RADIOLOGICAL CHANGES AS MARKERS OF ENVIRONMENTAL EXPOSURE AND ENVIRONMENTAL RISK OF LUNG CANCER AND MESOTHELIOMA

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Introduction

That certain mineral fibers can cause disease has been known since the early 20th century, when the first cases of asbestosis were described. In the 1940ies the risk of lung cancer was first described and later malignant mesothelioma. It is now well known that mineral fibers can cause diseases and changes in the lung parenchyma and the pleura, which are the main targets since the fibers are inhaled, but also in many other parts of the body. The medical studies come mainly from occupational exposures, but environmental exposure is also possible and can pose grave dangers.

There are many hundred different fibers in the mineral world, both naturally occurring and man-made ones. Only a few do, however, occur in amounts and environments that make it possible for humans to be exposed. Those that are known are the ones collectively known as asbestos and a fibrous zeolite called erionite. There might well exist other fibers in various parts of the world that could lead to human disease but has not yet been recognized.

This review will first describe the benign pleural lesions which can be caused by asbestos and discuss whether they can be used as "sentinel signs" of such exposure, and then give a short review of findings and diseases in "endemic areas", i e places in the world where lesions and/or diseases due to environmental exposure to asbestos have been reported. The different asbestos fibers can give different medical findings.

Diseases and radiological findings caused by asbestos and erionite

Benign pleural lesions

The benign radiological findings which occur after exposure to asbestos are of two main types: firstly, these involving the parietal pleura, i. e. the inside of the chest wall, the diaphragm, and the mediastinal surfaces. These are called ple ural plaques. Since the lung is not involved, there is only minor or no affection of lung function by these lesions. Secondly, there are those lesions which involve the visceral pleura, i.e. the outer layer of the lung. These lesions often cause affection of the lung function (1,2).

Pleural plaques

The by far most common asbestos-related lesions are the **pleural plaques**. Macroscopically, they are shining white elevations with sharp borders. Microscopically, they consist of fibro-hyaline connective tissue containing very few cells. There are no inflammatory cells within the plaques, but small aggregates can be seen in their periphery, indicating a low-grade inflammation there.

Radiology. Pleural plaques are best seen in the flanks of the lungs in a frontal view. This is because they are most evident when the X-rays hit them tangentially. If they are thick enough, they can be visible even if not viewed tangentially. When they are calcified, they are much easier to recognize. Diaphragmal plaques can be visible as button-like elevations. The costovertebral sinuses are unaffected. A slow progression over the years is a very typical characteristic (3).

Plaques are always more widespread and numerous at autopsy than at the chest roentgenogram. Only 10 to 15 per cent are seen with conventional radiography (4). If less strict criteria are used at radiology, a few more true plaques will be diagnosed - but the main problem is an overdiagnosis, and in fact half or more of all the diagnosed plaques do not exist in reality. The ILO system is not useful here: the smallest "plaques" diagnosed there (less than 5 mm thick) is very unspecific (5). Computed tomography will demonstrate more plaques but is not suitable for studies on large population groups. In fact, the number of more plaques seen are limited, and plaques on the diaphragm are often missed (6).

It has to be realized that radiological criteria for plaques differ very much between various readers. In any study concerning the occurrence of plaques the criteria used for diagnosing them should be clearly stated. If not very strict criteria are used, a considerable overdiagnosis is unavoidable. This is one possible explanation behind the different opinions about the importance of plaques.

In the general population in a society where there are no "endemic plaques", 80-90 per cent of strictly defined pleural plaques are due to occupational exposure to asbestos (7,8). However, they can be found also in persons with only low-level or sporadic exposure.

There are many normal intrathoracic and extrathoracic structures that can lead to X-ray findings which may be mistaken for pleural plaques. Here are some of the more common:

Fat pads are common, especially in overweight persons. Typically, they are even thickenings along the flanks which start apically and can be followed sometimes down to the costodiaphragmal junction. However, they can also be irregular, and plaques can at times be situated on the fat (9). CT scan can show the fat density (9,10).

Intrathoracic muscles can also cause regular and bilateral findings. *Extrathoracic muscles*, especially the anterior serratus muscle, can also sometimes be a problem. These shadows can be followed outside the thoracic cage, and are regular and "saw-shaped".

"Companion shadows" are soft tissue shadows along the ribs, and are often seen apically but are also common in the flanks further down, and can be very difficult to discriminate from early pleural plaques.

