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We have identified 13 asbestos workers with lymphoplasmacytic neoplasms: six with chronic lymphocytic leukemia, four with IgG myeloma, two with IgA myeloma, and one with histiocytic lymphoma. The subjects' occupations were varied, but all had experienced protracted asbestos exposure (ranging from 3–37 years). Tumor latency periods were similar to other known asbestos-related malignancies and ranged from 16–41 years. Stigmata of asbestos-related pulmonary disease were evident in 12 subjects. Malignant pleural mesotheliomas coexisted with IgG myelomas in two individuals, an association which seems unlikely to be fortuitous. It has been speculated previously that asbestos may be a lymphoid system carcinogen. Our findings strongly support this view and indicate that patients presenting *de novo* with lymphoproliferative neoplasms should be investigated for previous occupational or environmental exposure to asbestos. (Key words: Asbestos; Asbestosis; Mesothelioma; Pleural plaques; Lymphoma; Myeloma; Chronic lymphocytic leukemia) Am J Clin Pathol 1983; 80: 14–20

THE CARCINOGENIC POTENTIAL of asbestos is now well-recognized and there is little doubt about the relationship between asbestos exposure and malignant mesotheliomas of the pleura and peritoneum.[24,28,29] An issue that is, however, receiving considerable current attention is the association of asbestos exposure with the development of other neoplasms. The latter include bronchogenic carcinomas,[24,28,29] gastrointestinal malignancies,[24,28,29] oropharyngeal cancers,[24,28] laryngeal carcinomas,[21,25,29] and ovarian neoplasms.[24,28,29] Several reports of asbestos-associated lymphocytic and plasma cell dyscrasias have appeared in the literature.[3,4,7–11,13,18–20,22,23,33,34,36,40] These have, however, mainly been anecdotal single case reports encompassing a variety of lymphoproliferative disorders in which no specific tumor category has predominated. Two recent epidemiologic studies have provided tentative support for the role of asbestos as a possible lymphoid carcinogen,[10,24] but definitive conclusions could not be reached in this regard, due either to a paucity of clinical information or to other possible etiologic cofactors.

We previously documented three instances of asbestos-associated neoplasms of B-cell lineage.[18] The number of cases, however, was inadequate to derive definitive conclusions concerning the latency periods of such tumors after initial asbestos exposure and the types of occupational settings associated with the development of these neoplasms. The present study was undertaken in order to address these specific issues. We now report an enlarged series of 13 cases in which lymphoplasmacytic neoplasms were detected in asbestos workers: six instances of myeloma, six of chronic lymphocytic leukemia, and one of histiocytic lymphoma.

Materials and Methods

Selection of Cases

Three cases were reported previously (patients 1, 2, and 7).[18] Ten patients, seen initially by other physicians, were referred to us for hematologic appraisal because of our interest in asbestos-associated hematologic disorders. A definite history of occupational asbestos exposure was elicited in all instances. Each patient had been evaluated previously for the presence of asbestos-related pulmonary disease, as evidenced by parenchymal fibrosis, pleural plaques, bronchogenic carcinoma, or malignant mesothelioma. The diagnosis of pulmonary disease was established by chest radiography (patients 1–3, 5–9, 11, and 13), computerized tomography (patients 2, 5, and 13), thoracotomy (patients 2, 4, 12, and 13) and/or necropsy examination (patients 3 and 4).

Hematologic Evaluation

The diagnosis of chronic lymphocytic leukemia was based on the presence of a persistent lymphocytosis in the peripheral blood and bone marrow. Myeloma was diagnosed on the basis of an abnormal marrow plasmacytosis (exceeding 15% of nucleated cells) in associ-

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tion with a persistent serum monoclonal gammopathy having an M-component concentration in excess of 2 and/or free immunoglobulin light chains in the . The identity of serum M-components and urinary immunoglobulin light chains was established by immunoelectrophoresis. The diagnosis of histiocytic lymphoma (patient 13) was determined by histopathologic examination.

