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Artificial Pneumothorax as a Risk Factor for Development of Pleural Lymphoma

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An etiologically important role of chronic tuberculous empyema for development of pleural lymphocytic lymphoma of B-cell type has been suggested. To examine risk factors for development of pleural lymphoma in patients with chronic tuberculous empyema, a case-control study was carried out. Onset age of lung tuberculosis and empyema, 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 empyema alone (70 controls) and empyema complicated with lymphoma (42 cases): the date of birth and sex were matched by group. The patients receiving artificial pneumothorax showed a significant increase in risk for development of pleural lymphoma (relative risk = 4.92, $P<0.05$). We could not find any report describing development of pleural neoplasias in patients with chronic empyema receiving surgical resection of pleural pyogenic membrane. From these findings, it is suggested that artificial pneumothorax left chronic non-healing inflammation in the pleural cavity, which resulted in development of pleural lymphoma.

Key words: Chronic empyema — Tuberculosis — Malignant lymphoma — Artificial pneumothorax

Chronic stimulation by autoimmune reaction is considered as one of the causes of development of lymphocytic lymphomas in patients with autoimmune diseases such as Sjogren's syndrome and chronic lymphocytic thyroiditis.[1,2] In 1987, we suggested an etiologically important role of chronic tuberculous empyema in the development of lymphocytic lymphoma in the pleural cavity.[3] Because an autoimmune mechanism was not thought to be likely in the formation and continuation of the empyema, our findings suggested that chronic inflammatory stimulation of a non-autoimmune nature could also be an etiologic factor in the development of lymphocytic lymphoma. To confirm this further, we carried out nation-wide study of the pleural lymphoma and 37 cases were collected from Japanese hospitals.[4] Clinicopathologic study of these patients revealed that all of them had been admitted after a 22–55 (mean 33) year history of empyema resulting from artificial pneumothorax for the treatment of pulmonary tuberculosis or tuberculous pleuritis. Immunological and immunohistologic studies revealed a B-cell nature of the proliferating cells in all but one tumor. These findings indicated that malignant B-cell lymphoma arose as a monoclonal growth from a pool of proliferating polyclonal lymphocytes in tissues affected by the chronic tuberculous empyema.

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In this study, a case-control comparison was carried out to examine risk factors for the development of pleural lymphoma in patients with chronic tuberculous empyema.

MATERIALS AND METHODS

Forty-two cases of chronic tuberculous empyema complicated with pleural lymphoma in 16 hospitals in Japan were collected from the period April 1988 to December 1990. These patients were admitted to hospitals as having pleural lymphoma during 1975–88. Chronic empyema is defined by chest roentgenogram or CT as pleural thickening with varying degrees of calcification in patients with histories of lung tuberculosis or tuberculous pleuritis. Pleural puncture during the course of the empyema yielded a purulent discharge in which bacteria, including tuberculous bacilli, were not necessarily present. The duration between onset of empyema and the histologic diagnosis of pleural lymphoma ranged from 22 to 58 (35 on average) years (Table I). Clinical stage of the tumors was determined by physical examination, chest roentgenogram, chest computed tomography (CT), bone roentgenogram, blood count, and routine clinical chemistry. Gallium scintigram, abdominal CT, and bone marrow aspiration were carried out in some patients. From these procedures, 70% patients were concluded to be at stages I and II and 30% at stages III and IV. Tumors were

histologically classified according to the Working Formulation[5] as 27 cases with diffuse immunoblastic type, 8 with diffuse large predominantly non-cleaved cell type, and 4 with small lymphocytic type with plasmacytoid features. In another 7 patients, subtyping of lymphoma was not possible because of degenerative or necrotic change of the histologic specimens.

Seventy patients with chronic tuberculous empyema alone admitted to National Tokyo Hospital for Chest Diseases and National Kinki Central Hospital for Chest Diseases during the period from 1971 to 1989 were chosen as the control group. They had had empyema when they were admitted to these two hospitals. The follow-up period from the onset of empyema ranged from 20 to 60 (35 on average) years. The date of birth and sex ratio (M:F) in 42 cases and 70 controls were 1921 ± 6.8 vs. 1922 ± 6.8 and 7.4:1 vs. 7.8:1. Risk factors examined in this study were as follows: onset age of lung tuberculosis, presence of chemotherapy, surgical treatment which included artificial pneumothorax, air plombage, thoracoplasty and pulmonary resection, extent (total or partial) of empyema, presence of fistula, history of smoking, and height and weight at first admission. These data for cases were provided by attending physicians, and those for controls were obtained through review of clinical records by one of the authors (M.O.). Information on these eight factors was available in all controls but only in 14 cases for chemotherapy, nine for extent of empyema, twelve for presence of fistula, and ten for height and weight. Relative risk (odds ratio) was calculated for exposure to the binary variables as listed in Table I.

Table I. Clinical Course of Tuberculosis and Empyema

	Age at diagnosis of tuberculosis (yr) range (average)	Chemotherapy for tuberculosis (% of patients)	Duration of empyema (yr) range (average)
Cases	18–55 (26.9)	78.6	22–58 (35)
Controls	10–42 (25.7)	60.4	20–60 (35)

RESULTS

The relative risks for pleural lymphoma in the selected exposure categories are shown in Table II. The median onset age of lung tuberculosis in cases and controls was 25 years. The most relevant factor among surgical treatments seemed to be artificial pneumothorax. Then we compared the frequency of patients receiving artificial pneumothorax for treatment of lung tuberculosis. The patients receiving the artificial pneumothorax showed a significant increase in risk for development of pleural lymphoma ($RR=4.92$, $P<0.05$). The patients over 25 years at the onset of tuberculosis, receiving chemotherapy for tuberculosis, with a history of smoking, and height over 165 cm also showed increments of risk but the effects were not statistically significant. Because data on chemotherapy and height were missing in many cases, the significance of risks of these factors remains inconclusive.