Tuberculous infection and haemorrhagic exudations after trauma can lead to calcifications, usually unilateral, but typically these are situated in the visceral pleura.

Rib fractures, when healed, can appear very much like plaques. Since fractures are often multiple and, especially in alcoholics, bilateral, careful study of the films is necessary. Each rib should be normal and the contours without any defects for a diagnosis of pleural plaques to be made, unless other changes typical of pleural plaques are present.

Other pneumoconioses. In silicosis, pleural calcification can occur but is rare. Talcosis can be very similar clinically and roentgenologically to asbestosis, but it is probably the asbestos found in almost all types of talc that causes the pulmonary and pleural changes (11).

Dose-response. The relation between dose and response for pleural plaques is much weaker than that for parenchymal asbestosis. A good correlation between pleural plaques and asbestos fibers in the lung has been shown by many researchers (12-16). The mean of asbestos fibers or bodies in persons with plaques is as a rule higher than in the normal population, but there is a fairly large variation and a number of persons with plaques will have values little or no different from the general population (15,16). In other words, plaques are associated with a wide range of asbestos burdens which overlaps with that of the control population.

Latency time. Plaques are more related to time after exposure than to the dose. Very few plaques will be seen earlier than 15 years after the first exposure to asbestos, and most will appear only after 30 years. In areas where the population is exposed from birth the first pleural changes will appear after age 30 and the incidence then increases with age. Thus, occurrence of plaques is dependent on cumulative exposure and time since first exposure (17). Many plaques are not seen until long after exposure has ceased. Once seen, they will slowly grow larger over the years, and with time many will calcify (3).

Occurrence of pleural plaques

Plaques are a common occurrence in most countries, reflecting the extensive use of asbestos some decades ago. In industrialized countries in the cities, 2 to 4 per cent of all males above age 40 are usually carriers of plaques; the prevalence is lower in females and in the countryside (12).

Clinical importance of pleural plaques

Plaques are in themselves harmless. They may be regarded as an objective sign of previous asbestos inhalation, and it is this exposure that is of possible importance for the future health. In the literature, it is sometimes recommended that persons with plaques should be followed. However, since they are a fairly common finding, regular investigations of such persons would be costly, and this cost has to be weighed against the potential gains.

Apart from being a sign of asbestos inhalation, plaques are also an indication that sufficient time has elapsed since the first exposure to increase the risk of malignancy from the asbestos exposure. In many occupational cohorts, the incidence of bronchial carcinoma is twice or more as high in those with pleural plaques as in those without but with similar exposure (8,13,14). Persons with plaques also have a risk of developing mesothelioma (8). However, as will be described later, the risk of mesothelioma (and possibly also lung cancer) is related also to the type of asbestos which has caused the plaques: thus, for example, there is a much higher risk to develop mesothelioma if the plaques have been caused by crocidolite exposure than if they had been casused by anthophyllite exposure.

Theoretically, wide-spread calcified plaques might restrict the movements of the chest wall and thereby restrict the lung function. In fact, persons with pleural plaques have as a group a somewhat lowered lung function, but whether this is due to the effect on the chest wall or an associated slight pulmonary fibrosis is unclear.

VISCERAL PLEURAL LESIONS

Typical for the visceral pleural lesions is that the visceral pleura, i e the pleura which covers the lung, is involved. Invariably, this leads to an affection of the lung parenchyma as well, with an affection of the lung function. The so-called diffuse pleural thickening always blurs more or less diffusely with the

parenchyma, and there are always more or less developed "fibrous strands" or "crow´s feet" which reach into the lung parenchyma; and most often there is a blunted costophrenic angle. A peripheral atelectasis of the lung parenchyma can occur; this has been termed "rounded atelectasis" (1,2).

Exudative pleurisy. This can occur suddenly in asbestos-exposed persons. It can be of any magnitude, but can amount to up to two liters. Despite this, the patients are often free of symptoms, and the condition can be a surprise finding at X-ray. The exudate usually persists for some months and can recur after drainage; however, within a year the exudate is usually resolved. Recurrences can occur, either on the same or on the other side. Residually, a diffuse thickening of the pleura or a rounded sinus may be observed, but often the exudate will disappear without trace. Any middle-aged or elderly man with acute or subacute pleurisy should be suspected of having been exposed to asbestos. The diagnosis of asbestos pleurisy is at present based on the history of exposure and the absence of another etiology (18).