Tissue Analysis for Ferruginous Bodies

The paraffin-embedded tissue block of a biopsy from the lingular region of patient 13 was submitted to Dr. Victor L. Roggley for quantitation of ferruginous bodies. The tissue, which contained tumor, was deparaffinized and then digested in 5.25% sodium hypochlorite and 8.0% oxalic acid. Ferruginous bodies were quantitated by light microscopy.

Results

General Clinical Features

All the subjects were male. Their occupations, circumstances of asbestos exposure, and hematologic diagnoses are listed in Table 1. They had all worked in occupational settings associated with the mining, milling, or handling of asbestos fibers. These occupations all are considered to be potentially at risk for the development of asbestos-related diseases.[2] It is noteworthy that stigmata of asbestos-related pulmonary disease were detected in all but one individual (Table 1). Parenchymal asbestosis was evident in nine subjects; localized pleural plaques were noted in four instances; bronchogenic adenocarcinoma was detected in one case; and two individuals developed malignant pleural mesotheliomas. There was considerable variation in the length of time subjects were exposed to asbestos, ranging from 3–37 years (mean, 22.8 years). Prolonged asbestos exposure, however, was the general rule. Five individuals also were exposed occupationally to materials other than asbestos. Two (patients 1 and 7) were exposed to quartz dust, one (patient 1) to coal dust, two (patients 3 and 8) had worked with fiberglass, and one (patient 11) had inhaled organic solvents.

No single type of asbestos emerged as a common denominator of exposure. Thus, one subject (patient 1) was exposed exclusively to amosite, another (patient 2) was exposed exclusively to chrysotile, while yet another (patient 8) sustained mixed exposure to chrysotile, crocidolite, and amosite. It is probable that the majority of

Table 1. General Clinical Features of Cases Studied

Case	Length of Asbestos Exposure (Years)	Asbestos-related Occupation	Evidence of Prior Asbestos Exposure	Cigarette Smoker Status	Hematologic Diagnosis
1	3	Amosite miner	Parenchymal silico-asbestosis	Unknown	Myeloma
2	25	Installation of auto brake linings	Right malignant mesothelioma	Smoker	Myeloma
3	24	Shipyard insulator	Parenchymal asbestosis and pleural plaques	Non-smoker	Myeloma
4	5	Shipyard electrical technician	Bilateral malignant mesotheliomas	Non-smoker	Myeloma
5	29	Insulator	Parenchymal asbestosis and pleural plaques	Smoker	Myeloma
6	21	Pipe lagger	Parenchymal asbestosis	Ex-smoker	CLL*
7	28	Asbestos mill supervisor	Parenchymal asbestosis and pleural plaques	Smoker	CLL
8	24	Insulator	Parenchymal asbestosis	Smoker	CLL
9	20	Fireproofing insulator	Parenchymal asbestosis	Smoker	CLL
10	16	Shipyard boilermaker	—	Non-smoker	CLL
11	37	Brake lining machinist	Parenchymal asbestosis and pleural plaques	Smoker	CLL
12	35	Shipyard insulator and pipe lagger	Parenchymal asbestosis associated with bronchogenic adenocarcinoma	Smoker	CLL
13	29	Shipfitter and construction site carpenter	Pleural plaques	Non-smoker	Histiocytic lymphoma

* Indicates chronic lymphocytic leukemia

Table 2. Hematologic Features of Myeloma Cases

Age at Diagnosis (Years)	Nature of Serum M-Component	Proportion of Marrow Plasma Cells	Bence-Jones Proteinuria	Tumor Latency Period* (Years)
54	IgA	30%	Negative	28
71	IgG kappa	60%	Negative	25
68	IgA kappa	>30%	Positive	35
60	IgG	30%	Negative	37
72	IgG kappa	30%	Not tested	35
65	IgG lambda	>30%	Positive	21

*Indicates the period between initial exposure to asbestos and the date the neoplasm was first diagnosed

The remaining individuals also had experienced mixed asbestos exposure, when the nature of their occupations is considered.[29,39]

The cigarette-smoking status of each individual also is given in Table 1. Four subjects were non-smokers, seven were regular cigarette smokers, and one was an ex-cigarette smoker.

