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Asbestos-Associated Neoplasms of B Cell Lineage

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Three different neoplasms of B cell lineage, chronic lymphocytic leukemia, immunoglobulin A (IgA) myeloma and immunoglobulin G (IgG) myeloma were detected in three patients who had been occupational exposure to asbestos dust. Two of these patients had coexistent pulmonary asbestosis, whereas the third patient had pleural mesothelioma subsequent to his initial presentation with myeloma. Defective cell-mediated immunity and hyperactivity of B cell function have previously been noted in patients with asbestosis. We suggest the possibility that these asbestos-associated immunologic derangements may predispose to the development of immunoproliferative and lymphoproliferative neoplasms, since such tumors have been observed in a variety of other settings characterized by protracted hyperactivity of the immune system.

Exposure to asbestos dust has been [illegible] with an increased risk of a variety of malignancies primarily of the [illegible]. Although a cause-effect relationship has been suggested, only asbestos-related malignant mesotheliomas and bronchogenic carcinomas have been [illegible]. Increasing evidence that exposure to asbestos may [illegible] the subsequent development of other neoplasms, including cancers of the gastrointestinal tract, [illegible] and mesothelioma [1].

There have been comparatively few reports suggesting a possible association between asbestos exposure and neoplasms of the lymphoreticular system. However, in those instances where such an association has been documented, there has been a striking predilection for lymphoproliferative and immunoproliferative neoplasms. These have included chronic lymphocytic leukemia/lymphoma [2–4], chronic lymphocytic leukemia [5], myeloma [6–8, 10] and Waldenstrom's macroglobulinemia [9]. We report three cases here, in which asbestos-associated neoplasms of B cell lineage (one case of chronic lymphocytic leukemia and two cases of plasma cell dyscrasia) were found.

[illegible]

CASE REPORTS

Case 1. [illegible] Clinic of the Johannesburg General Hospital [illegible] assessment of asbestos-related pulmonary disease. He had been employed for approximately three years in 1947–1950 and again for nine months in the Transvaal province of South Africa. His exposure to asbestos had been heavy since he was [illegible] at the mine. The patient was subsequently employed in various coal and gold mines in South Africa, [illegible] to his present retirement. [illegible] with streptomycin, isoniazid and [illegible].

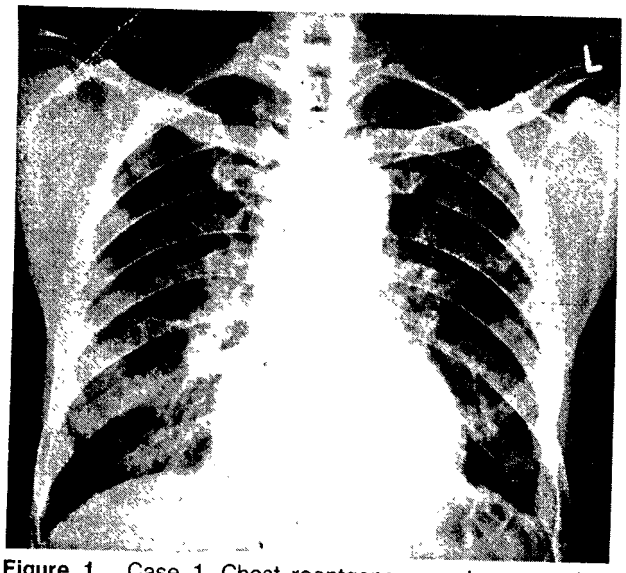


Figure 1. Case 1. Chest roentgenogram demonstrating obliteration of the left costophrenic angle as well as thickening of the right horizontal and oblique fissures. Bilateral reticulonodular infiltrates are noted in lower lobes of both lungs.

