資料 5

PLEURAL DISEASE

Edited by

Demosthenes Bouros

Demokritos University of Thrace Medical School
and University Hospital of Alexandroupolis
Alexandroupolis, Greece

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Benign Asbestos-Related Pleural Disease

E. BRIGITTE GOTTSCHALL and LEE S. NEWMAN

National Jewish Medical and Research Center
University of Colorado School of Medicine
Denver, Colorado, U.S.A.

I. Introduction

Asbestos has attracted attention for centuries, first because of its valuable physical properties, but sadly for the last 50–80 years, mostly because of its multiple and varied pulmonary health effects, ranging from simple pleural changes, to extensive pleural and parenchymal fibrosis, to malignancy. The benign pleural manifestations, including circumscribed pleural plaques, benign pleural effusions, diffuse pleural thickening, and rounded atelectasis, are the subject of this chapter. Mesothelioma is discussed elsewhere in this volume.

II. History

The characteristics that made the industrial use of asbestos popular include insulation against heat, cold, and noise, incombustibility, great tensile strength, flexibility, and weavability, and resistance to corrosion by acids and alkali. Archeological studies reveal that asbestos fibers were integrated in Finnish pottery as far back as 2500 B.C. Plutarch (ca. 45–124 A.D.) wrote of asbestos wicks for oil lamps. Charlemagne (742–814 A.D.) surprised guests by cleansing his asbestos napkins and tablecloths in fire. Asbestos was used in body armor in the

fifteenth century. Gloves, socks, and handbags were made with asbestos in the eighteenth century. Commercial use of asbestos began in earnest with the Industrial Revolution at the end of the nineteenth century and peaked after World War II. Over 3000 commercial applications for asbestos were known in 1973 when the first ban against an asbestos product, asbestos spray-on insulation, was enacted by the U. S. Environmental Protection Agency. Further asbestos product bans and tighter asbestos exposure regulations have followed in North America, the European Union, Japan, and Australia. Regrettably, extensive asbestos usage continues in the developing world, making another epidemic of asbestos-related lung disease in the workplaces of these countries almost inevitable. The pleural and parenchymal consequences of asbestos exposure are for the most part incurable. Thus, primary prevention, especially the elimination of asbestos use, holds the key to control of the epidemic.

III. Pathogenesis

Asbestos is the name given to a group of fibrous hydrated magnesium silicates that occur naturally in the environment. Two major geological types of asbestos exist. *Serpentine* fibers are wavy and pliable and readily degrade into finer particles. Chrysotile, the only serpentine fiber, accounts for nearly 95% of commercially used asbestos worldwide. *Amphibole* fibers are needle-shaped and straight and prove to be more resistant to biological degradation. Several amphibole fibers are known, namely crocidolite, amosite, anthophyllite, tremolite, and actinolite. While crocidolite, amosite, and anthophyllite have been used commercially in small quantities, tremolite and actinolite are mostly found as contaminants of other minerals such as chrysotile, vermiculite, and talc. The mechanism by which asbestos fibers induce pleural and parenchymal disease is not completely understood; however, various pieces of the puzzle have been solved.

Fiber size has been clearly established as a deciding factor of pathogenicity. Stanton et al. in animal studies demonstrated the importance of fiber length in relation to neoplasia (1). Rats exposed to different length asbestos fibers were most likely to develop mesothelioma after the administration of fibers greater than 8 μm long and less than 0.25 μm wide. These findings were further corroborated in animal studies conducted by Pott (2).

Fibrogenicity is also linked to asbestos fiber length. King (3) exposed rabbits to different length asbestos fibers and later examined them for the development of pulmonary fibrosis. Significantly more fibrosis was produced by long (15 μm) fibers than by short (2.5 μm) ones. Other investigators subsequently confirmed these results (4,5).

The pathogenic importance of fiber size relates in part to how different length fibers are lodged in the lung tissue, processed once inhaled, and translocated to the pleura. Short fibers are often phagocytosed and moved from the lung via alveolar clearance mechanisms into the gastrointestinal tract, the hilar

lymph nodes, or the pleural space (6). Macrophages are unable to fully engulf the longer fibers, triggering a complex cascade of events, including the release of oxygen radicals, cytokines, chemokines, and growth factors (7). In vitro studies have also demonstrated that long fibers interfere with the cell cytoskeleton, damage chromosomes, and interfere with the mitotic spindle during mitosis (8,9).

While fiber dimension is integral to asbestos pathogenicity, the chemical composition of a fiber plays an important role as well. Fiber composition contributes to fiber durability. When immersed into liquid environment chrysotile fibers quickly lose their magnesium content leaving behind only a silicon shell. In tissue, they readily separate into their individual fibrils. Consequently, chrysotile is removed from lung tissue much more rapidly than are amphibole fibers. This is an important phenomenon to remember when drawing conclusions regarding pathogenicity of different fiber types based on fiber counts measured in human lung tissue many years after exposure has ceased.