Lymphoplasmacytic neoplasms were detected in all cases studied. A preponderance of myelomas (six cases) and chronic lymphocytic leukemias (six cases) were noted. Histiocytic lymphoma was diagnosed in one subject.

Hematologic Features

The hematologic features of the myeloma cases are summarized in Table 2. When myeloma was diagnosed, the subjects' ages ranged from 54–72 years (mean, 65.0 years). The serum M-component was of the IgG variety in four instances, and IgA in two. Bence-Jones proteinuria was detected in two cases. The tumor latency periods after initial asbestos exposure were lengthy, ranging from 21–37 years (mean, 30.2 years). A striking finding was the coexistence of malignant pleural mesothelioma with IgG myeloma in two individuals. The histologic features of these neoplasms in patient 4 are illustrated in Figure 1.

Table 3 summarizes the hematologic features of the cases of chronic lymphocytic leukemia. The subjects' ages ranged from 50–62 years (mean, 57.7 years) at the time of diagnosis. The tumor latency periods were similar to those noted in the myeloma cases, ranging from 16–41 years (mean, 30.2 years).

One individual (patient 13) had been investigated elsewhere for progressive effort dyspnea and interstitial pulmonary roentgenographic infiltrates. A lingual biopsy was performed when the subject was 61 years old. Microscopic examination showed extensive pulmonary infiltration by large lymphoid cells, many of which had prominent nucleoli. Mitoses were numerous (Fig. 2). The features were consistent with a histiocytic lymphoma. Occasional ferruginous bodies were evident in areas infiltrated by the neoplasm (Fig. 2). Analysis of the tumor tissue block revealed 521 ferruginous bodies/g of wet lung. The tumor was diagnosed 35 years after the subject's initial exposure to asbestos.

Discussion

Exposure to asbestos has been documented infrequently in association with neoplasms of the hematopoietic system. However, when this association has been observed, lymphoid and plasma cell dyscrasias have predominated. The latter include chronic lymphocytic leukemia,[4,18,20] myeloma,[9,13,18,20,33,40] malignant lymphoma,[10,11,13,19,20,23,34] Waldenström's macroglobulinemia,[13] immunoblastic lymphadenopathy,[22] alpha chain disease,[36] amyloidosis,[3,7] and giant lymph node hyperplasia.[8] Nearly all have been single case reports. In most instances, the subjects' occupations were not stated and few details were provided concerning the circumstances of asbestos exposure.

In the present study, we have identified 13 individuals with asbestos-associated neoplasms of the lympho-reticular system (six cases of myeloma, six of chronic lymphocytic leukemia, and one of histiocytic lymphoma). A definite history of occupational asbestos exposure was elicited in each instance. There were, however, no unusual features of our cases which clearly distinguished them from the spectrum of clinical and pathologic patterns seen when the same lymphoplasmacytic neoplasms occur within the general population. Nevertheless, our

FIG. 1 (*upper*). Coexistence of malignant pleural mesothelioma (panel A) and myeloma (panel B) in Case 4. Panel A (*left*) shows features of a tubulo-papillary epithelial neoplasm, stained with hematoxylin and eosin (original ×320). Panel B (*right*) shows marrow replacement by numerous bizarre plasma cells with prominent nucleoli. Hematoxylin and eosin (original ×480).

FIG. 2 (*lower*). Histiocytic lymphoma of lung in Case 13 composed of lymphoid cells with numerous mitotic figures. Hematoxylin and eosin (original ×360). Arrow indicates a ferruginous body in inset panel.

