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Primary Well Differentiated Lymphocytic Lymphoma of the Lung

– A Clinical and Immunohistochemical Study of Four Cases –

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Four cases of well differentialted lymphocytic lymphoma with or without plasmacytoid differentiation of the lung are described. Two cases were single and the others were multiple. Histologic pictures of the lesion showed mass with perivascular, interstitial and alveolar extension in three cases and only interstitial and perivascular involvement in one. Histologically three cases were lymphoplasmacytic lymphoma and one was small lymphocytic lymphoma. Dutcher bodies, granulomas and germinal centers were also found in tumors. Immunohistochemical study revealed monoclonal lymphocytic proliferation in all cases in fresh frozen sections and in three in paraffin sections. Treatment is surgical resection. Chemotherapy is used for residual disease after surgery.

Key Words: *Primary lymphoma of lung, small lymphocytic, lymphoplasmacytic, immunohistochemistry.*

INTRODUCTION

The dense infiltrates of mature-appearing small lymphocytes in extranodal sites such as skin, orbit, salivary gland, lung and gastrointestinal tract pose the problem in differential diagnosis between non-neoplastic process and true malignant lymphoma. In 1963 Saltzstein used the term "pseudolymphoma" in the pulmonary lesions, which was considered as some sort of chronic inflammatory process and proposed morphologic criteria to distinguish from malignant lymphoma; a mixed cellular infiltrates, the presence of true germinal centers and lymph nodes free of lymphoma.

Recent change in concept of malignant lymphoma (monoclonal proliferation of lymphoid cells) has led to use immunocytochemical determination of monoclonal immunoglobulin on the tumor cells as the most accurate and definite means of differentiating benign from malignant lymphoproliferative disorders (Julstrud et al, 1978, Evans, 1982, Knowles et al, 1982). However, the demonstration of monoclonal intracytoplasmic immunoglobulin in paraffin section is only useful in the lesions with plasmacytoid differentiations, and so it has a limited value (Pangalis et al, 1980). This article describes an author's experience in Massachusett's General Hospital in Boston of four cases of well differentiated lymphoproliferative lesions primarily involving the pulmonary parenchyma. The diagnosis of lymphoma in these patients was made on the clinical and histopathologic features and confirmed by immunohistochemical studies.

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MATERIALS AND METHODS

The subjects of this study consisted of four cases of primary well differentiated lymphomatous lesions of the lung, which were confirmed as lymphoma by the demonstration of monoclonal surface and/or

cytoplasmic immunoglobulin. Clinical informations and laboratory findings were examined by a review of the medical records of the patients.

Formalin-fixed tissues were sectioned at 4 μm and stained with hematoxylin-eosin (H & E), periodic acid-Schiff (PAS) and Giemsa stains. Immunohistochemical staining was done using an avidin-biotin peroxidase conjugate (ABC) method (Vector Laboratories, Burlingame, Calif.) with 3-amino-9-ethylcarbazol (AEC) as an enzyme substrate. For the demonstration of cytoplasmic immunoglobulin in formalin-fixed tissue the paraffin sections were pretreated with 0.1% trypsin at 37°C for 30 minutes and stained with rabbit antisera to human immunoglobulin heavy chains (gamma, mu, alpha, and delta) and light chains (kappa and lambda) (Dako Accurate Scientific and Chemical Co., Hicksville, N.V.). For surface membrane antigen, frozen sections were air-dried and fixed in acetone. All four cases were stained with monoclonal antibodies for heavy chains (gamma, mu, alpha and delta) and light chains (kappa and lambda) as well as monoclonal antibodies, anti-CALLA, anti-B1, anti-B2, anti-T1, anti-T3, anti-T4 and anti-T8, (Ortho Pharmaceuticals, Raritan, N.J.).