The surface charge of fibers varies. While crocidolite has a negative surface charge, chrysotile is positively charged, resulting in the adsorption of and interaction with different biological materials in the target organ (10).

In summary, the toxicity of asbestos appears intricately related to its morphology and physicochemical properties, but the complete cycle of the events that leads to such varied pulmonary manifestations remains patchy.

IV. Pleural Plaques

A. Epidemiology

The epidemiological evidence for a connection between asbestos exposure and the occurrence of pleural plaques is compelling. The prevalence of pleural plaques is dependent on the population studied. Most estimates of prevalence are based on radiological surveys. The highest attack rates for pleural thickening are found in villages in Turkey and Greece where outcrops contaminated with naturally occurring asbestiform fibers, namely tremolite, actinolite, or eronite, are used to prepare a whitewash or stucco applied to the inside and outside of dwellings. By the age of 70, 69% of the population of a Turkish village showed evidence of pleural thickening on chest x-ray (11). In Finland, Kiviluoto showed that the vast majority of Finns with bilateral pleural plaques lived in the vicinity of open anthophyllite asbestos pits (12). It is possible that these high rates of pleural thickening in these environmentally exposed populations can be explained by a fiber gradient, with anthophyllite and tremolite showing the strongest association with pleural plaques.

In occupational cohorts with known asbestos exposure, the prevalence of pleural thickening varies widely, ranging from 7.6 % in asbestos miners and millers (13) to 58% in insulators (14,15). The large variation in the incidence and prevalence reported in these cohorts can be explained in part by differences in mean age, length of time since first exposure (latency), and dose of exposure among the cohorts studied.

Rogan et al. estimated that 3.9% of the U.S. population aged 35–74 is afflicted with pleural thickening due to occupational asbestos exposure. They based their estimates on chest x-ray data from the National Health and Nutrition Examination Survey (NHANES) II (1976–1980) (16). This prevalence is approximately twice that estimated from NHANES I data (1971–1975) (17). Hillerdal (18) also reported an increase in pleural thickening in Uppsala county residents over the age of 40 from 0.2% in 1965 to 2.7% in 1985.

Epidemiological studies may either over- or underestimate the true incidence of pleural plaques when based on radiographs. Recently, increased body mass index (BMI >30 kg/m^2) was shown to correlate with a greater prevalence of circumscribed pleural thickening on chest radiograph in former crocidolite miners in Wittenoom, Australia (19). This was especially true for thin (<10 mm) shadows covering 25–50% of the lateral chest wall. Whether this is due to extra pleural fat or other causes is not clear at this time. However, the finding is of interest in view of the continuing increase in prevalence of obesity among the U.S. population. That chest radiographs can underestimate the presence of pleural plaques has long been known based on autopsy (20–22) and computed tomography (CT) studies (23–25).

Pleural plaques are the most common manifestation of asbestos exposure. When bilateral and partially calcified, they are virtually pathognomonic of past asbestos exposure. The plaques develop slowly over time, with an average latency period from first exposure to radiographically identifiable plaque of 20–30 years (26,27). They are not affected by smoking (28). Pleural plaques are associated with lower lung fiber counts than asbestosis (29,30). No threshold exposure has been identified for the occurrence of pleural plaques. While asbestosis has been associated with cumulative, continuous exposures, pleural disease occurs at proportionally higher rates in individuals who have had intermittent exposures (15). Nishimura et al. (31) speculated that intermittent exposures may allow more time for fiber clearance from the lung and for greater accumulation of fibers in the pleura.

Pleural plaques are not known to transform into mesothelioma. However, Hillerdall reported an increased risk for mesothelioma in those with pleural plaques on chest x-ray (32). In a necropsy-based study Bianchi et al. demonstrated that the presence of plaques >4 cm was a risk indicator for the development of mesothelioma (33). Whether radiographic evidence of pleural plaques is associated with an increased risk of developing lung cancer is controversial. The issue has been addressed in a number of studies of varying design and in reviews without a definitive conclusion. (20–22, 34–42). Plaques are not causative in the development of lung cancer, but are thought to serve as a surrogate of the magnitude of asbestos exposure. However, temporality of the exposure may play a role in addition to dose, as mentioned earlier for pleural plaques and asbestosis. Any lung cancer in an asbestos-exposed individual should be very closely examined as an asbestos-related lung cancer whether pleural plaques are present or not.

Inhalation of asbestos fibers results in a spectrum of thoracic manifestations unparalleled by most other toxins. For unknown reasons, the pleura is a major target. The mechanism by which asbestos fibers produce the pleural disorders discussed below is not known for certain, but increasingly sophisticated theories have been proposed. In the 1960s Kiviluoto (12) suggested that asbestos fibers poking out of the visceral pleura scratch the parietal pleura during respiration and thus induce an inflammatory reaction in the parietal pleura that eventually leads to pleural thickening. This theory has since been discarded.

