

Pleural Mesothelioma in a Woman Whose Documented Past Exposure to Asbestos was From Smoking Asbestos-Containing Filtered Cigarettes: The Comparative Value of Analytical Transmission Electron Microscopic Analysis of Lung and Lymph-Node Tissue

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Asbestos has had many commercial applications, including its use as a major component in various types of filters. Between 1952 and 1956, crocidolite asbestos was used as a component of filters for cigarettes, reportedly greatly reducing tars and nicotine from mainstream smoke. This case report quantifies asbestos burden in lung and lymph node tissue in a 67-yr-old woman who succumbed to mesothelioma. Her only historically documented exposure to asbestos was from smoking crocidolite asbestos-containing filtered cigarettes between 1952 and 1956. Tissue digestion analysis by analytical transmission electron microscopy (ATEM) identified crocidolite fibers in lungs and thoracic lymph nodes. Combined ATEM data of lung and lymph node tissue clarified the patient's exposure to asbestos and particularly to crocidolite asbestos and thus to the presence of an entity recognized as the causal agent for mesothelioma.

Mesothelioma is a very rare tumor that arises from the linings of the body cavities (Dodson et al., 2003). Wagner et al. (1960) clearly established the link of exposure to asbestos with the risk for development of mesothelioma in a study of individuals exposed to crocidolite asbestos in South Africa. This study and further observations of the development of this rare tumor in asbestos-exposed cohorts led to the recognition that with rare exception, the cause of mesothelioma is asbestos (Craighead et al., 1982). There have been extensive efforts to link other causes for the development of mesothelioma, such as exposure to SV-40 virus. A review of this issue by Manfredi et al. (2005) concluded that their "findings strongly argue against a role of SV 40 by any known transformation mechanism in the etiology of the majority of human malignant mesothelioma." Additionally, a review of the subject by López-Ríos et al. (2004) concluded, "SV 40 appears unlikely to have a major role, if any, in human

mesotheliomas, [and] clinicians should continue to consider asbestos exposure as the most likely and most thoroughly established aetiological factor in individuals with this cancer."

Chrysotile asbestos is the most common commercially used type of asbestos, accounting for 97% of the world's production in 1976 (Wagner & Pooley, 1986). The amphiboles, amosite and crocidolite, are the other commercially used asbestos types, with crocidolite reported by Langer and Nolan (1998) to average "from 1–2% of the total (asbestos) fiber used in commerce (in the United States) over many decades." Amosite and crocidolite forms of asbestos are found in most applications because of their desired specific properties.

A unique application for crocidolite was in the manufacture of filters for cigarettes (Knudson, 1956). This crocidolite-containing filter was stated to have a functional efficiency that removed 40–60% by weight of tars and nicotine from mainstream cigarette smoke. This appeared to offer a protection to the smoker and was marketed accordingly. Longo et al. (1995) stated that 11.7 billion crocidolite-containing filtered cigarettes (585 million packs) were sold in the United States during the 1952–1956 period of production. Langer and Nolan (1998) stated that the use of crocidolite in these filters resulted in "110 metric tonnes consumption between 1952–1956 or approximately 20 metric

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tonnes annum with approximately 8,000 metric tonnes-annum of crocidolite consumed in other applications."

The clinical observations of diseases associated with exposure to the filter material have been reported. In 1989 Talcott et al. reported on a cohort of 33 men who worked in a factory in Massachusetts that manufactured cigarette filters that contained crocidolite asbestos between 1951 and 1957. Twenty-eight men had died as of December 31, 1988 (eight from lung cancer and five from mesothelioma). Nineteen of 28 workers had asbestosis and 5 workers had died of asbestosis.

Huncharek (1994) reported a left pleural epithelial mesothelioma in a 53-yr-old woman who had bystander exposure to crocidolite asbestos in three ways: (1) from her husband, who had worked in the filter manufacturing plant for several months where acetate, cotton, and crocidolite asbestos fibers were blended; (2) while working as a part-time payroll clerk at the filter-producing plant, requiring her to make trips through the plant to pick up payroll material; and (3) while working in the payroll office, where contaminated workers would enter.

