cases showed the B-cell phenotype. Because an autoimmune mechanism was not thought to be likely in the formation and continuation of the phyothorax, these findings suggested that chronic inflammatory stimulation of a non-autoimmune nature could also be an etiological factor in the development of malignant lymphomas.

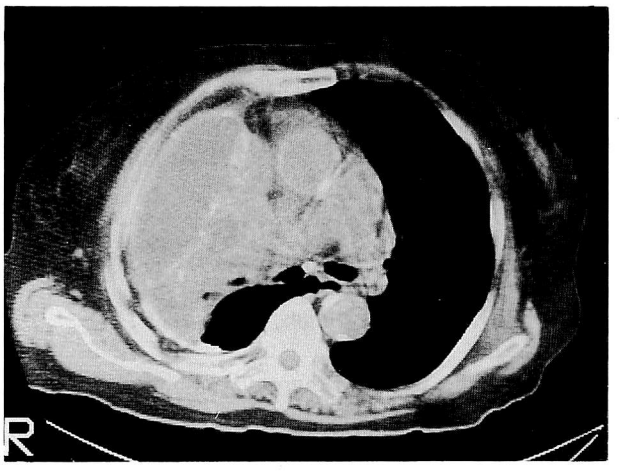

Photo. 1. Development of lymphoma in the right pleural cavity of a chronic empyma patient.

To examine risk factors for development of PAL in patients with CP, a case-control study was carried out[7]. The factors including onset age of lung tuberculosis and pyothorax, presence of chemotherapy, surgical treatment, extent of empyema, presence of fistula, history of smoking, and height and weight of patients at first admission were compared in patients with CP alone (70 controls) and CP complicated with lymphoma (42 cases), by which the date of birth and sex were matched. The patients receiving the artifical pneumothorax showed a significant increase in risk for development of PAL (relative risk$=4.92$, $p<0.05$). This finding suggested that chronic non-healing inflammation in the pleural cavity left by artificial

Table 2. Summary of chinical findings in pyothorax-assoicated lymphoma patients

Age at diagnosis	48-81 years(mean 63)
Male: Female ratio	5.2:1
Tuberculosis history	
lung tuberculosis	81%
tuberculous pleuritis	16%
Interval between pyothorax and onset of lymphoma	22-55 years(mean 33)
Presenting symptoms	
chest pain	51%
productive cough and dyspnea	54%
Tumor of chest wall	14%
Diagnosis at admission	
chronic pyothorax	49%
chronic pyothorax complicated with malignancy	38%
lung tumor	5%
Detection	
chest X-ray	35%
computed tomographic scan	77%
Definitive diagnosis	
biopsy	84%
autopsy	16%

%: percentage of all cases positive

pneumothorax resulted in the development of PAL. Repeated rentogenographic examinations carried carried out at the procedure might be causative factor.

Role of Epstein-Barr virus (EBV) in pleural lymphomagenesis

Previous study showed the presence of Epstein-Barr virus (EBV) genome together with the expression of latent infection genes in the tumor cells of PAL in five and four patients, respectively[8,9]. We examined the presence of EBV genome in cases with PAL (34 cases) and CP without PAL (16 cases) to evaluate an association of EBV with PAL[10]. Combined polymerase chain reaction (PCR), in situ hybridization method, and immunohistochemistry showed that EBV genome was detected in lymphoma cells in 85% of PAL with almost constant expression of latent membrane protein-1 (Fig. 1, Table 3). On the contrary, EBV genome was detected by PCR in one of 16 CP cases. These findings suggested that neoplastic transformation of infiltrated lymphocytes in CP by the EBV is one of the factors for the development of PAL under the long-standing inflammatory circumstances.

Relationship between lymphocytic lymphoma developing from long-standing inflammation and lymphoma of the mucosa-associated lymphoid tissue (MALT)

Lymphomas of the MALT, firstly discribed by Isaacson et al[11], are heterogenous entity in histology, immunologic character, and primary site of origin. MALT lymphomas are defined as lymphomas arising from the mucosa-associated lymphoid tissue (extranodal organ), such as Peyer's patch[11]. Under the normal conditions, however, the extranodal organs, where the MALT lymphomas develops, such as thyroid, salivary glands, gastrointestinal tract, do not have lymphoid tissue. The lymphoid tissue in these organs is formed through chronic inflammation such as CLTH and Sjogren's syndrome. Recently an association between gastric lymphoma and chronic follicular gastritis caused by the Hericobacter pylori has been suggested[12].