Hillerdal (43) in 1980 published a report in which he suggested that some asbestos fibers that have reached the visceral pleura penetrate the pleural space and are swept up by the lymphatic flow and transported to the parietal pleura. As they pass through the parietal pleura, some fibers will actually remain there inside macrophages and initiate an inflammatory response that in time leads to pleural thickening. More recently Boutin et al. (44) published an elegant study adding to our knowledge of how pleural plaques may form. He and his coworkers obtained parietal pleura and lung biospy specimens during thoracoscopy in asbestos-exposed individuals. In the parietal pleura, they secured samples from anthracotic "black spots" and from adjacent normal pleura. Black spots are thought to be part of the lymphatic system in the pleura and correspond to Kapmeier's foci or "milky spots," which are collections of immune cells surrounding lymphatic stomata (44,45). Transmission electron microscopy (TEM) revealed high concentrations of asbestos fibers in the "black spots" and almost none in the normal pleura. In some cases, higher concentrations of fibers were found in the anthracotic areas of the pleura than in the lung tissue. One fifth of the fibers recovered from the "black spots" were >5 μm long. This study suggests that the distribution of asbestos fibers throughout the parietal pleura is heterogeneous and could explain the uneven distribution of circumscribed parietal pleural plaques.

Analysis of pleural plaques has identified mainly short, fine asbestos fibers <2 μm long. Animal studies have confirmed that fibers travel into the pleura after tracheal instillation (46,47). Pathology shows that asbestos fibers are embedded (48,49) in the pleura, and in vitro studies of disease mechanism have shown that mesothelial cells exposed to asbestos fibers promote inflammatory events leading to fibrosis (7,50–53).

C. Clinical Presentation

Macroscopically pleural plaques are discrete, raised, irregularly shaped, shiny lesions of the parietal pleura, with no associated pleural adhesions. Microscopically, on their surface is a normal appearing layer of mesothelial cells. Beneath the mesothelium is fairly acellular, dense, collagenous tissue arranged in a coarse basket weave pattern. Many submicroscopic fibers are visible in these plaques when examined by electron microscopy (54). Plaques are most often found on

the posterior and lateral wall of the lower half of the thoracic cage, where they follow the course of the ribs (Fig. 1). They can also form on the domes of the diaphragm, on the mediastinal pleura (especially overlying the heart) (Fig. 2), and rarely on the pericardium itself. They spare the lung apices and costophrenic angles. As Nishimura and Broaddus (31) point out, the intriguing aspect of this distribution is that it corresponds with the distribution of the lymphatic system involved in the clearance of particles from the pleural space. This assumes that asbestos fibers can travel against the normal direction of the lymph flow, as has been reported for coal dust particles (55). Asbestos-related pleural plaques are most often bilateral and symmetrical. If unilateral, most of them seem to form in the left hemithorax based on chest x-ray (56,57). However, a recent CT study did not corroborate this left-sided predominance (58).