Blunting of the costophrenic angle in asbestos-exposed persons is a common finding, but is very unspecific, and a large number of persons who have never been exposed to asbestos can show the same.

Crows´feet are fibrotic strands reaching into the lung from a "shrinkage center" in the visceral pleura. CT scan will beautifully show these lesions, which can reach deep into the lung.

Rounded atelectasis. Although rounded atelectasis was originally described in association with pleural effusions and after therapeutic pneumothorax, there is no doubt that asbestos is the principal cause today. However, any effusion, no matter what the cause, can result in a rounded atelectasis.

The classic mechanism of rounded atelectasis is that described by Hanke (19): within a pleural effusion a part of the lung becomes atelectatic and adheres to another part of the lung. When the exudate is resorbed, the adhesions remain, and when the adjacent parts of the lung expand, some bronchi will be folded, and thus part of the lung cannot refill with air - it has become "trapped". Another mechanism is that a fibrotic changes involving the peripheral part of the lung contracts, forcing part of the lung to become atelectatic.

Occurrence of visceral pleural lesions
The visceral pleural lesions are much less common than are plaques. There are no good studies on their prevalence, probably mainly due to the fact that they are only rarely recognized to be due to asbestos. In most cases they are diagnosed as remnants of unspecific pleurisy.

Importance of visceral pleural lesions
The visceral pleural lesions are associated with a usually quite considerable lowering of lung function (20). Visceral pleural lesions usually also imply a fairly heavy exposure to asbestos, with a risk of other asbestos-related diseases.

Specificity of benign pleural lesions
Strictly defined pleural plaques are practically pathognomonic for asbestos exposure. The visceral types of pleural lesions are more unspecific and may be found with many other types of pleuritis (21).

For the purpose of “sentinel radiologic findings” only pleural plaques are feasible, even if a cohort with a large number of unspecific pleural lesions of the visceral type should alert the epidemiologist. To my knowledge, this has not been described in the literature, however.

It is important to realize the “shortcomings” of pleural plaques in this regard: the long latency time of 30 years or more; the strict definitions that are necessary to avoid overdiagnosis; and the fact that plaques are not rare in an industrialized society.

ASBESTOSIS

Asbestosis, or pulmonary fibrosis can occur with exposure to all types of asbestos. The lung becomes fibrotic and stiff and gas exchange dramatically decreases. It is a dose-related disease, and a fairly high exposure is necessary to cause the clinical manifestation which is shortness of breath. Once the process has started, it continues to worsen. Asbestosis is rare with environmental exposure but can occur after many years of slight exposure.

MALIGNANT TUMORS

The malignant diseases due to asbestos are mainly **lung cancer**and **malignant mesothelioma**. A number of other tumors in the body has been claimed to be increased in asbestos workers but the scientific proof varies and they can be disregarded in a review like this one.

Lung cancer is mainly a disease caused by smoking. However, exposure to asbestos will increase the risk in a dose-related manner. Most data point to a multiplicative effect for smoking an asbestos. In a non-smoker, the risk of developing a lung cancer is very small, and even if this risk is doubled due to asbestos exposure, the risk will remain low. In other words, most "asbestos lung cancers" are also "smoker´s cancers". It is also easily understood that lung cancer is a difficult disease to use as a marker of low dose exposure to mineral fibers, since the main numbers of this disease are caused by smoking which might vary much in the population.

Malignant mesothelioma, however, has no correlation to smoking. Apart from a very small portion which is believed to be the "basal level" of the disease and the very rare cases that are due to other known causes (for instance radiation), all cases can be considered to be due to exposure to asbestos (or erionite). The tumor arises in the pleura and grows slowly there, compressing the lung and in later stages invading the ribs and causing the death of the patient often within a year of diagnosis. Rare cases occur, however, with many years of survival. No curative treatment exists, though some cytostatics seem to have some effect on the tumor. The disease is dose-related but even a slight exposure can be enough. Like pleural plaques, the latency time is usually more than 30 years. Rarely, the disease starts in the peritoneum.

Thus, two findings – pleural plaques and malignant mesothelioma – are useful as "sentinel" diseases, indicating that asbestos (or erionite) exposure has occurred in the cohort.