DISCUSSION

Pleural lymphoma developing in patients with chronic tuberculous empyema is a relatively rare disease, and therefore cases were collected from 16 hospitals in Japan. As reported previously,[4] all of the present cases had been admitted after a longer than 20-year history of empyema. Controls were collected from two major hospitals specializing in chest diseases in Japan. Generally chronic tuberculous empyema results from two patterns of disease; one is tuberculous pleuritis and the other is artificial pneumothorax for lung tuberculosis. The present study revealed that the patients receiving artificial pneumothorax showed the highest relative risk for development

Table II. Relative Risks and 95% Confidence Intervals for Selected Exposure Categories

Factors	Relative risk	95% confidence interval	No. of positive findings	
			case	control
Age of onset of lung tuberculosis (>25 years)	1.50	0.68–3.29	24	32
Chemotherapy	2.83	0.83–12.1	11	35
Artificial pneumothorax	4.92	1.99–12.2	33	31
Total empyema	0.24	0.06–1.03	4	46
Presence of fistula	0.38	0.09–1.54	3	33
History of smoking	1.71	0.73–4.02	19	27
Height of patients (>165 cm)	1.41	0.36–5.47	6	34
Weight of patients (53.0 kg)	0.86	0.23–3.25	5	35

of pleural lymphoma among patients affected by chronic tuberculous empyema. It is likely that the artificial pneumothorax, originally established in Western countries as the surgical therapy for lung tuberculosis, has been much more widely performed in Japan than in Western countries. In Japan, artificial pneumothorax for the treatment of lung tuberculosis became popular in the 1930s, reached a peak in 1951, and fell into disuse following the application of new modalities of treatment such as thoracoplasty, anti-tuberculous drugs, and pulmonary resection. Malignancies arising in the pleural cavity other than malignant lymphoma have been reported among patients with chronic empyema both in Japan[6] and in Western countries.[7] Few cases of malignant lymphoma, however, has been reported in Western countries as a complication of chronic empyema. This difference might reflect the different frequency of artificial pneumothorax as a treatment for lung tuberculosis in the past decade between the two countries.

Why has the frequency of artificial pneumothorax affected the incidence of development of pleural lymphoma? It is interesting that we could not find any report describing development of pleural neoplasias in patients with chronic empyema receiving surgical resection of the pyogenic membrane in the pleural cavity.[8] From these findings, it is suggested that artificial pneumothorax left chronic non-healing inflammation in the pleural cavity, and this resulted in the development of pleural lymphoma. Because a vast majority of pleural lymphoma is B-cell in nature, the possible etiological role of Epstein-Barr virus should be examined.

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REFERENCES

1) Kassan, S. S., Thomas, T. L., Moutsopoulous, H. M., Hoover, R., Kimberly, R. P., Budman, D. R., Costa, J., Decker, J. L. and Chused, T. M. Increased risk of lymphoma in sicca syndrome. *Ann. Intern. Med.*, **89**, 888–892 (1978).
2) Kato, I., Tajima, K., Suchi, T., Aozasa, K., Matsuzuka, F., Kuma, K. and Tominaga, S. Chronic thyroiditis as a risk factor of B-cell lymphoma in the thyroid gland. *Jpn. J. Cancer Res.*, **76**, 1085–1090 (1985).
3) Iuchi, K., Ichimiya, A., Akashi, A., Mizuta, T., Lee, Y.-E., Tada M., Mori, T., Sawamura, K., Lee Y.-S., Furuse, K., Yamamoto, S. and Aozasa, K. Non-Hodgkin's lymphoma of the pleural cavity developing from long-standing pyothorax. *Cancer*, **60**, 1771–1775 (1987).
4) Iuchi, K., Aozasa, K., Yamamoto, S., Mori, T., Tajima, K., Mukai, K., Komatsu, H., Takagi, T., Kobashi, Y., Yamabe, H. and Shimoyama, M. Non-Hodgkin's lymphoma of the pleural cavity developing from long-standing pyothorax. Summary of clinical and pathological findings in thirty-seven cases. *Jpn. J. Clin. Oncol.*, **19**, 249–257 (1989).
5) The non-Hodgkin's lymphoma pathologic classification project. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of a Working Formulation for clinical usage. *Cancer*, **49**, 2112–2135 (1982).
6) Myoui, A., Aozasa, K., Iuchi, K., Mori, T., Yamamoto, S., Kuratsu, S., Ohsawa, M., Ono, K. and Matsumoto, K. Soft tissue sarcoma of the pleural cavity. *Cancer*, **68**, 1550–1554 (1991).
7) Roviano, G. C., Sartori, F., Calabro, F. and Varoli, F. The association of pleural mesothelioma and tuberculosis. *Am. Rev. Respir. Dis.*, **126**, 569–571 (1982).
8) Iuchi, K. Empyema and malignancies. *Igaku no Ayumi*, **161**, 980 (1992) (in Japanese).