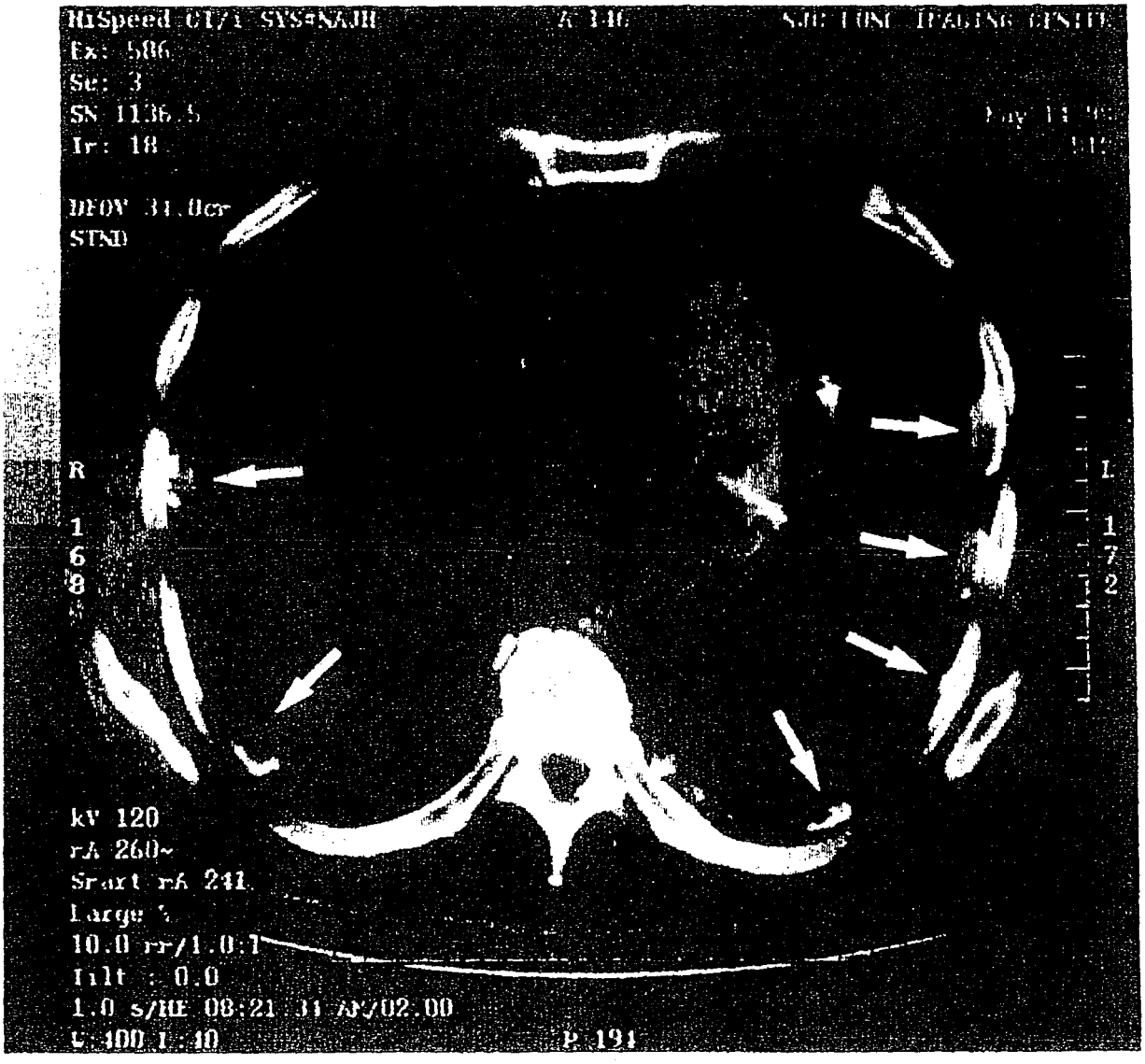

Figure 1 Chest CT with multiple large, localized, partially calcified pleural plaques (white arrows) in classic bilateral distribution along the posterior and posterolateral parietal pleura.