Mineral fibers of medical interest

The main types of asbestos are those consisting of straight fibers (amphiboles), of which the most important are crocidolite ("blue asbestos"), amosite ("brown asbestos"), tremolite, and anthophyllite, and those with curly fibers, of which there is only one important type, namely chrysotile ("white asbestos"). These fibers all differ in their diameters and lengths and also in their ability to resist breakdown in biological tissues. Chrysotile is by far the most widely used. It also has the fastest clearance from the body. Most diseases seem to be mainly associated with the amphiboles (22). Environmental exposures are reported only for the amphiboles, probably due to the fact that chrysotile breaks down to a much larger extent.

Crocidolite is the most dangerous of the asbestos fibers and is not mined any more. It has certain abilities, such as a high resistance to acids, that made it a very useful industrial substance. *Amosite* is also nowadays rarely used. *Tremolite* has been mined only to small extent but is a common contaminant of chrysotile, talc and many other ores, such as nickel and iron, all over the world. In addition, it is a

common mineral, occurring in outcrops in many places of the world. *Anthophyllite* has been mined in Finland and Japan, but it has today no industrial use.

Erionite, finally, is not a very common mineral. It was formed under certain conditions in volcanic areas of the world and contaminates other zeolite formations there.

Local deposits of fibrous minerals

In many areas of the world, asbestos fibers occur in the soil, as remnants of broken down rocks. Farmers working with the soil are exposed to the fibers, and in many places the locally occurring asbestos has been used for white-washing of houses, construction of fireplaces or sauna stones (23-25). As a result there are areas of the world where pleural plaques are endemic. Such "endemic pleural plaques" were first described from Finland and since then many other areas have been reported (Table I).

The older age groups can show calcified plaques in 50 per cent or more radiographically and even more at autopsy (up to 100 per cent in persons above age 50) though usually the incidence is more modest. Where the fibers occur in the soil, farmers are exposed and then the plaques are more common among males. Where the mineral fibers are used for white-washing of houses, the women also have a high incidence of plaques.

One of the best described countries is Turkey, where there are not only villages with exposure to asbestos but also some where a non-asbestos fibrous mineral has been found to cause endemic pleural changes. This fiber is erionite, a fibrous zeolite, which was formed during volcanic activity and occurs locally in some few villages, the best known of which is called Karain. The erionite occurs in roads, fields, and building stones. Apart from the pleural changes, these villages also have an extremely high incidence of malignant mesothelioma. In fact, this dreadful disease is the main cause of death there (48).

Endemic plaques are of interest also in other countries, since many persons born in these places and living there in their childhood and youth now have moved to other places, taking with them not only the plaques but also the risk of mesothelioma and lung cancer.

What should be done about asbestos and erionite occurring locally?

As mentioned, Turkey is the best investigated country for these local findings, but as can be seen from table II, many other countries are also affected. Most probably, the problem is much more wide-spread and many other countries in the world probably have similar problems, only the risk has not been identified as yet. This is probably most likely in the developing countries, but many of the risks (for instance, in Corsica and Greece) have been identified only within the last one or two decades, so it is quite possible that new findings can be made also in industrialized countries.

Once the problem has been identified, the most important next step is to inform those affected of the risk and which habits should be avoided. For instance, white-washing of houses should be abandoned or rather other substances should be used. Good results will be achieved by this method alone, as shown in a recent paper from Turkey where there are indications that the incidence of mesothelioma is going down (49), and from Metsovo. In the erionite case in Turkey, where the problem is not any particular use of the substance but rather that it occurs in the ground, the only solution is to move the village.

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TABLE I. Local deposits of mineral fibres (asbestos or erionite), incidence of plaques, and of malignant mesothelioma

Country or area	Type of fiber	Population or activity	Incidence of plaques	Mesothelioma risk	Reference
	Tremolite				
Austria		Vineyard & field workers	Increased	Not increased	26,27
Bulgaria		Tobacco growers	Increased	Not increased	28
Corsica		General population	Increased	High	29,30
Cyprus		General population	Increased	High	31
Greece		White-washing houses	High	High	32-35
New Caledonia		White-washing houses	High	High	36,37
Turkey		White-washing houses Farmers	High	High	25,38,39
	Amosite				
South Africa		Population around mine	High	High	40
	Crocidolite				
South Africa		Population around mine	High	High	40
Rep. of China		General population	High	High	41
	Anthophyllite				
Finland		Population around mine	High	Not increased	42-44
Japan		Population around mine	High	Not increased	45
	Unknown				
Czechoslovakia		Farmers	High	Unknown	46
USSR		General population	Increased	Unknown	47
	Erionite				
Turkey		Villagers	High	Extremely high	39,48