The purpose of this article is to report findings of asbestos content in tissue from lung tissue and thoracic lymph nodes from a case of a left pleural mesothelioma in a 67-yr-old woman whose only known exposure to asbestos was from smoking cigarettes between 1952 to 1956 whose filters contained crocidolite asbestos.

CASE REPORT

A 67-yr-old woman at the time of her death had been a life-long homemaker and her husband was an engineer who had no known exposure to asbestos. She had a history of smoking cigarettes for a major portion of her life. The preferred cigarette brand she smoked while it was available (1952–1956) was one whose filter contained crocidolite asbestos. She was diagnosed approximately a year and a half prior to her death with a left pleural mesothelioma. Following diagnosis in February 1996, she entered a phase I clinical trial with Gancyclovir gene therapy for malignant mesothelioma. She tolerated the treatments well and in September 1996 was discharged. In April 1997 she was admitted to a hospital with a left chest wall mass, pain, fever, and anemia. She received radiation therapy to the left chest wall mass. Her condition gradually deteriorated, and in July 1997 she suffered a stroke and expired.

At postmortem examination, the left pleural cavity was found to be extensively involved by tumor that extended into the chest wall. The left hemidiaphragm was invaded by tumor. There was metastatic tumor involving the right pleura and the parietal pericardium, was directly invaded by tumor. The left pleural tumor had the histologic and immunohistochemical features of a predominantly epithelial, biphasic mesothelioma. No hyaline pleural plaques were observed radiographically or macroscopically at autopsy, and iron-stained sections of lung tissue revealed no asbestos bodies.

Lung samples from this individual had been analyzed in a laboratory using scanning electron microscopy (SEM) at 1000×

Five fibers were analyzed, with one having features of tremolite asbestos, three identified as talc fibers, and one an aluminum silicate fiber. The referral to our laboratory for fiber analysis by analytical transmission electron microscopy (ATEM) was in part due to a desire to obtain a better base of information regarding the overall asbestos burden; including those that were short ($<5 \mu\text{m}$) and those that were short or longer fibers but whose diameter was below the "detectability" permitted in "routine" operational conditions of the SEM (Upton et al., 1991). This detection limit in the Health Effects Institute Asbestos Research Report (Upton et al., 1991) has been suggested as "only slightly better than that achievable in the PCOM (that is, approximately $0.2 \mu\text{m}$)."

METHODS

Autopsy lung tissue was submitted for digestion analysis using light microscopy for determination of asbestos body content and analytical transmission electron microscopy for determination of uncoated asbestos fiber burden in lung tissue and tissue from thoracic lymph nodes.

Fifteen pieces of formalin-fixed left lung and 23 pieces of formalin-fixed right lung were received in the laboratory of one of us (RFD) in individual containers labeled left lung and right lung. Five formalin-fixed bronchopulmonary hilar lymph nodes were received in a separate container. A sample of each piece of tissue from the left and right lungs was collected and provided the material for establishment of the dry:wet ratio and for tissue digests. The lung samples were carefully chosen to avoid areas with visible larger airways, thus representing more homogeneous samples of parenchymal tissue. The left lung digest pool weighed 2.9011 g wet tissue (0.5488 g dry). The right lung digest pool weighed 3.8998 g wet tissue (0.7033 g dry). The samples of 4 lymph nodes contained 0.0523 g wet tissue (0.0094 g dry).

The tissue pools were prepared for analytical analysis for the determination of asbestos bodies and uncoated asbestos fibers via tissue digestion with a modified sodium hypochlorite procedure (Williams et al., 1982) that permitted a more "direct" method for tissue preparation. All solutions used in the analysis were prefiltered through $0.2\text{-}\mu\text{m}$ -pore polycarbonate filters. Solutions and filter blanks were used for quality control assessments (Dodson, 1989). Aliquots representing digestates from left lung, right lung, and lymph nodes were collected on $0.22\text{-}\mu\text{m}$ mixed cellulose (Millipore) filters for examination by light microscopy to determine the numbers of asbestos bodies (AB) per gram of tissue. The detection limits for the respective samples were: left lung, 20 AB/g wet (106 AB/g dry); right lung, 20 AB/g wet (111 AB/g dry); and lymph nodes, 233 AB/g wet (1290 AB/g dry).

