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Short Course 3

Progress in non-neoplastic pulmonary pathology

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Mimics of asbestos-related disease

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Introduction

Asbestos refers to naturally occurring fibrous hydrated silicate minerals with an aspect ratio of greater than 3:1. There are two major groups with distinct physiochemical properties, as follows:

l) Amphiboles (long, straight, rigid fibres), comprising amosite, crocidolite, anthophyllite, tremolite and actinolite.
ii) Serpentine (wavy, coiled fibres), chrysotile. In the United Kingdom —95% commercial asbestos is chrysotile.

Inhalation of foreign particulate matter may cause the lungs to react in a wide variety of ways, some of which are clinically asymptomatic and pathologically insignificant to life-threatening conditions such as malignant mesothelioma. The response to the presence of mineral particles in the lung are governed by particle size, deposition, biopersistence and surface properties.

Asbestos inhalation can result in the development of both pleural and lung parenchymal disease (Table 1). In general, the pleura appears more sensitive than the lung parenchyma to asbestos and pathological changes occur at much lower doses.

Table 1. Spectrum of asbestos-related disease.

Pleural	Parenchymal
Effusion	Fibrosis
Plaque	lasbestosis)
Diffuse fibrosis	
Mesothelioms	Carcinoma
Rounded atelectasis	

The spectrum of asbestos-related conditions is well described, but many conditions can mimic these. An awareness of this is important for disease ascription and medicolegal compensation. The presentation addresses those issues and their distinction from bonafide asbestos-related disease.

Pleural effusion (1'

Asbestos-related effusions are unilateral or bilateral exudates and can appear within 10 years of initial exposure. In some studies, they are observed in 3-5% of asbestos workers. Spontaneous remission may occur. Recurrent cases may be associated with diffuse pleural fibrosis. The diagnosis is based on: l) positive asbestos exposure history; ii) absence of other conditions causing effusion; and iii) an indolent course with no tumor development after 3 years duration.

Exudative pleural effusions of any etiology may initially mimic benign asbestos-related effusion, in particular rheumatoid associated effusion, and those associated with cirrhosis. If strict criteria are applied with full clinical examination, serous fluid culture and cytology, other causes can be excluded.

Pleural plagues (1-3

Asbestos-related plaques occur as discrete grey-white nodular lesions, most commonly situated on the posterolateral aspect of the parietal pleura and diaphragm. The apices and costophrenic angles are usually spared. Plaques have also been described on the visceral pleura, pericardium, peritoneum and aortic adventitia. They are nearly always asymptomatic and manifest on chest X-ray 20 years or more following initial exposure. Their incidence increases with both exposure duration and latent period. In South Wales, UK, they are seen as an incidental finding in 8% routine postmortems in men. About 50% of the plaques identified in this way show normal lung asbestos fibre burdens and have no asbestos exposure history. Pleural plaques are not predictors of mesothelioma or lung cancer and their extent does not correlate with severity of lung fibrosis (Table 2).

Table 2. Nonasbestos agents causing pleural plaques.

Agent	Diagnostic considerations
Talc (4, 5)	Occupation* pleural fhickening; progressive massive fibrosis; interstitial fibrosis
Mica (6)	Occupation~ pleural thickening; interstitial fibrosis
Woolastonite (7)	Occupation~ pleural thickening, chronic bronchitis, nodules
Erionite (8)	Geographic association with Anatolia, Turkey: interstitial fibrosis, mesothelioma, lung cancer
Trauma	Clinical history, unilateral
Infection	Clinical history, culture (acid fast bacilli)

Occupational considerations: ~Talc (serpentine, tremoline, anthophyllite breakdown): ceramics, paper, plastic, rubber, paint, cosmetics, pharmaceuticals; *MiCa (muscovite, phlogopite, vermiculite: paints, plastic, heat textiles; *Woolastonite: asbestos substitute in insulation, brake linings, ceramic filler.

Calcifying fibrous oseudotumor (9

This represents a pathological mimic of pleural plaque. The lesion has been described in the pleura and peritoneum and the author has seen a case in the tunica vaginalis. It is characterized by abundant hyalinized collagen containing multifocal psammomatous calcifications and focal lymphoplasmacytic infiltrate. Etiology is unknown.