RESULTS

The clinical symptoms, radiologic and laboratory findings, operative or biopsy procedures and treatment are summarized in Table 1. Two patients were asymptomatic and the lesions were incidentally discovered on routine chest roentgenogram for the study of bladder tumor and GI bleeding respectively. The third patient complained of nonproductive cough and neck pain and the fourth presented hemoptysis, intermittent chest pain and dyspnea. The duration of symptoms in these patients were two and three months respectively. One patient had been treated for breast carcinoma eighteen years ago and also had a two-year-history of intermittent mixed cryoglobulinemia with purpuric lesions on the lower extremities and lupus erythematosus. Three patients had normal complete blood counts and one had mild anemia and leukopenia. Serum protein electrophoresis and immunoelectrophoresis were normal in three patients and a moderate to marked increase of gamma globulin with an increase of immunoglobulin G and A was seen in one. The radiologic pattern of the patients was that of nodular densities; two had solitary nodule and two had multiple nodules. One of the latters had coarse linear densities on both lower lobes in addition to small nodules. Bone marrow examination was done in all patients; three were normal and one showed paratrabecular involvement of tumor. Three cases in which computed tomogram was performed were free of adenopathy.

Table 1. Clinical findings in four patients

Patient	Age / Sex	Chief Complaints	Duration	Chest x-ray	Laboratory findings	Other malignancies or hx. of autoimmune di.	Staging procedure	Operation / biopsy	Follow-up
Case 1	48/M	None (incidental x-ray fx)	2 yrs	Multiple nodules, bilateral	Normal CBC & serum EP	Bladder TCC	BM- L/S scan- CT-	Wedge resection of RLL	1 yr later tx c̄ chemo-tx
2	66/M	None (incidental) x-ray fx)	2 yrs	Single nodule, LLL	Normal CBC		BM-	Wedge resection of LLL	
3	64/M	Nonproductive cough & rt. neck pain	3 mos	Single nodule, RLL	Normal CBC & serum IEP		BM+ CT-	Open lung bx of RLL	10 mos later symptom free
4	65/F	Hemoptysis, chest pain & intermittant dyspnea	2 mos	Multiple nodules, bilateral	Slight anemia & leukopenia Increase of IgG & IgA	Breast cancer 18 yrs ago Mixed cryoglobulinemia & lupus erythematosus	BM- CT-	Open lung bx of RLL	Chemotx c̄, Leukeran

Table 2. Pathologic findings in four patients

Patient	Gross findings	Microscopic findings: Distribution	Plasma cells	Dutcher bodies	Granulomas	Germinal centers	Pleural (P), bronchial (B) or vessel (V) involvement	Histologic diagnosis
Case 1	4x2.8x1.2cm firm, homogeneous tan	Mass c̄ slight perivascular extension	+	+	+	+	P+ B+ V+	Lymphoplasmacytoid
2	2 cm firm, yellow-tan	Mass c̄ interstitial & perivascular extension	+	–	–	+	–	Lymphoplasmacytoid
3	0.9x0.5x0.5cm firm, white	Mass c̄ alveolar extension	–	–	–	–	B+ V+	Well differentiated lymphocytic
4	No obvious nodularities, yellow-gray	Interstitial & perivascular involvement	+	+	+	–	–	Lymphoplasmacytoid

Table 3. Immunologic findings in four patients

Patients	Immunoperoxidase staining: Frozen section	Paraffin section	Surface marker study: IgG(%)	IgM(%)	K(%)	λ(%)	E-rosette (%)
Case 1	IgMk	IgMk	11	37	22	12	45
2	IgMk	IgMk	22	23	11	11	49
3	IgMk	Negative	18	49	10	0	10
4	IgMk	IgMk			Not done		Not done

Two patients who had a solitary nodule was treated by resection of the lesions without further treatment. The other two patients, in which the lesions were multiple, were treated with chemotherapy, in addition to resection; in one patient chemotherapy was started immediately after operation and in the other patient after one year follow-up.