Additional aliquots from the respective digestates representing right lung, left lung, and lymph nodes were collected on a $0.2\text{-}\mu\text{m}$ -pore polycarbonate (Nuclepore) filter. A carbon replica was made of the filter and pieces of this carbon extraction replica were collected on 100-mesh copper grids for analysis

at 16,000 $\times$ in a JEOL 100CX ATEM for the determination of size and types of uncoated asbestos fibers in the samples. This ATEM was interfaced to an EDAX NX-2 x-ray analyzer used to determine the elemental composition of observed fibers. Selected-area diffraction (SA diffraction) was used to characterize the crystalline nature of the fibers. Additional grid squares outside of the original count area were scanned at 1600 $\times$ to look for asbestos bodies; if found, the cores were analyzed by ATEM. The detection limits for uncoated fibers for the respective samples were: left lung, 4004 fibers/g wet (21,018 fibers/g dry); right lung, 4004 fibers/g wet (22,209 fibers/g dry); and lymph nodes, 116,478 fibers/g wet (650,909 fibers/g dry).

RESULTS

There were no ferruginous bodies found in the scan of the mixed cellulose filters (within the limits of detectability) from the left or right lung. There was one classical asbestos body found in the scan of the mixed cellulose filter prepared from the digested lymph nodes. This was equivalent to 233 AB/g wet tissue (1290 AB/g dry).

Transmission electron microscopic evaluation of the sample area on the grids prepared from the left lung tissue digestate revealed 12 fibers. Four were amphibole asbestos fibers (one each of amosite, tremolite, crocidolite, and anthophyllite), and one was a serpentine asbestos fiber (chrysotile). The remaining fibers consisted of three titanium, three talc, and one aluminum silicate fiber. The five asbestos fibers were equivalent to 20,018 fibers/g wet tissue (105,827 fibers/g dry). The shortest amphibole fiber was amosite (4 μ m), with the lengths of the other three amphibole asbestos fibers being as follows: tremolite 6.4 μ m, anthophyllite 6 μ m, and crocidolite 8.8 μ m. The chrysotile fibril was 6.2 μ m in length. Two of the talc fibers were the only uncoated nonasbestos fibers that were longer than 5 μ m.

In the sample from the right lung, there were 11 fibers identified, 4 of which were amphibole asbestos fibers. These consisted of two tremolite fibers and one each of crocidolite and anthophyllite asbestos. The remaining fibers consisted of three talc fibers, two aluminum silicate fibers, one glass fiber, and one calcium-rich fiber. The total asbestos burden based on these 4 asbestos fibers was 16,021 fibers/g wet tissue (88,838 fibers/g dry). The tremolite fibers were 8 and 2.2 μ m in respective length, the anthophyllite fiber was 13 μ m long, and the crocidolite fiber was 6.6 μ m long. Two talc fibers and the one glass fiber were the only nonasbestos fibers longer than 5 μ m in length.

The highest population of fibers was found in the sample of lymph nodes, in which there were 101 fibers. Twenty-two of these fibers were fibers of amphibole asbestos. These consisted of 10 crocidolite, 8 tremolite, and 4 anthophyllite fibers. The 22 asbestos fibers were equivalent to 2,562,526 fibers/g wet (14,319,998 fibers/g dry) weight of tissue. The remaining fibers were determined to consist of 15 talc fibers, 36 aluminum silicate fibers, 9 titanium fibers, 12 ferroaluminum silicate fibers, 3 magnesium-aluminum silicate fibers, 3 ferromagnesium/aluminum silicate fibers, and 1 silica (crystalline)

fiber. The distribution of size within the crocidolite fibers was: 6 below 4 μ m long, 2 were 6 μ m long, 1 was 8 μ m long and 1 was 12 μ m long. The 8 tremolite fibers consisted of 6 that were less than 5 μ m long, with the longest tremolite fiber being 7.2 μ m. The 4 anthophyllite fibers were 4 μ m or less in length. Among the nonasbestos fibers, only 4 talc fibers and 1 ferromagnesium/aluminum fiber were longer than 4 μ m.