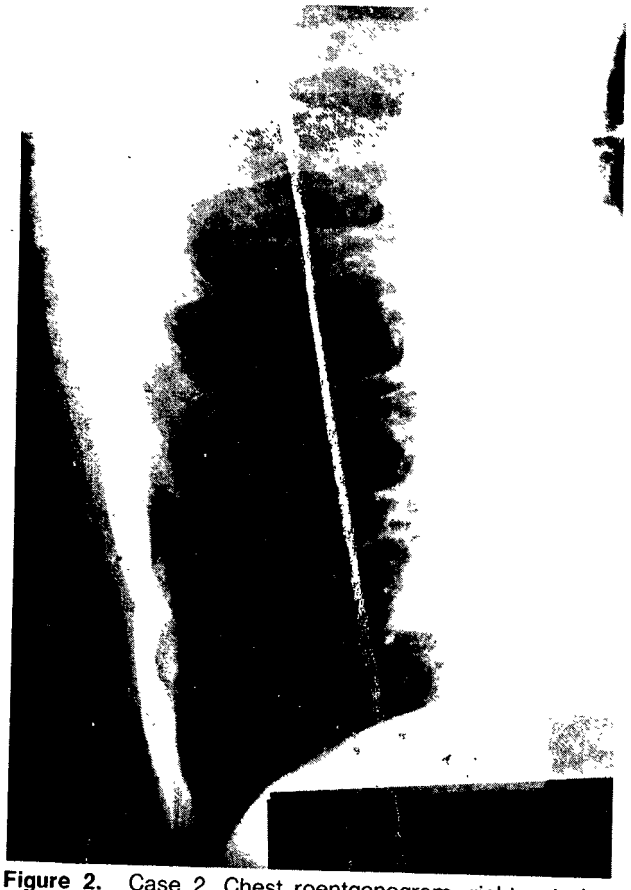


Figure 2. Case 2. Chest roentgenogram, right anterior oblique view, demonstrating pleural thickening and plaque formation.

enced progressive dyspnea on effort and a chronic cough, productive of mucoid sputum.

Physical examination disclosed no cyanosis or clubbing, but decreased air entry was evident bilaterally, affecting the left side predominantly. Rales were present in the left mid-zone and left basal regions. There was no cardiomegaly or congestive heart failure, and no bone tenderness, hepatosplenomegaly or lymphadenopathy were noted.

A roentgenograph of the chest demonstrated bilateral reticulonodular infiltrates involving the lower lobes of both lungs and perihilar regions. The horizontal and oblique fissures on the right side were thickened, and blunting of the left costophrenic angle was noted (**Figure 1**). There was also pleural thickening along the diaphragmatic surface. These findings were consistent with healed tuberculosis, asbestos-related pleural thickening and parenchymal silico-asbestosis. A roentgenographic skeletal survey did not reveal any osteolytic lesions.

Arterial blood gas analysis showed an oxygen tension (pO_2) of 52.5 mm Hg, a carbon dioxide tension (pCO_2) of 35.5 mm Hg, a pH of 7.38 and a blood oxygen saturation of 85 per cent. The blood urea nitrogen was 12 mg/dl and the serum calcium 9.0 mg/dl. The hemoglobin level was 16.9 g/dl, the hematocrit value 50.7 per cent, the white cell count 7,700/μl (69 per cent segmented neutrophils, 25 per cent lymphocytes, 5 per cent monocytes and 1 per cent eosinophils) and the platelet count 155,000/μl. The erythrocyte sedimentation rate was 55 mm/hour. The total protein was 8.6 g/dl with 3.9 g/dl of albumin. A prominent serum M component was detected, measuring 2.7 g/dl. The serum immunoglobulin A (IgA) measured 2,972 IU/ml, immunoglobulin G (IgG) 145 IU/ml, immunoglobulin M (IgM) 163 IU/ml and immunoglobulin E (IgE) 900 IU/ml. Bence Jones protein was not detected on electrophoretic analysis of the urine. The patient's serum was positive for rheumatoid factor by the latex fixation test [12] (titer 1:1280). A bone marrow aspirate revealed 20 per cent plasma cells including numerous atypical and immature forms. The morphologic features of the bone marrow aspirate, in association with an abnormal serum IgA M-component, were consistent with a diagnosis of IgA myeloma.