Histopathology and immunohistopathology (Table 2 and 3): Macroscopically three lesions presented as a circumscribed, yellow, tan or white homogeneous, firm nodule which measured one, 2 and 4cm in maximum diameter respectively (Fig. 1 and Fig. 2). In one case the lung was yellow-grey in color but there was no obvious nodularity. Microscopically Case 1 had central confluent area with slight peripheral infiltration along the alveolar septa and perivascular spaces. Case 2 and 3 were composed of confluent sheets of tumor cells which obliterated normal architectures; one invaded the surrounding tissue along the bronchovascular structures (Fig. 3) and the other extended through the alveoli. In Case 4 the cellular infiltrates were predominantly confined to the interstitium and perivascular spaces without any confluent nodule formation. One tumor was histologically classified as well differentiated small lymphocytic lymphoma and three were lymphoplasmacytoid lymphoma.

In small lymphocytic lymphoma the tumor cells were composed of small mature lymphocytes with occasional paraimmunoblasts. In two of three lymphoplasmacytoid lymphomas, intranuclear inclusion (Dutcher bodies) were found.

Multinucleated giant cells and noncaseating

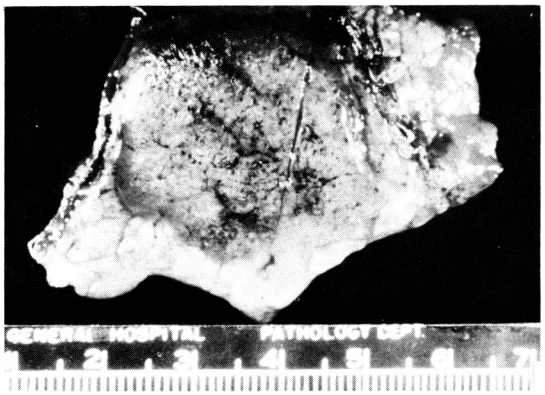


Fig. 1. Gross specimen of Case 1 showing a round mass covered by pleura.

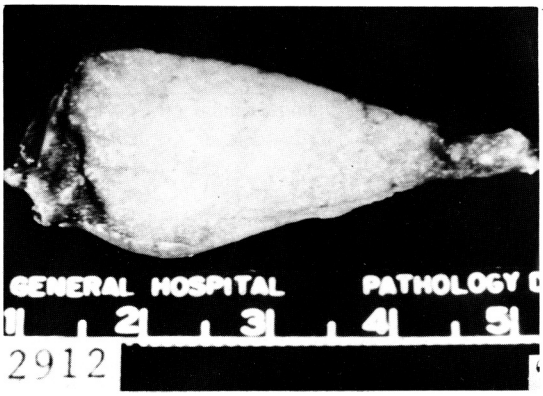


Fig. 2. Cut surface of the tumor of Case 1. The tumor is yellowish tan in color.

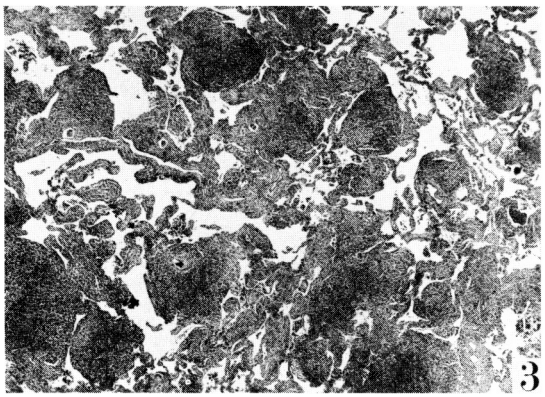


Fig. 3. Microscopic findings of Case 2 showing dense infiltration of small lymphocytes with extension to alveolar septa along the bronchovascular structures (H & E, x26).