In characterizing the asbestos fibers as potentially detectable at the light microscopy level based on a diameter of fiber greater than 0.25 μ m, it was determined that 6 (1 amosite, 1 anthophyllite, 1 crocidolite, and 3 tremolite) of the 9 asbestos fibers seen in the lung samples could have theoretically been detected. In the lymph-node sample, 1 of 10 crocidolite fibers, 5 of 8 tremolite fibers, and 2 of 4 anthophyllite fibers could have been detected.

In a count scheme including only fibers 5 μ m or greater in length (given sufficient resolution to detect the fibers based on their diameters), the 2 crocidolite fibers in the lung would have been included in a count, as would the chrysotile fibril, 2 tremolite fibers, and the 2 anthophyllite fibers. In the lymph-node tissue, 4 of 10 crocidolite fibers, 2 of 8 tremolite, and no anthophyllite fibers would have theoretically been counted. The average length of asbestos fibers in the left lung was 6.28 μ m and in the right lung the average length was 7.45 μ m. By contrast, the average length of asbestos fibers in the lymph nodes was 4.12 μ m.

There was one crocidolite-cored ferruginous body in the ATEM scan of the grids prepared from the lymph node digestate. This asbestos body was 20 μ m long, with the exposed core measuring 0.25 μ m in diameter.

DISCUSSION

The small amount of crocidolite asbestos used per year in North America as reported by Langer and Nolan (1998) has been reflected in the limited numbers of crocidolite fibers found in studies involving tissue burden of asbestos. Earlier studies that defined the cores of ferruginous bodies collected from individuals from the general population resulted in Churg and Warnock (1979, 1981) concluding that the cores of ferruginous bodies in women were usually "noncommercial" asbestos—either anthophyllite or tremolite. The limited occurrence of crocidolite as the cores within ferruginous bodies even within individuals occupationally exposed to asbestos is illustrated in data from one of our studies, where 2.9% of the ferruginous bodies extracted from lung tissue of 55 cases of mesothelioma were formed on crocidolite cores (Dodson et al., 1997). These individuals resided in the northwestern United States and, based on occupational history and tissue burden of uncoated asbestos fibers, had appreciable exposure to various types of asbestos in their workplaces (Dodson et al., 1997).

The limited exposure to crocidolite in North America is further reflected in data on tissue burden of uncoated asbestos fibers. Churg and Vedal (1994) studied tissue burden in workers with heavy asbestos exposure. These individuals were primarily exposed to amosite and chrysotile, although many work

environments were prone to exposure to mixed asbestos dusts. These scientists concluded that "crocidolite fibers were found in only a few cases, usually in quite low numbers, and have been excluded from all analysis." Dufresne et al. (1996) reported finding very few amosite and crocidolite fibers in their reference group. Case and Sebastien (1987) in another study reported that "crocidolite was identified in lung tissue from only one environmental case and in none of the referents."

Uncoated crocidolite fibers were found in 22 of 55 mesothelioma cases in a study from our laboratories (Dodson et al., 1997). However, the majority of these individuals had other types of asbestos in their lungs as the predominate form. The uniqueness of finding crocidolite fibers in tissue samples was further supported in that it was represented in 15 of 22 positive cases by only 1 or 2 fibers per case. An additional study was carried out from our laboratory on lung tissue from 15 mesothelioma cases in females (Dodson et al., 2002). Crocidolite asbestos fibers were found in lung tissue in only one case, and this individual's husband had worked in an asbestos concrete manufacturing facility that had used crocidolite as part of the product.