Case 2. The patient was a 61 year old white man who presented in July 1975 for assessment of asbestos-related pulmonary disability. He had worked in the mining industry in Southern Africa almost continually since the age of 20. After approximately 13 years as a gold miner, the patient was subsequently employed for 28 years as an asbestos milling supervisor at a chrysotile asbestos mine in Swaziland. He was exposed mainly to chrysotile fibers, although he also supervised the mixing of chrysotile and crocidolite asbestos for the manufacture of insulation materials. For five years during this period, he also sustained heavy, intermittent exposure to crocidolite and amosite asbestos, while assisting in the dismantling and reconstruction of asbestos mills in South Africa. The patient smoked about 20 cigarettes daily for 40 years and had a cough, productive of mucoid sputum, and dyspnea on mild exertion.

Physical examination revealed no cyanosis or clubbing. Cardiovascular examination was within normal limits. The chest was barrel-shaped and, on auscultation, diminished air entry and bilateral basilar, crepitant rales were heard. There was no hepatosplenomegaly or lymphadenopathy.

Chest films revealed bilateral fine, linear opacities in the lower lobes of the lungs. Bilateral pleural thickening was also noted, with pleural plaques evident along the lateral costal margins (**Figure 2**). These findings were consistent with asbestos-related pleural thickening and parenchymal asbestosis.

The hemoglobin level was 16.1 g/dl, the hematocrit value 45.2 per cent, the white cell count 30,400/μl (79 per cent lymphocytes, 19 per cent segmented neutrophils and 2 per cent monocytes) and the platelet count 235,000/μl. As aspirate of bone marrow showed replacement by small lymphocytes. The serum total protein was 6.9 g/dl with 4.3 g/dl of albumin. The serum IgA measured 58 IU/ml, IgG 98 IU/ml, IgM 39 IU/ml and IgE 100 IU/ml. No ferruginous bodies or malignant cells were detected in the sputum.

The morphologic features of the peripheral blood and bone marrow were consistent with a diagnosis of chronic lymphocytic leukemia. The B cell nature of the leukemia was illustrated by the large proportion (76 per cent) of surface IgM-positive lymphocytes in the peripheral blood, as shown by immunofluorescence [11]. The percentage of circulating T cells, as determined by spontaneous rosetting with sheep erythrocytes [12], was correspondingly reduced (12 per cent).

Case 3. The patient was a 71 year old white man who was hospitalized in Washington, D.C. in March 1977 because of severe low back pain. He had experienced heavy exposure to chrysotile asbestos for 25 years, through the daily installation of brake lining in automobiles. Physical examination disclosed mild pallor and bone tenderness over the upper lumbar vertebral area. Roentgenograms of the spinal column demonstrated generalized osteoporosis and collapse of the eighth thoracic and the first and second lumbar vertebral bodies. Chest roentgenograms revealed normal lung parenchyma and pleura. Osteolytic lesions were present in multiple ribs, in the left scapula and in the right humerus (**Figure 3A**).

The hemoglobin level was 8.6 g/dl, the hematocrit value 26.8 per cent, the white cell count 5,100/μl, the platelet count 230,000/μl and the reticulocyte count 1.1 per cent. A differential leukocyte count showed 5 per cent band forms, 34 per cent segmented neutrophils, 42 per cent lymphocytes, 3 per cent basophils and 16 per cent monocytes. The peripheral blood smear showed prominent red cell rouleaux formation. The blood urea nitrogen was 25 mg/dl, serum creatinine 1.3 mg/dl, uric acid 11.0 mg/dl, calcium 9.3 mg/dl and serum total protein 11.2 g/dl with 3.4 g/dl of albumin. Serum protein electrophoresis showed a monoclonal spike in the gamma fraction with an M component of 6.0 g/dl. The serum IgG measured 893 IU/ml, IgA 27 IU/ml and IgM 22 IU/ml. Serum immunoelectrophoresis showed an abnormal heavy arc of IgG, kappa type. No Bence Jones proteinuria was demonstrated. A bone marrow aspirate and biopsy revealed sheets of plasma cells with numerous immature forms.