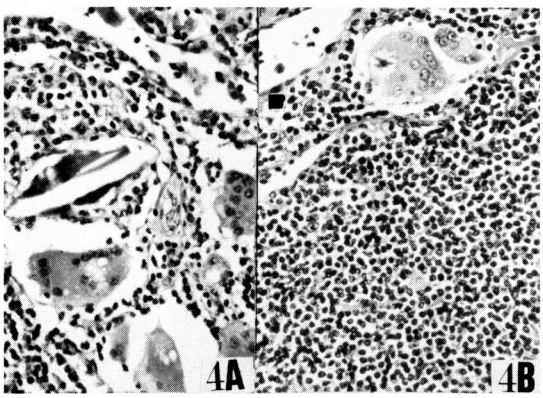


Fig. 4. Multinucleated giant cells containing cholesterol clefts (4A) and asteroid body (4B). From Case 4 (H & E, x256).

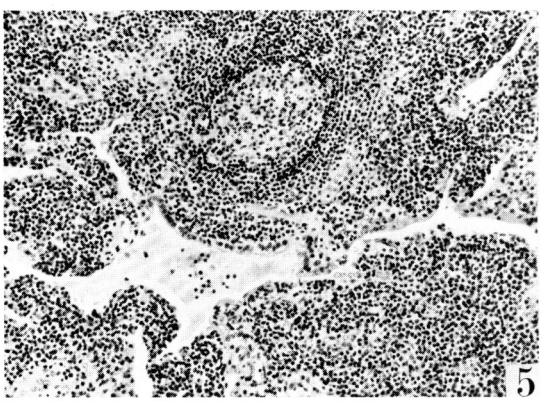


Fig. 5. Lung biopsy from Case 1 showing diffuse infiltration of small lymphocytes and plasmacytoid lymphocytes and presence of germinal center in middle field (H & E, x 160).

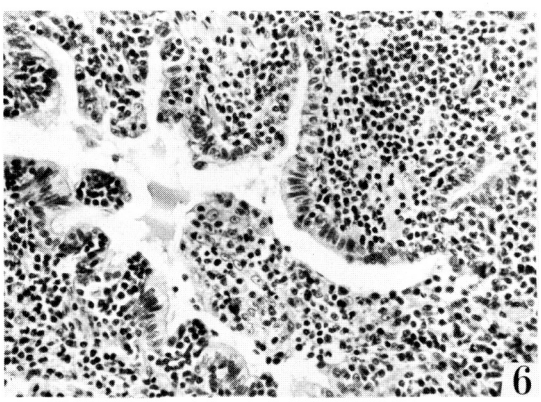


Fig. 6. Lung biopsy specimen from Case 1 showing invasion of bronchiole by small lymphocytes (H & E, x256).

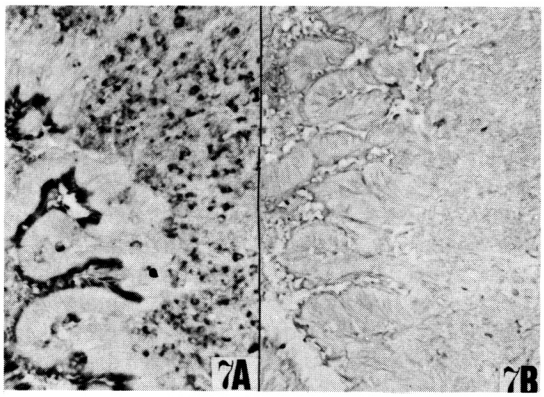


Fig. 7. Lung biopsy specimen from Case 1. Immunoperoxidase staining for kappa chain is positive in the cytoplasm of most of lymphoplasmacytoid cells (7A) and for lambda light chain is negative (7B) in paraffin section (Immunoperoxidase staining, x256).