Two studies were conducted in our laboratory of tissue burden in samples of lung tissue from the general population (Dodson et al., 1999, 2001). A single crocidolite fragment was found in lung tissue in 3 of 33 individuals (Dodson et al., 1999). These structures were short and averaged $2.11 \mu\text{m}$ in length, which contrasts with the length of crocidolite fibers found in lung tissue of the present case. No crocidolite fibers were found in the second series of tissue obtained from 15 individuals representative of the general population (Dodson et al., 2001). The findings in our study from general populations were similar to those reported by Churg and Warnock (1980, 1981) in that fibers found in lung tissue were represented by a predominance of short fibers. Most short fibers were noncommercial amphiboles and/or chrysotile. Thus, if long asbestos fibers or elevated numbers of commercial types of asbestos were found in tissue, that case was likely to have had an "occupational-like" exposure. Churg and Warnock (1980, 1981) suggested that the source of noncommercial asbestos fibers (tremolite and/or anthophyllite) in women was likely cosmetic talc. Therefore, the finding of low levels of tremolite, anthophyllite, and an occasional chrysotile fiber is not unexpected in lung samples from the general population (Dodson et al., 1999, 2001; Churg & Warnock, 1980; Sprince et al., 1991), and in the present case fibrous talc was found in all samples, indicating a past exposure to talc had occurred.

Studies from our laboratory have also evaluated the types and numbers of asbestos fibers that reach the extrapulmonary sites—the thoracic lymph nodes (Dodson et al., 1990, 1991, 2000b), and omentum and mesentery (Dodson et al., 2000a, 2001). No crocidolite fibers have been found in these extrapulmonary sites in tissue from the general population (Dodson et al., 2000b, 2001).

Longer crocidolite fibers in samples of tissue should raise the question as to whether a unique exposure had occurred. In this case report, the individual was considered as being from

the general population (housewife) and yet was found to have longer ($>5 \mu\text{m}$) crocidolite fibers in samples from both lung samples. One was $8.8 \mu\text{m}$ and the other $6.6 \mu\text{m}$, thus suggesting an exposure to fibers of a length and type more likely found in an occupational-type setting than in tissue from general populations (Dodson et al., 1999).

The lung has very efficient clearance mechanisms, which can result in 98–99% efficiency of dust elimination; however, these include processes that can result in dust reaching lymphatics (Gross & Detreville, 1972). The bronchial lymph nodes, due to this function, have been referred to as potential "reservoirs of retained material" and "respositories" for dust (Gross & Detreville, 1972). In some chronic inhalation exposures to mixed dusts in rats the conclusion was reached that transfer to the lymph nodes accounted for most of the postexposure clearance for some of the tested dusts (McMillan et al., 1989).

While the healthy lung has excellent clearance mechanisms, clearance via the lymphatics system has been defined as relatively slow (Ferin, 1976; Sorokin & Brain, 1975). Schlesinger (1985) has indicated that for this reason the lymph nodes become major reservoirs of retained materials.

Lymph nodes were a tissue of choice for assessing past exposure via inhalation because, as Lippmann et al. (1980) stated, lymphatics relocate particles from the lung to pleura, hilar, and more distant lymph nodes. Data from our studies have shown the thoracic lymph nodes as providing useful supplemental data regarding past exposure when that information is combined with asbestos burden obtained from lung digests (Dodson et al., 1990). Becklake (1976) and Hillerdal (1980) suggested asbestos may relocate from the original site of deposition (the lung) through the lymphatics to other parts of the body. Limited quantitative data exist that indicates correlation of ferruginous body burden in thoracic lymph nodes in exposed individuals (Dodson et al., 1990; Roggli & Benning, 1990). Work from our laboratory (Dodson et al., 1990) indicated that uncoated asbestos burden in the thoracic lymph nodes from exposed individuals may offer a better indication of past exposure to asbestos than the burden in lung tissue. This is based on the fact that lung tissue is constantly subject to clearance, while lymph nodes represent a more static environment (Ferin, 1976; Sorokin & Brain, 1975; Schlesinger, 1985; Gross & Detreville, 1972). As an example, findings from an analysis of lung, pleural plaque, and thoracic lymph nodes from one former shipyard worker (Dodson et al., 1990) revealed no detectable levels of chrysotile within the lung sample (within limits of detection in the study), yet the individual was found to have 6.2 million chrysotile fibers per gram of tissue in pleural plaques and 1.7 million chrysotile fibers per gram of tissue from thoracic lymph node. This observation, plus additional work conducted in our laboratory, led us to speculate that the lymph nodes may offer, in some cases, a better reference for past exposure to asbestos than lung tissue (Dodson et al., 1990, 2000b).