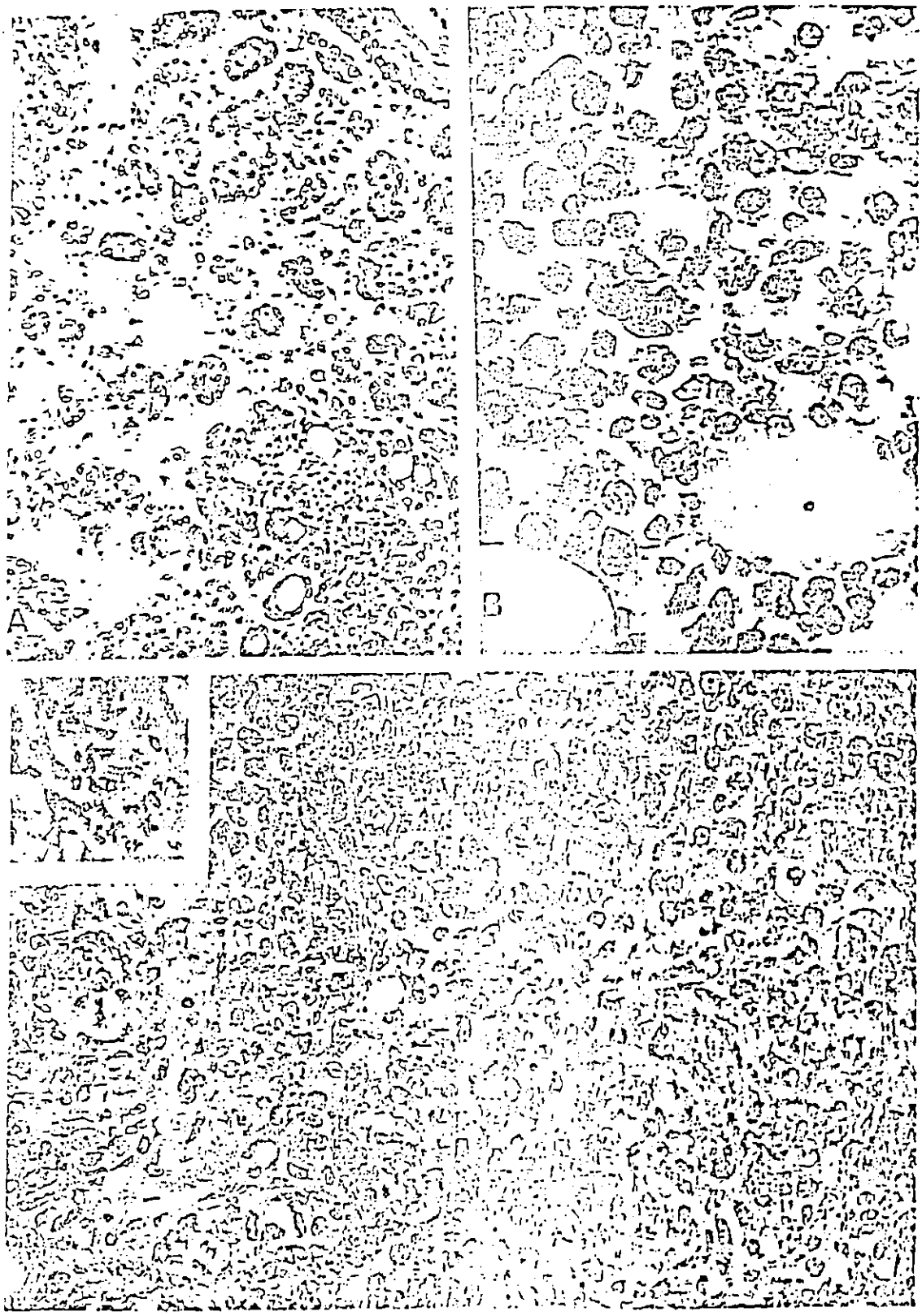
A
B

Table 3. Hematologic Features of Chronic Lymphocytic Leukemia Cases

	Age at Diagnosis (Years)	Total Leukocytes ($\times 10^{-3}/\mu L$)	Proportion of Lymphocytes	Presence of Organomegaly	Tumor Latency Period* (Years)
	61	30.4	79%	None	28
	50	76.0	90%	Lymphadenopathy and hepatomegaly	24
	59	26.6	78%	None	32
9	55	155.0	94%	Hepatosplenomegaly	16
	62	20.0	75%	Lymphadenopathy and hepatomegaly	41
12	59	19.0	65%	None	40