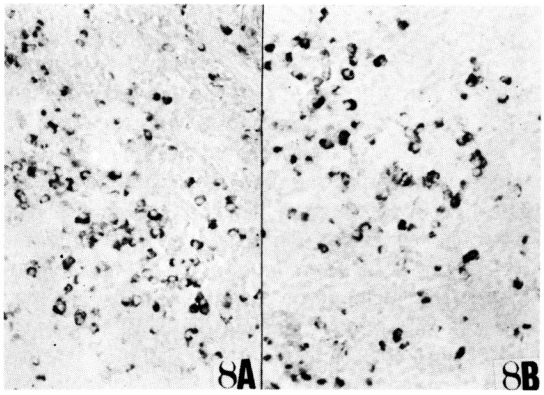
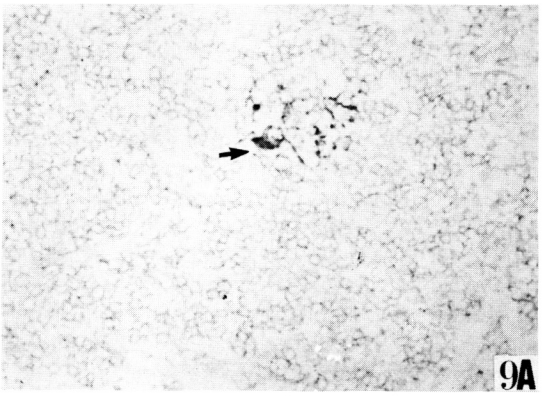
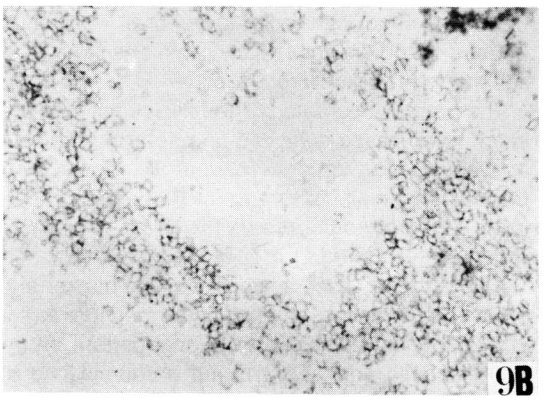
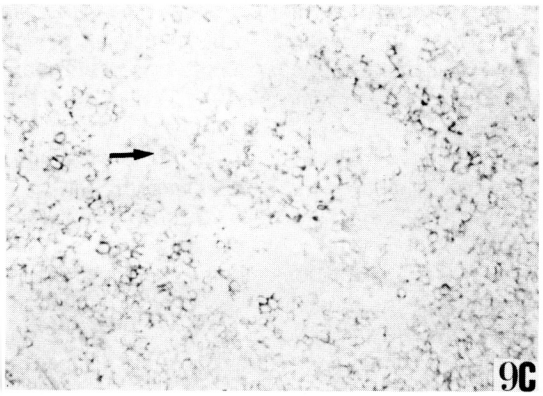


Fig. 8. Lung biopsy specimen from Case 2. Immunoperoxidase staining for kappa light chain (8A) and mu heavy chain (8B) are positive in the cytoplasm of many lymphoplasmcytoid cells in paraffin section (Immunoperoxidase staining, x256).







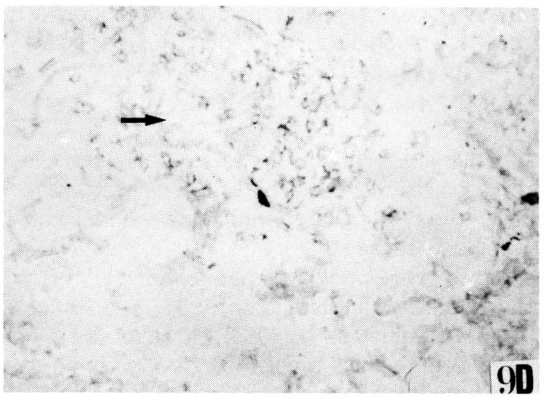


Fig. 9. Immunoperoxidase staining in frozen section from Case 1. (9A) Positive membrane staining for mu heavy chain in most of the tumor cells. Focal staining in extracellular space of germinal center (arrow) is found. (9B) Positive membrane staining for delta heavy chain in many of the tumor cells. Germinal center is negative. Positive staining for kappa light chain (9C) and negative staining for lambda light chain (9D). Germinal center is positive for both light chains (arrows). (Immunoperoxidase staining, x 256).