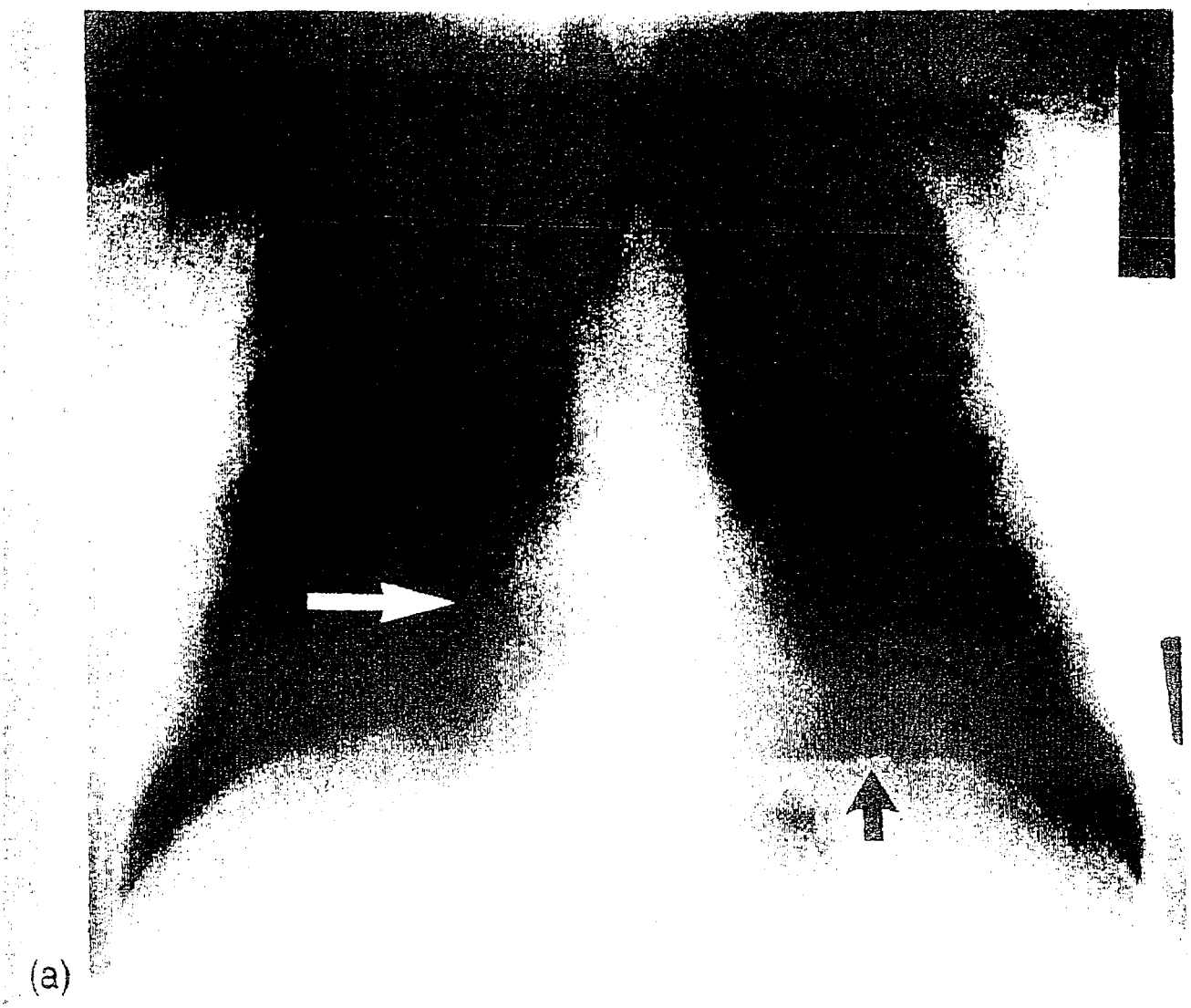

Figure 2 A former insulator with pleural plaques in multiple locations. (a) The chest radiograph shows a thin calcified plaque along the right heart border (white arrow) and overlying the dome of the left diaphragm (black arrow). (b) The chest CT also shows the delicate pleural plaque in the mediastinal pleura overlying the heart (small white arrow), but the plaque in the right paraspinous region on chest CT (large white arrow) was not visible on chest x-ray.

Chest CT scan has proven to be more sensitive than chest radiography for detecting pleural plaques and for discriminating between pleural fibrosis and extrapleural fat (23–25,59). Gevenois et al. (25) performed a conventional and high-resolution CT scan (HRCT) on 159 asbestos-exposed workers with normal chest radiographs. Of these workers, 37.1% demonstrated pleural thickening on CT scan. Conventional CT proved superior to HRCT in detecting these plaques.

Simple circumscribed asbestos-related pleural plaques usually do not produce clinical symptoms. Often they are discovered incidentally during the clinical evaluation of unrelated health problems or during participation in a screening program. Despite their subclinical presentation, pleural plaques are associated with statistically significant pulmonary function abnormalities. Most

(b)