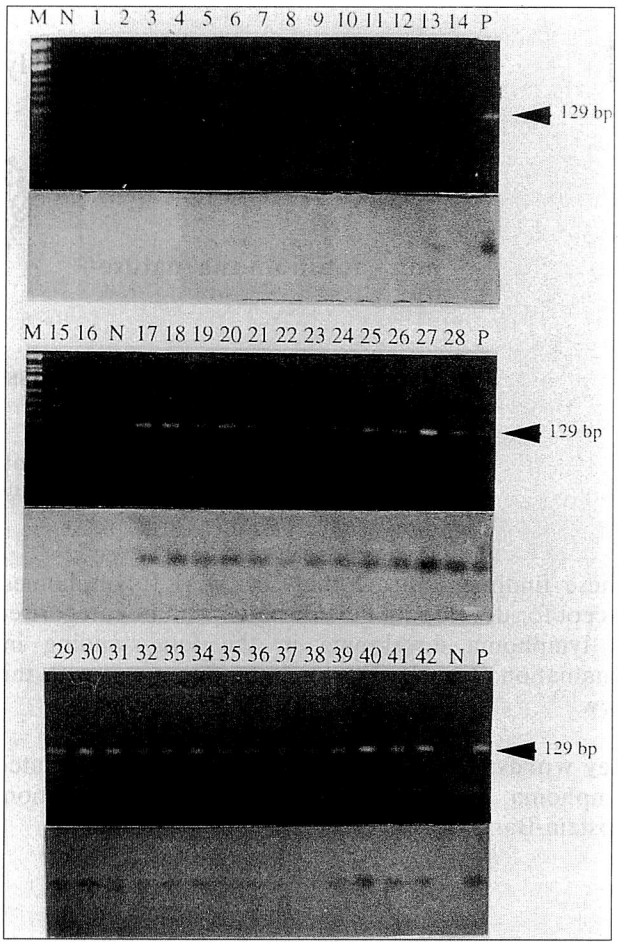

Fig. 1. Southern blot analysis of PCR amplified products for Epstein-Barr virus genome. N: negative control, P: positive control(Raji cell line), Cases 1-16: chronic pyothorax(CP), Cases17-41: Pyothorax-associated lymphoma(PAL), The positive results are shown by the band at 129 base paire in all PAL and one of CP(Lane 13)

Table 3. Summary of Epstein-Barr virus study

	PCR				
	EBV genome	EBNA2A	EBNA2B	ISH	LMP-1
Pyothorax-associated lymphoma	26/26	14	10	28/33	30/34
Chronic pyothorax	1/16	0	0	0/1	1*/1

*: a few lymphocytes

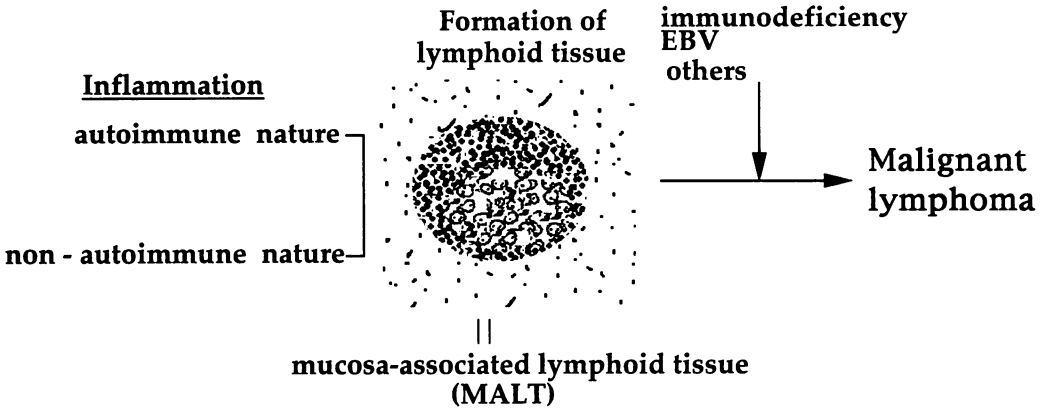

Fig. 2. Development of extranodal lymphoma from chronic inflammation of an autoimmune and non-autoimmune nature

These findings indicate that the MALT lymphomas, except for developing Peyer's patch, can be categorised as lymphoma developing in the long-standing inflammation (Fig. 2). Doctor Isaacson agreed with this view[13].

Key words: Thyroid lymphoma, pyothorax-associated lymphoma, MALT lymphoma, chronic inflammation, Epstein-Barr virus

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