epithelioid granulomas were present in two cases; in one of them giant cells contained cholesterol clefts or asteroid bodies (Fig. 4A and 4B). Reactive germinal centers were found in two cases (Fig. 5) The alveoli between the lymphoid infiltrates contained desquamated, often foamy macrophages. The invasion of the bronchiole and arterial wall was present in two cases (Fig. 6) and the involvement of the pleura was seen in one case. Immunohistochemical staining on paraffin section showed monoclonal intracytoplasmic immunoglobulin of kappa light chain and mu heavy chain in all three cases in which plasmacytoid differentiation was seen (Fig. 7A-D and Fig. 8A and 8B).

One case, which was well differentiated lymphocytic lymphoma, showed negative staining for all heavy and light chains. Immunohistochemical staining on frozen section showed monoclonal staining for kappa light and mu heavy chains on the majority of neoplastic lymphocytes of all four cases. In Case 1, surface delta heavy chain was positive in addition to mu chain (Fig. 9A-D).

The germinal centers of the follicles which were seen in two cases exhibited polyclonal staining for light chains. The tumor cells were also positive for B1 antigens in all cases and for B2 antigen in one case. Moderate numbers of T1, T4 or T8-positive cells were scattered or grouped in all cases.

Two of three cases in which surface marker and E-rosette formation studies performed on tumor cell suspension showed polyclonal pattern of immunoglobulin and one showed predominance of kappa-positive cells, but not diagnostic for lymphoma. Two cases had considerable numbers of E-rosette forming cells, 45% and 49%, respectively.

DISCUSSION

Malignant lymphoma may involve the lung either as the initial manifestation of the disease or secondary to disseminated lymphoma. Approximately two hundred seventy cases of the primary lymphomas of the lung have been reported in the literatures (Colby and Carrington, 1982, Peterson et al, 1985, McNamara et al, 1969). However, there has been controversial problem in distinguishing true lymphoma from reactive lymphoid processes. From the extensive studies of pulmonary lymphomas Saltzstein (1963, 1969) proposed morphologic criteria for pseudolymphoma and since then many authors considered the lymphoid lesions with germinal centers and a mixture of the cells as a pseudolymphoma.

In 1972 Greenberg et al reported nine cases of lymphomas and psuedolymphomas, two of the latters which progressed to true lymphomas and led to state that pseudolymphoma may occasionally represent a "pre-malignant" or "an intermediate phase between hyperplasia and lymphoma" and the multiplicity of the lesion and destruction of bronchial cartilage by the infiltrates are suggestive findings of malignancy. However, Julstrud et al (1978) did immunocytochemical study on 27 lymphoid lesions of the lung and described the monoclonality of lymphoid cells seemed the most accurate predictor of biologic behavior. During the past several years, the demonstration of monoclonal immunoglobulin in the tumor cells has been repeatedly stressed in differential diagnosis between malignant lymphoma and pseudolymphoma (Julstrud et al, 1978, Faguet et al, 1981, Feoli et al, 1981, Evans, 1982, Knowles et al, 1982, Colby and Carrington, 1983, Kradin and Mark, 1983, Koss et al, 1983, Harris et al, 1984). In recent year Le Tourneau et al (1983) demonstrated monoclonal immunoglobulin in nine of fourteen cases of primary low grade lymphoma of the lung and Peterson et al (1985) described monoclonality in five of six cases. In 1983 Colby and Carrington commented that some of the previously reported cases of pseudolymphoma and lymphocytic interstitial pneumonia that progressed to lymphoma (Julstrud et al, 1968, Pangalis et al, 1980, Evans, 1982, Knowles et al, 1982, Colby and Carrington, 1982) were probably lymphomas all along.