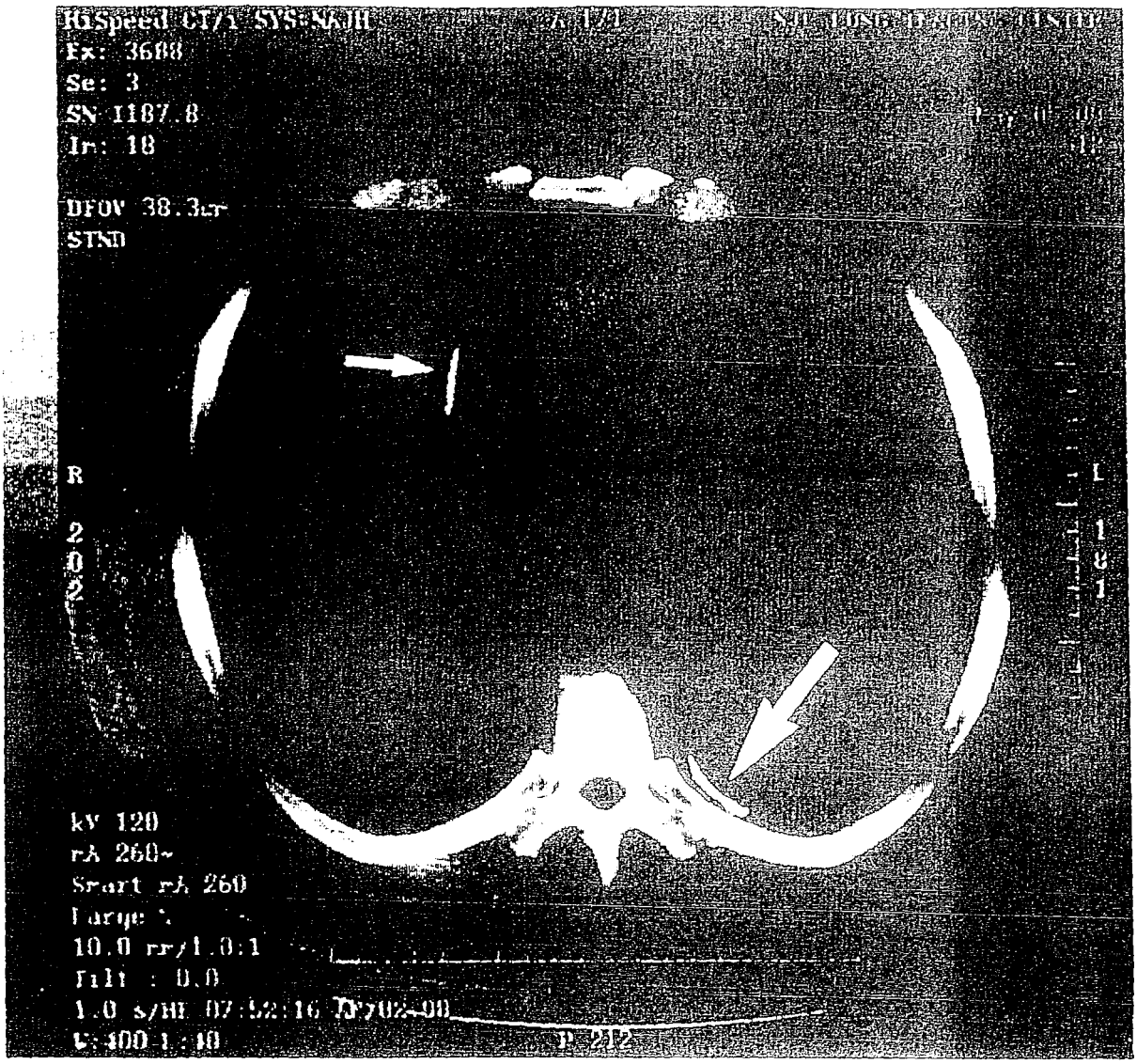

Figure 2 Continued.

consistently they lead to a reduction of the forced vital capacity (FVC) (14,60). Pleural plaques have also been associated with airflow limitation (61–65) While this can be partially attributed to the prevalence of tobacco use in asbestos-exposed cohorts, reports in nonsmokers (62) suggest an independent asbestos-related mechanism responsible for airflow limitation. The most plausible scenario is that physiological airflow limitation is a reflection of pathologically apparent, but radiographically occult peribronchiolar fibrosing alveolitis, the early tissue response to inhalation of asbestos fibers (66).

D. Treatment

No specific treatment is needed for circumscribed pleural plaques. However, since they are a marker of exposure and as such are associated with the risk of developing asbestosis and malignancy, regular follow-up of affected individuals is prudent. Recently much attention has focused on low-dose spiral CT as a lung

cancer–screening tool (67–69) motivated by persistently poor 5-year survival rates (70). Asbestos-exposed workers are a well-defined high-risk group in which this screening tool has great potential. An expert panel recently met to review the advances in radiology and screening of asbestos-related disease (71). They concluded that data available do not justify broad-based lung cancer screening in asbestos-exposed cohorts. For now, the decision to screen with low-dose spiral CT must be made on a case-by-case basis.

Regular follow-up visits also offer opportunities to emphasize the importance of smoking cessation and to assist with achieving this, if necessary, and to assure updated immunization records especially for the influenza vaccine and Pneumovax.

V. Diffuse Pleural Thickening

A. Epidemiology

Diffuse pleural thickening has been recognized only recently as a distinct asbestos-related entity. For many years it was considered to be part of the spectrum of parenchymal asbestosis (48). On the other hand, it was often not clearly distinguished from circumscribed parietal pleural plaques. It is often touted as the sequel of an asbestos-related benign pleural effusion (72–75). Diffuse pleural thickening is not as specific for asbestos exposure as bilateral partially calcified pleural plaques are, since it has also been associated with other disorders, including parapneumonic exudative effusions, hemothorax, collagen vascular disease, drug exposure, especially bromocriptine (76), and Dressler's syndrome. The incidence of diffuse pleural thickening is thought to be significantly lower than that of pleural plaques. This is supported by a study conducted by Hillerdal et al. (77), who followed 891 cases with pleural thickening due to asbestos exposure and observed that 84 individuals (approximately 10%) developed diffuse pleural thickening over time. Schwartz et al. examined the chest radiographs of 1211 sheet metal workers and concluded that 260 (21.5%) had developed circumscribed pleural plaques, while again a smaller proportion, only 74 (6.1%), suffered from visceral pleural fibrosis. McLoud et al. (74) could not confirm a significantly lower incidence of diffuse pleural thickening compared to circumscribed pleural thickening when they reviewed chest radiographs of 1373 asbestos-exposed individuals. They found that 10% of the cohort had diffuse pleural thickening and only 16.5% had circumscribed pleural thickening. Some of these differences likely relate to how diffuse pleural thickening is defined by the different investigators or related to the type of asbestos fiber. De Klerk et al. studied workers exposed to crocidolite and found more diffuse pleural thickening than plaques (78).

Diffuse pleural thickening incidence increases with time since first exposure. It is associated with asbestos fiber burden levels that are intermediate between those of levels associated with pleural plaques and those of asbestosis (79–82).