In comparison, pleural plaques are histologically composed of hyaline acellular collagen with basket-weave reticulin pattern and parallel slit-like spaces on hematoxylin and eosin sections. While calcification is not uncommon, psammoma bodies are not seen.

Diffuse Dleural fibrosis (1. 10

Diffuse thickening of the visceral pleura may occur in asbestos-exposed persons without significant parenchymal fibrosis. Bilateral cases can result in restrictive lung disability. Parietal pleural thickening and extensive adhesion can occur (fibrothorax).

Diffuse pleural fibrosis usually occurs after 10 years from initial exposure to asbestos. Mineral analysis of lung reveals raised levels of asbestos, but below the range associated with significant asbestosis (Table 3).

Table 3. Nonasbestos causes of diffuse pleural fibrosis.

Cause	Diagnostic consideration
Rheumatoid arthritis (11)	Clinical history: other pleuropulmonary change
Systemic lupus erythematosus (12)	Clinical history: other pleuropulmonary change
Infection	Fibrocaseous (culture) tuberculosis
Drugs	Methysergide
Idiopathic	

Rheumatoid pleuritis represents the most common pulmonary manifestation of rheumatoid arthritis, estimated at between 5% and 50%, often in severe diffuse arthritis cases. Effusion (d.glc, .J~pH), diffuse fibrosis and rheumatoid nodules may occur. Males are more commonly affected (M:F; 5:1) (despite the overall predilection of rheumatoid arthritis for females: M:F; 1:3).

Systemic lupus erythematosus (SLE) pleuritis is one of the more common findings. At postmortem, pleuritis (often asymptomatic) may be seen in up to 80% of cases and are often bilateral. Antinuclear antibodies and lupus erythematosus cells are present.

Desmoplastic malignant mesothelioma (13

The pathological mimic of diffuse pleural fibrosis is desmoplastic malignant mesothelioma. This morphological subtype is often associated with sarcomatous mesothelioma. The diagnosis of desmoplastic mesothelioma should be suspected if a paucicellular fibrotic lesion shows bland necrosis, chest wall/visceral invasion or is associated with a component of cellular sarcomatous mesothelioma. Immunohistochemistry may be useful to highlight cytokeratin positive neoplastic spindle cells invading adipose tissue and muscle, although the method has its limitations.

In comparison, diffuse pleural fibrosis is histologically similar to hyaline pleural plaques.

Rounded atelectasis (folded luna syndrome) (14

This is characterized as a peripheral round mass (2-8 cm diameter) which is pleural-based and often situated in the posterior aspect of the right middle or lower lobe. The condition is usually asymptomatic but mimics neoplasia. By light microscopy there is dense pleural fibrosis, subjacent lung is atelectatic and fibrotic, and there are visceral adhesions. Organized pleural effusion with adhesion formation is considered important in the pathogenesis. Any cause for effusion could produce rounded atelectasis. Radiological findings show characteristic comet-tail appearance and recognition is important to prevent thoracotomy.

Asbestosis (1. 14. 15'l

Simply defined this is interstitial lung fibrosis due to asbestos. However, there is considerable controversy regarding interpretation of the histology and consequently in disease ascription of fibrosis and lung cancer in the asbestos-exposed population. The term "pleural" asbestosis should not be used. Pleural and subpleural fibrosis may be seen at lung fiber burdens well below that causing significant parenchymal disease.

Diffuse interstitial fibrosis (grade 3-4 asbestosis) manifests as clinically significant disease and is associated with heavy, prolonged asbestos exposure. It has a latent period of 15 or more years but in very heavy exposures the latent period may be less than 10 years (this is very uncommon nowadays). In these cases, light microscopy reveals numerous (clustered) asbestos bodies. Electron microscopic counts reveal extremely high asbestos fiber burden.

The terms "microscopic" asbestosis/mineral duct-induced airways disease/minimal criteria asbestosis (15), although not directly synonymous are used for grade 1 (peribronchiolar) fibrosis in association with an occasional asbestos body. These persons are asymptomatic and show no radiographic abnormality. Interpretative ambiguities exist when a potential link to lung cancer exists. The term should be cautiously used as a number of conditions may produce this histological picture.