*See explanation, see Table 2.

six cases of chronic lymphocytic leukemia are of special interest, since no other occupational environmental agent has been implicated previously in the cause of this lymphoid neoplasm.

The subjects' occupations were varied, but each individual had worked with asbestos-containing materials in jobs potentially at risk for developing asbestos-related diseases.[2] Exposure to asbestos had been prolonged in every instance, ranging from 3–37 years. Since the airborne asbestos concentrations were not monitored at the workplace at the time of exposure, there is no reliable means of assessing the severity of asbestos exposure in these subjects. However, it is likely that those individuals who had worked in United States shipyards during World War II (patients 3, 4, 6, 10, 12, and 13), and those who were employed in the mining (patient 1) and milling (patient 7) of asbestos had sustained "heavy" asbestos exposure.[39] The detection of stigmata of asbestos-related pulmonary disease in 12 cases provides additional objective evidence of prior asbestos exposure in these individuals. In all instances, the lymphoid and plasma cell dyscrasias manifested clinically a considerable time after the initial asbestos exposure occurred in the workplace. Comparable latency periods have been noted previously with respect to mesotheliomas and bronchogenic carcinomas in asbestos-exposed populations.[29,37,38]

A key question posed by this study is whether asbestos exposure is, indeed, causally linked to the development of lymphoproliferative malignancies. Because our cases were mainly referrals from widely differing geographic regions within the United States, it is not possible to determine whether these cases reflect an increase of lymphoid and plasma cell malignancies over those expected in the general population. There is, however, a considerable body of circumstantial evidence that supports a cause-effect relationship between asbestos exposure and lymphoid system neoplasia.

In a study of 68 asbestos workers, Lieben documented 35 malignancies.[30] Among the latter, a disproportionate number (19%) were lymphoid cancers. Gerber, who subsequently studied 1,334 autopsy specimens in patients aged 50 years or older, noted five hematologic malignancies (four of which were lymphoid) among 35 cases of asbestosis.[32] The incidence of these asbestos-associated hematopoietic neoplasms (14.3%) was significantly higher than the 2.8% overall incidence of such tumors in the total autopsy population of comparable age. More recently, Robinson and co-workers reviewed death certificates from a cohort of 3,276 white male asbestos workers employed in a manufacturing facility.[34] The authors reported four deaths resulting from "lymphosarcoma," and three from malignant lymphoma, whereas only 3.28 deaths were expected on the basis of age-specific rates for this tumor category. They suggested that male asbestos workers had an increased risk of developing lymphoid cancers. A similar mortality excess for lymphoid neoplasms, during the period 1950–1960, was observed in a study of shipyard workers and shipfitters in the state of Washington.[25] In the latter study, however, no mention was made of possible asbestos exposure in these occupational settings.

Of particular interest is a recent preliminary epidemiologic case-control study of non-Hodgkin's large cell lymphomas primary to the gastrointestinal tract.[10] In that study, Dworsky and associates documented previous heavy asbestos exposure in 11 of 22 cases, but in only two of matched neighborhood controls. The interpretation of their data, however, is clouded by a prior history of malaria, a disease characterized by immunologic stimulation,[30] in many of the cases having prior asbestos exposure.

There are reports of asbestos-related lymphoid and plasma cell dyscrasias produced in experimental animals. In one study, injection of asbestos into the air sacs of White Leghorn fowls induced one tumor consistent with a plasmacytoma and another classed as a "reticulosarcoma."[31] In another study, the intraperitoneal instillation of chrysotile asbestos in mice evoked considerable amyloid deposition in the livers and spleens of these animals.[33] The nature of the amyloid, however, was not defined.