A diagnosis of IgG myeloma was made. Treatment was begun with intermittent melphalan and prednisone, whereupon symptoms of bone pain subsided. Serum protein electrophoresis, four months later, showed the monoclonal spike had decreased to 3.1 g/dl.

The patient was readmitted in February 1978 because of increasing right-sided chest pain and progressive dyspnea. Examination revealed tachypnea and absence of breath sounds in the lower half of the right lung. A repeat chest roentgenogram (**Figure 3B**) revealed a moderate pleural effusion on the right side. Computerized thoracic tomography confirmed the right pleural effusion, together with multiple subpleural masses and a nodule on the right pericardial surface. An exploratory thoracotomy revealed 300 ml of sanguineous pleural fluid, and multiple tumor implants of various sizes were found on the diaphragm as well as the parietal and visceral pleura. Histopathologic examination of the tumors showed the features of an epithelial variety of malignant mesothelioma (**Figure 4**). Ferruginous bodies were not ob-

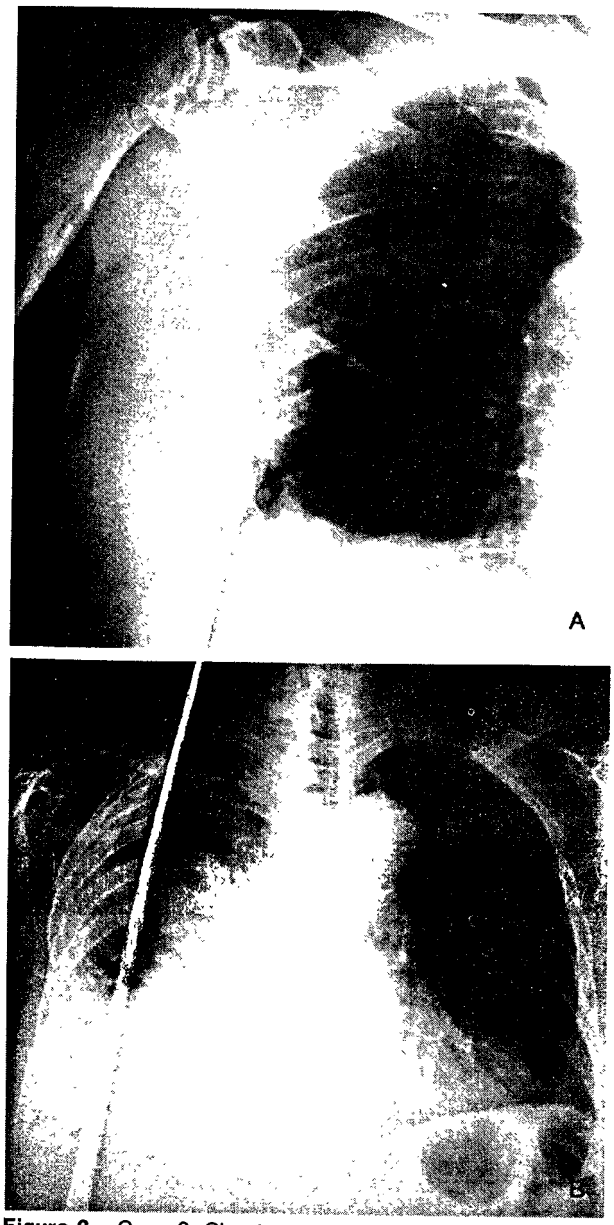


Figure 3. Case 3. Chest roentgenogram. **A,** film obtained in November 1977 demonstrates pleural thickening on the right. An osteolytic lesion is evident in the upper right humerus. **B,** film obtained on admission in February 1978 demonstrates a pleural effusion on the right side.