B. Pathogenesis

In contrast to circumscribed pleural plaques, diffuse pleural thickening affects the visceral pleura and typically covers a much larger surface area (Fig. 3). It initially forms in the posterior and posterolateral portions of the lower visceral pleura. With time, it evolves and extends into the costophrenic angles and apices. Diffuse pleural thickening is usually bilateral, but can occur unilaterally. Adhesions between the two pleural sheaths are common. Microscopically, the visceral pleura is replaced by a layer of dense collagenous tissue with a basket-weave pattern reminiscent of that found in parietal pleural plaques. Asbestos fibers and bodies can be recovered from the pleuroparenchymal tissue, especially in the vicinity of the pleural thickening (31).

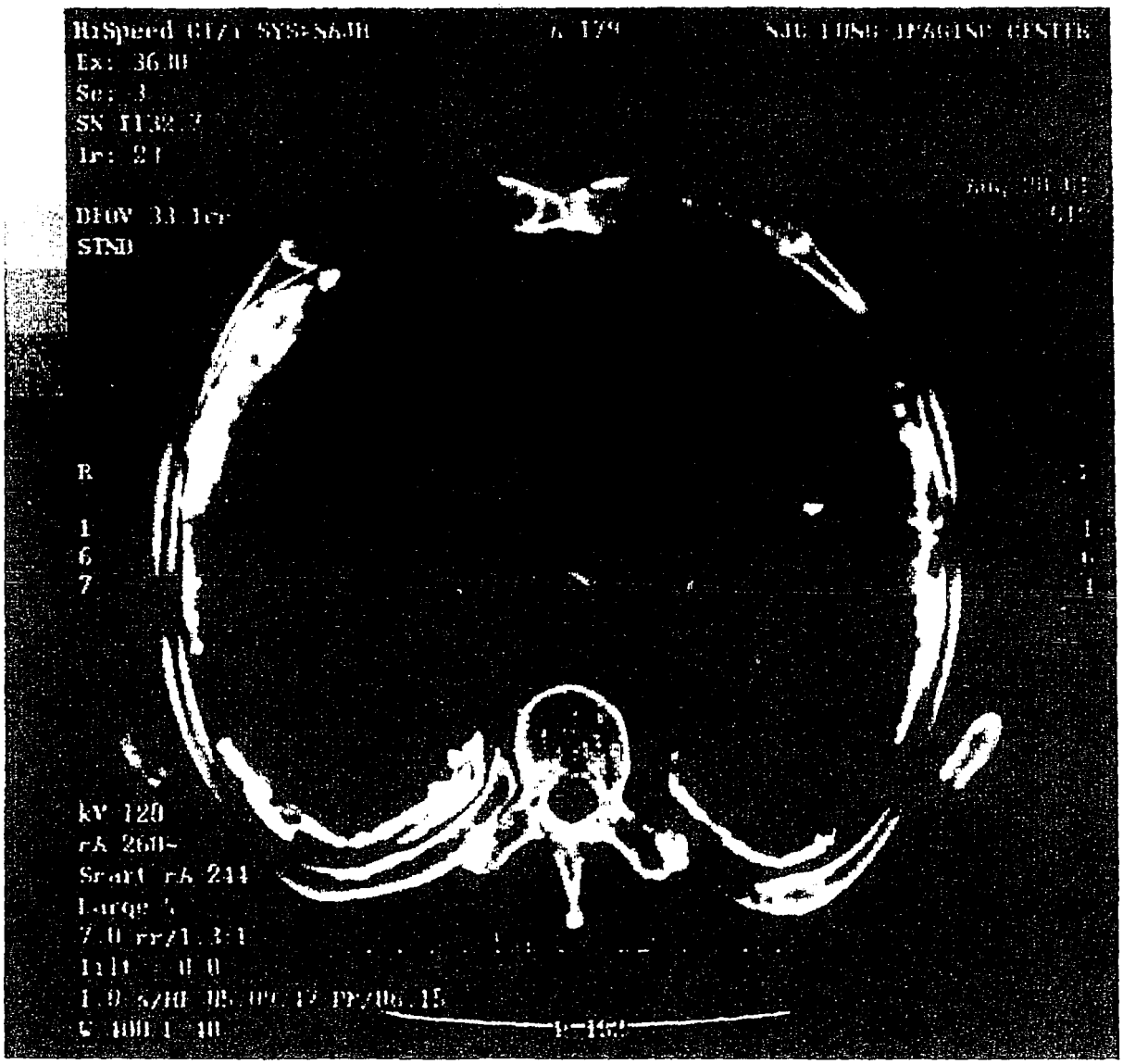

Figure 3 Chest CT depicting extensively calcified thick pleural rind extending around most of the circumference of the lung typical of diffuse pleural thickening.

The pathogenesis of diffuse pleural thickening is not precisely known. However, passage of asbestos fibers into the pleural space via lymphatics with a subsequent inflammatory response is also thought to play a role in diffuse pleural thickening. It is not known why some individuals develop circumscribed plaque while others develop diffuse pleural thickening.