The diagnosis of asbestosis (by any criteria) requires i) fibrosis and ii) asbestos bodies (Table 4). When asbestos is present there is frequently pleural disease (fibrotic thickening and/or hyaline plaques) present.

Table 4. Fibrosis distribution.

Site	Other causes
Peribronchiolar (grade 1) fibrosis	Smoking Imembranous bronchioles) Coal (black pigment, upper lobes) Talc (retractile material) Mica Silica (fibrotic nodules, upper lobes) Aluminium oxide Iron oxide
Subpleural fibrosis	Mica Talc (foreign body granulomas, fibrotic nodules retractile piety particles)
Lower lobe fibrosis	Unusual interstitial pneumonia, others

Asbestos bodies (16

Asbestos bodies are the hallmark of exposure and do not necessarily represent disease. In general, the number of asbestos bodies increases with the severity of fibrosis (one should consider other disease conditions if there is advanced fibrosis but very sparse asbestos bodies, particularly in the absence of pleural changes).

Strict criteria should be used for the term 'asbestos" body to prevent confusion with other "non-asbestiform" ferruginous bodies

(so-called "pseudoasbestos" bodies). The asbestos body core color and shape are important: golden brown, beaded, dumb-bell shaped structure 20-50 p long and 2-5 p diameter with transparent core (Table 5).

Table 5. Color and shape of asbestos bodies.

Erionite	Transparent (identical to asbestos by light microscopy) electron microscopy and energy dispersive X-ray analysis useful. Geographic variation: Turkey, environmental exposure
Sheet silicates Talc Mica Kaolin	Blood yellow, platy, rectangular Occupation: miners, stone, steel, rubber, enamel glass, ceramics
Carbon	Black variable thin platy segmented/dittuse coat Perpendicular 90 0extensions Occupation: coal mining, foundry workers
Metals (Aluminium oxide) (Iron oxide)	Brown-black Occupation: arc welders, steel workers, metal polishers
Man-made mineral (Glass-fiber)	Ferruginous bodies rarely form but may be indistinguishable from asbestos cores

In individuals with a history of asbestos exposure, awareness that other conditions can, on occasion, mimic those changes usually associated with asbestos is important for medicolegal compensation purposes.

Electron microscopic mineral analysis is useful when asbestos-related disease is suspected and, i) light microscopy reveals advanced tibrosis and few asbestos bodies; ii) light microscopy reveals fibrosis and many ferruginous bodies (mixed asbestos and pseudoasbestos type); iii) malignant mesothelioma cases where no asbestos bodies are identified by light microscopy; and iv) lung cancer cases in which there is minimal fibrosis and sparse asbestos bodies.

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Pathology of nonasbestos pneumoconiosis (silicosis and mixed dust pneumoconiosis)

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Pneumoconiosis represents a variety of pathological reactions of lung tissue to permanent deposition of inhaled particulate or fibrous matter of occupational or environmental origin. The nomenclature or concept of pneumoconiosis is somewhat confusing because of overlap resulting from heterogeneous definition of the disease. There are quite a few pneumoconioses named after occupation. On the other hand, there are only limited numbers of patterns of reaction of lung tissue to inhaled dust. As a result, exposures to different dust may produce the same pathology. This is the very reason the author recommends concentrating on pathological patterns prior to taking occupational history or mineralogy into account.

Etiologically specific features can be distinguished from nonspecific patterns in the pathology of pneumoconiosis. There are the following specific lesions: macule, nodule (silicotic, mixed dust fibrotic), granuloma and massive fibrosis, which essentially are upper-lung diseases.

Macules

A macule appears macroscopically as a nonpalpable, pigmented spot in a centrilobular distribution throughout the lungs, and represents one of the initial changes of pneumoconiosis and may progress to nodular disease as described below. Histologically, macules consist of peribronchiolar or perivascular collections of dust-laden macrophages accompanied by a delicate meshwork of reticulin fibers. There is little collagenous fibrosis in the macules.

Nodules

A nodule is a palpable, firm lesion of up to 3 mm in size. Generally, two types of nodules are distinguished. Firstly the silicotic nodule is a well demarcated, extremely firm lesion with variable pigmentation, composed histologically of paucicellular, hyalinous collagen fibers in a whorled or concentric arrangement. Silicotic nodule develops primarily in the centrilobular and/or subpleural locations,