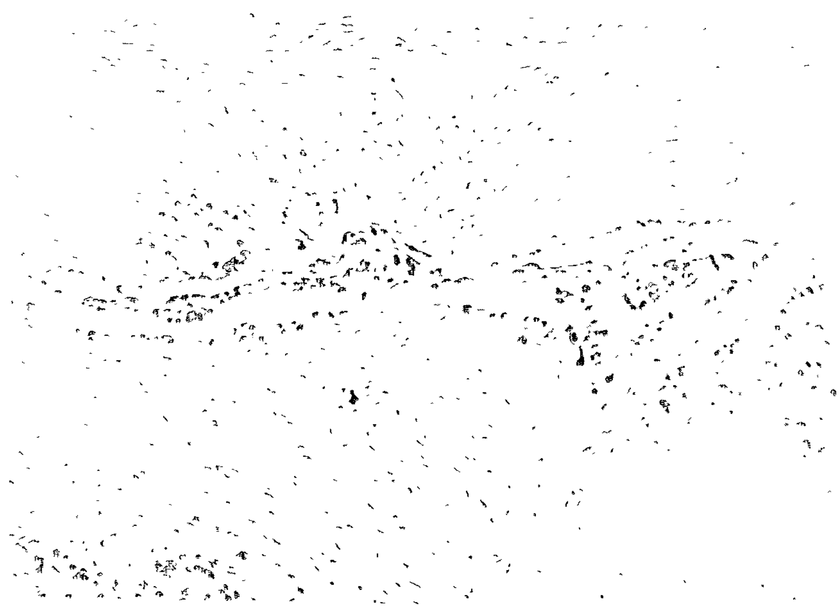


Figure 4. Case 3. Biopsy specimen of a thoracic tumor nodule demonstrating [illegible] epithelial type of malignant mesothelioma. Acinar spaces, lined by flattened columnar or cuboidal epithelium, are surrounded by a fibrocellular stroma. Hematoxylin and eosin stain; magnification × 250, reduced by 35 per cent.

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[illegible] study each [illegible] a clear-cut [illegible] occupational exposure to asbestos dust. [illegible] asbestos inhaled was common to all [illegible] to crysotile [illegible] crocidolite and [illegible] in Case [illegible] whereas [illegible] Cases 1 and 3 [illegible] were exposed exclusively to either amosite [illegible]. Well-defined roentgeno-[illegible] asbestos-related pleural thickening [illegible] asbestosis were evident in Cases 1 [illegible] in Case 3 a pleural mesothelioma de-[illegible] plasmacytoma, myeloma and [illegible] although highly unusual, has [illegible].

[illegible] incidence of chronic lymphocytic [illegible] Cases 1 and 2, respectively, is of particular [illegible] patients were referred with 24 [illegible] asbestos-related pulmonary disability [11,12] [illegible] of patients was insufficient [illegible] the combined incidence of these two lymphoid neoplasms [illegible] per cent [illegible] the 26 patients with asbestosis appears [illegible] greater than the combined incidence for [illegible] categories in the general South African population [illegible] and 0.8 per 100,000 for chronic lymphocytic [illegible] and myeloma, respectively [13].

In an earlier study of 62 hospitalized patients [illegible] asbestosis [6], Lieben detected a disproportionate [illegible] number of asbestos-associated lymphoproliferative [illegible] neoplasms [illegible] malignancies. Subsequently, [illegible] [8] [illegible] 135 autopsies described five instances of [illegible]poietic malignancies [illegible] amongst 3[illegible] cases of asbestosis. The incidence [illegible] asbestos-associated hematologic neoplasms [illegible] cent) was found to be significantly higher than the [illegible] per cent over-all incidence of such tumors in the [illegible] autopsy group. Recent observations in Yugoslavia [illegible] also suggested a possible relationship between [illegible] and asbestos exposure (D. Jovanović, personal communication).

Clinical studies of patients with asbestosis [illegible] revealed a remarkable abundance between the manifestations of the cellular and humoral components [illegible] immune response [11,12,[illegible],14]. These [illegible] played defective expression of cell-mediated [illegible] both in vivo and in vitro [11,14] and decreased [illegible] of circulating T cells were noted in their [illegible] blood [12,15]. On the other hand, increased con[illegible]tions of all classes of serum immunoglobulins [12,[illegible]] and secretory IgA [12] were observed, together [illegible]

ACKNOWLEDGMENT

REFERENCES