C. Clinical Presentation

In contrast to simple parietal plaques, diffuse pleural thickening is often associated with respiratory symptoms. Dyspnea on exertion represents the most common complaint. In a study by Yates et al. 61 out of 64 asbestos-exposed workers with diffuse pleural thickening complained of breathlessness with exertion (83). Occasionally pleuritic chest pain occurs, most likely due to pleural adhesions in those with diffuse pleural thickening (83,84). Sometimes the pain mimics angina (85).

The physical exam in patients with diffuse pleural thickening can reveal reduced chest expansion, dullness to percussion when the pleural peel has reached significant thickness, and sometimes crackles on auscultation due to concomitant parenchymal fibrosis. Al Jarad and colleagues noted that crackles could be heard in the absence of CT evidence of asbestosis in up to 40% of subjects with diffuse pleural thickening (86).

The radiological features of asbestos-related diffuse pleural thickening have recently been reviewed (82,87). The diagnosis of diffuse pleural thickening on chest radiograph relies on the obliteration of one or both costophrenic angles (74). Based on CT scan, Lynch et al. defined diffuse pleural thickening as a "continuous sheet of pleural thickening more than 5 cm wide, more than 8 cm in craniocaudal extent, and more than 3 mm thick" (88). CT scan often detects fibrous strands, or "crow's feet," extending from the thickened pleura into the lung parenchyma. High-resolution CT scan is superior to chest radiograph in demonstrating the extent of the pleural process. It allows much better visualization of the often-involved paraspinous regions of the pleura that are otherwise obscured by mediastinal structures on chest radiographs. CT scan is also superior in distinguishing between pleural thickening and extrapleural fat.

Several studies have shown that diffuse pleural thickening impairs lung function. The most consistent findings are a decrease in FVC, total lung capacity (TLC), diffusing capacity (DLCO), and exercise tolerance (83,89). In the study by Yates et al. (83) of 64 patients with diffuse pleural thickening, FEV_1 was reduced to 62% and FVC to 77% of predicted. TLC was 71% and DLCO 74% of predicted. Similar results were reported by Kee et al. who studied 53 asbestos-exposed individuals exposed in shipyards or in the construction trades. In this study, the FVC was reduced to 68% of predicted, with a mean DLCO of 72% of predicted (90). Neither study reported DLCO corrected for lung volume, which in the absence of concomitant asbestosis would be expected to be normal.

Interestingly, Al Jarad et al. showed in 20 patients that severity of disease by CT and chest radiograph scores correlated well with the extent of their pulmonary impairment (91). Schwartz et al. also demonstrated in 60 sheet metal workers with asbestos-related pleural fibrosis that the greater the volume of pleural fibrosis derived from a three-dimensional reconstructed thoracic HRCT image, the lower the total lung capacity (92).

D. Treatment

Treatment options for those with diffuse pleural thickening and pulmonary impairment are very limited. Attempts have been made at freeing the lung with decortication, but results have been disappointing (77,93). Supportive treatment is often the best option available. Intercurrent respiratory infections should be treated aggressively. Oxygen therapy is necessary for those with hypoxemia at rest or with exertion. The importance of smoking cessation should be stressed. Immunizations are warranted.

VI. Benign Asbestos Pleural Effusion

A. Epidemiology

The epidemiology of asbestos-related benign pleural effusions mirrors that of asbestosis and the other forms of asbestos-related lung and pleural disease. Risk is associated with the same forms of inhaled asbestos that have been linked to asbestosis, asbestos-related lung cancer, mesothelioma, and other pleural disorders. Described in the 1960s (94–100), the so-called benign pleural effusion may in fact portend development of other forms of asbestos-related disease, including pleural fibrosis and possibly mesothelioma (73). In one of the largest studies of prevalence and incidence, Epler and colleagues observed 34 effusions among 1135 workers exposed in a variety of industries, including shipyards, fireproofing product manufacture, and paper mills. The prevalence was dose-related, ranging from 0.2% for peripherally exposed individuals to 7% among those with most severe exposure. It is the most common asbestos-related condition in the first 20 years after exposure, with incidence of 9.2 effusions per 1000 person-years for those exposed at the highest levels and 0.7 effusions per 1000 person-years for those with the least exposure. The effusions can occur as soon as 5 years after first exposure and have almost always occurred within the first 20 years, although studies differ in their estimates of latency, ranging from a mean of 12 to 30 years. In the Epler study, pleural effusions were five times more likely to occur in asbestos-exposed individuals compared with a nonexposed control group, including effusions related to mesothelioma and lung cancer (73). In light of the rarity of benign pleural effusions in the general population, asbestos exposure should be considered whenever an unexplained exudative effusion is detected. The studies of prevalence and incidence may, in fact, have underestimated the true frequency of asbestos effusions, since many may remain subclinical, preceding development of pleural fibrosis (77).