Accordingly, the criteria proposed by Saltzstein seems not to be helpful in distinguishing benign from malignant lymphoproliferative disorders in extranodal sites including lung. Helbert et al (1984) studied nine cases of pulmonary lymphoma and demonstrated monoclonal B-cell proliferation in tissues of cell suspension of tumor in four cases.

However, because that for detection of surface immunoglobulin in lymphoma, fresh-frozen tissue or cell suspension should be used and on formalin-fixed tissue the monoclonality only can be demonstrated on the tumor showing plasmacytic differentiation, an immunologic study may be not successful in most of retrospective studies. In present study, monoclonal population was identified by the immunoperoxidase technique in fresh-frozen sections in all four cases, but in one pure lymphocytic lymphoma the result was negative in paraffin section. Surface marker study on cell suspension was

unsatisfactory in our cases. This result may be explained by the fact that germinal centers were present in the follicles and composed of the mixture of lymphocytes. In summary an immunohistochemical study on fresh-frozen section appears the best way to demonstrate the monoclonality of tumor cells.

Well-differentiated lymphocytic lymphomas of the lung showed an equal sex incidence and an average age of 52 years. Approximately one-third to half of the patients were asymptomatic and it was found on routine chest radiographs. Pulmonary symptoms such as cough, dyspnea, chest pain, hemoptysis and respiratory infections were frequent. Fever, fatigue or weight loss were also present (Papaioannou and Watson, 1965, Greenberg et al, 1972, Colby and Carrington, 1983). The ages of four patients of this study ranged from 48 to 66 years and three were male and one female. Two of them were asymptomatic and the remainders complained of pulmonary symptoms. Most common radiologic findings are a solitary nodule, but multiple nodules or nodule with diffuse infiltrates may be seen (Garrison et al, 1969, Greenberg et al, 1972, Colby and Carrington, 1983). In this study two had solitary nodule and two multiple nodules. A variety of autoimmune disorders have been considered to be associated with pulmonary lymphoproliferative disorders (Colby and Carrington, 1983, Koss et al, 1983). One case of this study had a history of mixed cryoglobulinemia and lupus erythematosus. Monoclonal gammopathy has been reported in association with malignant lymphoma and lymphocytic interstitial pneumonia (Montes et al, 1978, Ward et al, 1971, Liebow and Carrington, 1973).

Especially plasmacytoid lymphocytic lymphoma may show monoclonal immunoglobulin M peak on serum electrophoresis (Faguet et al, 1978, Koss et al, 1983). One patient who had a history of autoimmune disease showed monoclonality of immunoglobulin in tumor. Histologically three cases of present study consisted of a mixture of lymphocytes, plasma cells or plasmacytoid lymphocytes and two cases had well-formed germinal centers within the tumor. Granulomas or multinucleated giant cells containing asteroid bodies or cholesterol clefts were found in two cases. None of the cases had hilar lymph node involvement. Dutcher bodies which are considered as a finding suggestive for plasmacytoid lymphocytic lymphoma (Kradin and Mark, 1983, Koss et al, 1983) were found in 2 of three tumors of that histology.

Destructive bronchial invasion by the tumor was found in two cases and pleural invasion in only one case. From the present study, homogeneous population of small lymphocyte with or without plasmacytoid differentiation, the presence of Dutcher bodies and bronchial and pleural invasion by the tumor cells may be suggestive for malignancy. However, the presence of germinal centers and granulomas and the absence of hilar lymph node involvement seemed not to justify the diagnosis of benignity. As Evans' study (1982) indicated that monoclonality was associated with a more aggressive course, it is evident that monoclonality of lymphoid lesion is the best criteria and predictor of malignancy.

However, since in lymph node well-differentiated lymphocytic lymphoma generally follows an indolent course, treatment should be based on symptomatology (Julstrud et al, 1978, Colby and Carrington, 1983, Le Tourneau et al, 1983, Peterson et al, 1985). Treatment for primary lymphoma of the lung is surgical resection. Radiotherapy or chemotherapy is indicated in cases with incompletely resected lesions and dissemination.

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