The presence of 10 crocidolite fibers in the digested lymph nodes from the present case included representative populations

of longer fibers (2 over 6 μm , with 1 being 12 μm and a crocidolite-cored ferruginous body with a fiber length of 20 μm). Even with the inclusion of the longer crocidolite fibers as part of the asbestos burden reaching the lymph nodes, the tissue burden in the nodes consisted of an overall shorter population of asbestos fibers when compared to the average length of asbestos fibers found in the lung. It is reasonable to assume that a part of the explanation for this lies in the effectiveness of the lung to preferentially clear smaller (shorter) particulates (Hammar & Dodson, 1994). This relationship of distribution based on fiber length is consistent with our earlier findings regarding lung burden and fiber characteristics in extrapulmonary sites (Dodson et al., 1990).

The use of ATEM is critical in determination of both short (<5 μm) and longer yet thin uncoated fibers. One may emphasize this importance when comparing which fibers would have been seen in a light microscopy count that included only fibers >5 μm in length or the SEM analysis using the same limits of lengths of fibers of inclusion but assigning the resolution for detection based not only on length but also on limits of detection based on diameters (approximately 0.2 μm or slightly better in the SEM) (Upton et al., 1991). Among the asbestos fibers in the present case, only one tremolite fiber would have been detected under such counting parameters applied to analysis of the left lung. One crocidolite and one tremolite fiber would have been included in the count from the right lung. An analysis of material from lymph nodes would have included 1 of the 10 crocidolite and 2 of the 8 tremolite fibers.

This case is an illustration what exists in a tissue sample compared with what may be found in a sample if a restricted count scheme is used that only includes longer fibers (>5 μm) or with a count scheme that does not include short fibers and the capability for detection of longer/thin fibers (due to limits of resolution). With such application in tissue analysis in the present case a conclusion would have been reached that there was little or no crocidolite in the samples and therefore emphasis would be placed on findings of thicker forms of asbestos.

The husband of the individual reported herein was reported as working as an engineer in an industry where asbestos was most likely in place. However the limited use of crocidolite in industrial applications (except in those facilities where crocidolite products were made) makes it highly unlikely that the crocidolite in the lung and lymph tissue was the result of the asbestos being brought home on the husband's clothes. In terms of likelihood, this source of the crocidolite is speculative, whereas the exposures to crocidolite from inhaling the fibers liberated from the cigarette filters seem more plausible and realistic as a source of the crocidolite.

A review of the asbestos burden in the samples of right and left lung indicates a "mixed exposure" to asbestos. As discussed, our past findings in lung tissue from cases of mesothelioma often reflect such a mixed burden of asbestos (Dodson et al., 1997, 2002). As has been discussed, the presence of crocidolite fibers, even in occupationally exposed individuals, constitutes

a uniqueness of the past exposure. Of even more concern in a case of mesothelioma is the observation that appreciable crocidolite fibers have reached extrapulmonary sites—lymph nodes. This is of particular concern since exposure to crocidolite has been considered by some investigators as having the highest risk for inducing mesothelioma of the commercial types of asbestos (Hodgson & Darnton, 2000).

Data from the case reported herein indicate a unique exposure to crocidolite asbestos that was even more significant in that this type of asbestos was used in limited commercial applications. Since no other exposures to crocidolite asbestos were identified in this case, it seems reasonable to assume the exposure occurred from smoking crocidolite-containing filtered cigarettes. Furthermore, the data indicate that lymph nodes that drain the lung may offer important supplemental information to that gained from findings based on analysis of lung tissue alone and in this case clearly establish that crocidolite asbestos has reached the extrapulmonary sites, which as defined have links for drainage to the extrapulmonary sites where mesotheliomas develop.

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