

Original Contributions

MALIGNANT MESOTHELIOMA WITH MINIMAL ASBESTOS EXPOSURE*

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Abstract

The association of malignant mesothelioma and asbestos fibers is well established. The minimal exposure that may produce the tumor is not known. The present report documents the minimal exposure by thorough examination of occupational history and personal hobbies, and counting of the number of asbestos fibers in the lungs. The evidence for the elemental composition of asbestos fibers by electron probe (EDAX) is also presented.

The association of an increased incidence of malignant mesothelioma in industrial workers and others having extensive exposure to asbestos is well established epidemiologically.¹⁻⁴ The maximal safe exposure level remains a major problem because the presence of some asbestos in the lungs has been demonstrated in a large segment of the population.⁵ The great individual variation in responses to exogenous chemicals further complicates the problem.

The case of malignant mesothelioma reported here is significant because we have established the presence of pulmonary asbestos fibers by means of electron

probe analysis and we have obtained a complete and thorough history documenting a most casual and minimal exposure to asbestos in a nonsmoker. Estimation of the number of asbestos fibers in the lungs suggests the low level exposure and establishes that, for some individuals at least, slight exposure to asbestos can result in malignant mesothelioma.

CASE REPORT

A 59 year old white male, a non-smoker, was in relatively good health until July 1975, when he developed mild

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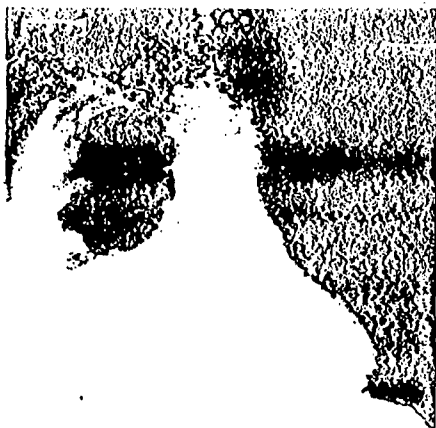


Figure 1. Chest x-ray film reveals massive right sided pleural effusion and thickening of the pleura with multiple nodules. The left lung appears to be normal.

chronic cough and exertional dyspnea. Chest x-ray examination showed tumor masses in the right upper and middle lobes and right pleural effusion (Fig. 1). Exploratory thoracotomy revealed tumor nodules studding the entire right parietal and visceral pleurae and a portion of the pericardium. Biopsy examination of this tumor was reported initially as "large cell undifferentiated carcinoma." A thorough metastatic work-up including upper gastrointestinal series, barium enema, and liver and spleen scans was negative. Subsequently the patient was treated with mul-

tipl chemotherapy agents (cytotoxic, methotrexate, 5-fluorouracil, adriamycin, and procarbazine) without response. His course had been one of gradual deterioration with marked shortness of breath and weight loss, and he expired 10 months after the onset of symptoms.

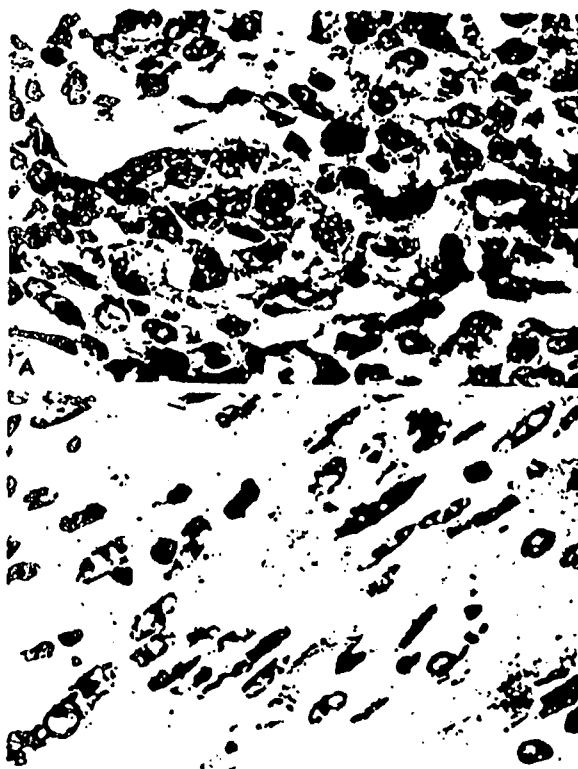
An extensive history of more than 30 years was obtained from the wife of the deceased. At no time in his life did he smoke. He grew up in Pennsylvania and graduated from a well known institute of technology as an engineer. Following a year of business management training by a large building materials firm, he served in the Army Chemical Warfare Division during World War II. However, he had no specific exposure to asbestos or other known respiratory toxins. Following the war he returned as an executive in the firm where he worked until six years prior to examination. He transferred to a fiberglass firm in a similar executive position where he worked until his death. At no time in his life did he work with building material production or fabrication. As an executive he occasionally inspected major construction sites but did not personally handle building materials. His avocational interests centered on sports. He was not a "do-it-yourselfer" and did not have a workshop at home or power tools. We were unable to uncover any activity that would suggest more than the casual exposure alluded to.

The autopsy revealed matted tumor masses encasing the entire right lung with extension to the subcutaneous tissue of the right chest wall and pericardium (Fig. 2). Microscopically the tumor consisted of



Figure 2. The autopsy specimen of the right lung is completely encased in a matted, pleural tumor mass. The tumor also invades by direct extension into the pericardium, diaphragm, and right chest wall.