The development of lymphoproliferative neoplasms in asbestos-exposed individuals may result from an underlying abnormality of immunologic homeostasis in these people, since striking alterations of immunologic function have been described in asbestos workers.[17] These abnormalities reflect an imbalance between defective cell-mediated immunity and hyperactive B-cell function, which may relate to deficient suppressor T-cell function in these subjects.[12] There is also evidence from animal experiments, that asbestos exposure can stimulate the immune system. Alveolar macrophages from asbestos-exposed rats have been shown to induce splenic lymphocyte proliferation,[26] an event preceded by enhanced attachment of these lymphocytes to the macrophages.[27] Moreover, the repeated intratracheal instillation of chrysotile in sheep has been associated with enhanced proliferative responses of bronchoalveolar lymphocytes to certain mitogens.[33] These phenomena may relate to the enhanced production of interleukin-1, a potent lymphoid mitogen, noted after asbestos exposure.[14]

It has been shown, in other situations, that lymphoid neoplasia may result from persistent immunologic stimulation in a milieu deprived of normal immunoregulatory influences.[31,32] Such neoplasms have been mainly histiocytic lymphomas ("immunoblastic sarcomas"). There is evidence, however, that myelomas can, under certain circumstances, occur excessively with diseases characterized by chronic antigenic stimulation or altered immunoregulation.[5,15,16] It is therefore conceivable that asbestos exposure may similarly provide a host environment that predisposes to the development of neoplastic immunocytes.

The finding of ferruginous bodies in the digest of the tumor tissue block from our case of pulmonary lymphoma (patient 13) is of interest, since the neoplasm occurred in the organ of primary asbestos insult. The number of ferruginous bodies identified in this case (52 i/g of wet lung) was within the range obtained for asbestos workers with mesothelioma or bronchogenic carcinoma (Roggley VL: personal communication). We have no information regarding the ferruginous body or asbestos content of the affected hemopoietic organs in our cases of myeloma and chronic lymphocytic leukemia. There is, however, evidence that inhaled asbestos can translocate from the lung to other viscera. Thus, Auerbach and co-workers have identified ferruginous bodies in the spleen and other organs anatomically remote from the lungs in asbestos workers.[1] The observation by Brody and associates[6] that chrysotile asbestos can breach alveolar capillary walls within five hours of inhalation also is pertinent in this regard.

The coexistence of IgG myeloma with malignant mesothelioma in two of our patients (patients 2 and 4) is especially noteworthy. Although the development of a second cancer in myeloma patients is not uncommon,[41] this particular tumor combination has only been documented twice by others.[33,40] In each instance, a history of asbestos exposure was either known or inferred. The coexistence of mesothelioma and chronic lymphocytic leukemia also has been reported in an asbestos worker.[4] The probability of myeloma and mesothelioma occurring by chance in an individual not exposed to asbestos is, however, remote, since only one instance of this tumor combination was found in a survey of a segment of the general population of the United States involving 20 million individuals who were followed for three consecutive years (Young JC, National Cancer Institute: personal communication). The coexistence of these two neoplasms in two of our patients thus seems unlikely to be a fortuitous occurrence.

It is conceivable that the lymphoplasmacytic neoplasms we have observed may be a consequence of occupational exposure to materials other than asbestos. Exposure to asbestos was, however, the only factor common to all our cases. Since seven subjects were cigarette smokers and one was an ex-smoker, it is possible that cigarette smoking also could be a cofactor, although the number of cases is too small to draw specific conclusions in this regard.

Although our observations are based on selected case material, they clearly underscore the need for large-scale epidemiologic studies to determine whether asbestos exposure can definitely be linked causally to lymphoid and plasma cell dyscrasias. Such studies should not only be performed on different categories of asbestos workers, but they also should include patients presenting *de novo* with lymphoplasmacytic neoplasms.

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