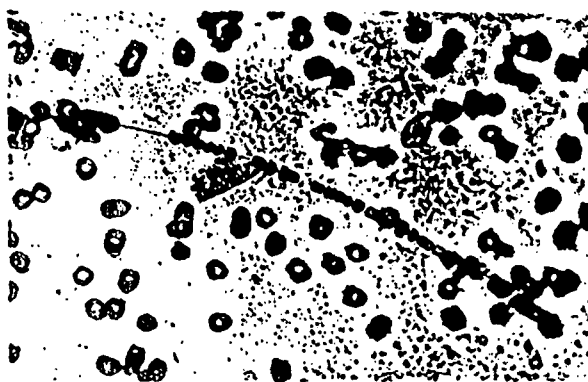
Figure 3. Sections of tumor from right pleura showing two different patterns (epithelial and mesenchymal) of tumor cells, characteristic of malignant mesothelioma. A. Sheets and aggregates of malignant epithelial cells. B. Spindle cells (sarcomatous pattern) with hyperchromatic nuclei.



components resembling both epithelial and mesenchymal cells characteristic of mesothelioma (Fig. 3).⁶ Five grams of parenchymal tissue was taken from each lung and digested with sodium hypochloride by the method of Smith and Naylor.⁷ The

extraction solution was filtered through a nuclepore membrane (5 μ). Figure 4 shows one of the unstained asbestos bodies on a filter membrane under light microscopy. The entire membrane with retained fibers and crystals was coated with a thin

Figure 4. Extracted asbestos body retained on nuclepore membrane after filtration. The center asbestos fiber (note) and beaded portions are clearly discernible. ($\times 400$.)



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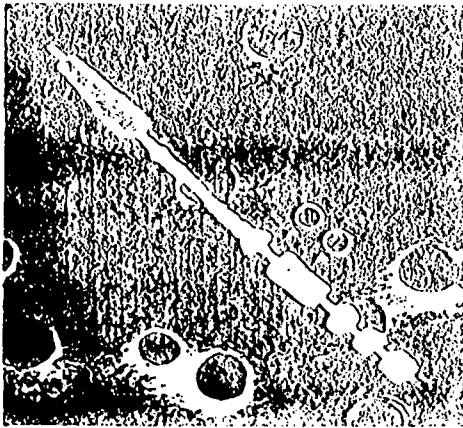
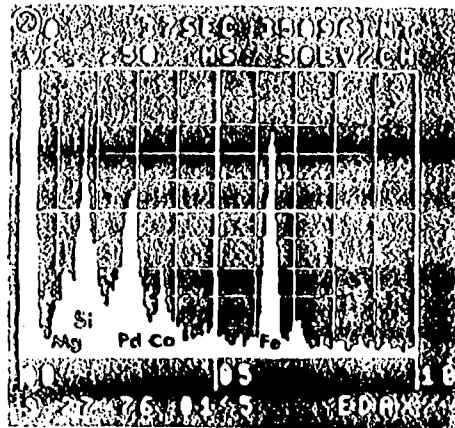


Figure 5. Asbestos body coated with a thin layer of palladium and viewed by scanning electron microscopy. The center fiber (core) and beaded portion are clearly seen. The background nucleopore is 5 μ m in diameter. (x 10,000.)

layer of palladium and then subjected to electron probe x-ray dispersion analysis. EDAX (energy dispersive x-ray analyzer) was used to analyze the x-ray dispersive spectrum of different elements.* Figure 5 depicts one of the asbestos bodies seen under a low power scanning electron microscope. The fiber core and beaded body portions are readily discernible. By directing the electron beam to either a thin



of asbestos bodies per 5 gm. of lung after the 1940s and also a gradual increase in the number of asbestos bodies per 5 gm. of lung with increased age at death.

The case we have presented illustrates that minimal exposure to asbestos can cause mesothelioma. We took multiple 5 gm. samples from both lungs and counted the asbestos fibers. There was an average of 168 fibers per 5 gram sample of lung. This figure is 14 times higher than the age-matched control (12.5 gm.) and about six times higher than the mean of asbestos fibers (28.6 5 gm.) in a control population reported by Bhagavan and Koss.⁵ If one assumed that both lungs weighed 1500 gm., there would have been approximately 50,400 fibers ($168 \times \frac{1500}{5}$) in the lungs. If one assumes the average exposure time for 20 years, the yearly accumulation of fibers in the lung would be 2520 per year (50,400/20). This figure is minuscule if we consider the enormous numbers of fibers that will be inhaled in an environment of 2 fibers per ml. set by the Occupational Safety and Health Administration as the safety limit.¹¹

Our method of quantitation of fibers differs markedly from that of Pooley.¹² He extracted the fibers from 6 µm. histologic section samples, whereas we used 5 gm. wet tissue samples. Our samples therefore are many thousands of times larger than his. We believe that the case presented here would have been included in his category 6 (zero fibers found per grid).

It is well established that the human body can remove most of the fibers inhaled. The accumulation of asbestos fibers in this patient to a level above the control levels resulted from either exposure or diminished clearance. The well documented minimal exposure in this case suggests that the latter may be important. The margin of safety between the average exposure and the level at which some individuals develop malignant mesothelioma may be narrow indeed.

With an awareness of the nonspecificity of the so-called "asbestos" body,¹³ we established the identity of the fibers and crystals by use of electron probe analysis. As shown in Figures 6 and 7, the chemical components (Si, Mg, Ca, Fe) are characteristic of asbestos.^{14,15} One important ob-

servation is the relatively small amount of iron in the core (fiber). Yet a large amount of iron is present on the beaded body portion. This finding is in agreement with the notion that the coating around the fiber is the aggregation of ferritin or ferritin-like particles deposited on the fiber surface.¹⁶

We report this case to emphasize again the association of malignant mesothelioma with a very limited exposure to asbestos, and the validity of (relatively) quick identification of "asbestos" bodies by electron probe x-ray dispersion analysis. This technique can serve to identify other crystals or metals present in tissue.

ACKNOWLEDGMENT

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