Asbestos - forbidden, but not forgotten

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Learning objectives

• To overview pulmonary and pleural diseases related to asbestos exposure.
• To present radiologic features of benign pleural thickening, pleural plaques, asbestosis and mesothelioma.
• To present case examples of TNM 8th edition staging.
Background

Asbestos is a name given for a group of six naturally occurring silicate minerals chrysotile, amosite, crocidolite, tremolite, anthophyllite, and actinolite. Asbestos crystals according to the form of fibers are divided into two groups:

- Serpentine has curly fibers and is the most hazardous form, as its fibets can easily reach terminal airways and alveoli. Chrysotile is the only crystal in this group and is the most commonly used worldwide.
- Amphibole is a wider group of crystals that have needle shaped fibers.

Asbestos is durable, strong and flexible material that was widely used in 19th-20th centuries due to its resistance to heat, electricity and chemicals. Not only having been popular in different types of industry and construction, it was also used for manufacturing many commercial and household appliances such as coffee pots, hairdryers, toasters and even toys or cosmetic talcum powder. The historical uses mean that not only occupational, but also household exposure is possible. Family members of workers who are exposed to asbestos are at a higher risk too, as asbestos dusts can be brought home on clothes, shoes and other items. Asbestos can also be found in old buildings where asbestos was used in constructions or for insulation when those materials start to deteriorate and small asbestos particles enter the air.

Nowadays asbestos is known as hazardous and very cancerogenous material that can cause mesothelioma, lung cancer and some other forms of neoplasms. In addition to malignancy, it can cause another debilitating lung disease - asbestosis. Benign pleural thickening, pleural plaques and pleural effusion are benign diseases caused by asbestos. Due to toxic properties asbestos is banned in Europe, Australia, Canada part of South America, China and some other countries. The usage is also regulated and restricted in the United States. Asbestos related diseases are still widely spread worldwide despite all restrictions due to long latency period (15-60 years). Due to this people with known asbestos exposure have to be followed up. Lung function tests, different imaging modalities, cytology, histology and various biomarkers are used for screening and differential diagnosis.

Asbestos fibers present in the air can be inhaled. Serpentine fibers are more dangerous, because they are more capable to reach alveoli. Mucociliary clearance can remove asbestos dusts from the upper respiratory tract, but the fibers cannot be eliminated once they reach the terminal airways and alveoli.

When settled in the lung, asbestos fibers activate local immune response (macrophage phagocytosis), cause chronic inflammatory reaction, fibroblast activation and reduced
tumour immunity due to various cytokines/chemokines release and immune changes. Iron is a compound of asbestos crystals and is thought to be responsible for the release of reactive oxygen species (ROS) and reactive nitrogen species (RNS) which cause DNA damage to surrounding tissue cells and are related with cancerogenesis.

Asbestos is also known to be related with telomere shortening of mesothelial cells.

After apoptosis of the macrophages, asbestos particles are released, causing a repetition of the same immune response, thus causing progressing inflammatory changes and pulmonary fibrosis. Macrophages with phagocytosed asbestos particles can also be eliminated from airways through lymphatic system to the regional lymph nodes. As a result, fibers can be found everywhere along the lymphatic pathways, including pleural spaces.
Benign asbestos pleural effusion (BAPE) can be the earliest presentation of asbestos-related disease, but latency period is variable. The fluid is exudative in origin, often hemorrhagic with lymphocyte dominancy and does not contain asbestos bodies. BAPE can also coexist with other benign asbestos related diseases and is usually not related with mesothelioma formation. Effusion can resolve without treatment, but diffuse pleural thickening (DPT) can develop as a consequence, especially in recurrent cases (Fig. 1 on page 12).

Fig. 2: Benign asbestos pleural effusion and diffuse pleural thickening

References: MD Laima Tamkeviciute

DPT does not calcify and surrounds whole lung including apices and costophrenic angles. The localisation and shape of pleural thickening can help differentiate DPT from mesothelioma. High-level irregularity, mediastinal localisation, and interlobar fissure thickening should raise the suspicion of malignant changes. Positron emission tomography combined with computed tomography (PET-CT) is a noninvasive diagnostic method that can allow to assess the metabolic activity within the pleura and thus be used to differentiate DPT from mesothelioma.
BAPE has to be differentiated from other causes including malignant (lung cancer, mesothelioma, metastases, etc.) and non-malignant (tuberculous pleuritis, bacterial pleuritis, collagen diseases, and heart failure). Microscopy, staining, bacterial cultures of the pleural fluid and pleural biopsy are useful to exclude alternative diagnoses. Biochemical fluid analysis can also be of value: elevated hyaluronic acid, adenosine deaminase, and carcinoembryonic antigen levels suggest other diagnoses.

**Pleural plaques (Fig. 3 on page 12)** are localised areas of calcified or non-calcified pleural thickening usually occurring on parietal pleura, but can be found on visceral layer too. Pleural plaques are most frequently bilateral, but can be unilateral in rare cases. They can be seen in paracostal, mediastinal and diaphragmatic surfaces with sparing of apices and costophrenic angles. The size differs from small measuring 1-2mm to very large (Fig. 4 on page 13). If a plaque is located in visceral pleura, fibrotic parenchymal lung bands arising from the plaque can develop. Extensive pleural plaques can result in reduced lung function.

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**Fig. 5**: Pleural plaques and round atelectasis

**References**: MD Laima Tamkeviciute

**Round atelectasis** (Fig. 1 on page 12 C-D) can virtually be caused by any pleural pathology, including infection and asbestos related pleural disease. Radiologically it appears as a round or oval shaped mass adhered to pleura with distorted bronchovascular bundles coming towards the mass and forming a comet tail sign. Volume
loss and pleural fissure distortion can also be seen. Pleural thickening is the most common cause, but mesothelioma or lung cancer can also be the reason of the atelectasis. Hence, follow-up or further investigation with PET/CT, MRI or biopsy is needed.

**Asbestosis** is a dose dependent fibrotic lung disease and develops after prolonged exposure to high doses of asbestos. In cases of lower dose exposure, low grade fibrosis may develop and it may not be visible on CT. The diagnosis of asbestosis is based on exposure history, clinical and radiological findings. Biopsy may be necessary in difficult cases when clinical or radiologic features are atypical or non-diagnostic.

Patients with asbestosis usually complain of breathlessness and dry cough. On physical examination end-inspiratory crackles in the lower zones can be found. Lung function is restricted with reduced lung volume, forced vital capacity and diminished carbon monoxide diffusing capacity. Asbestosis patients may even have hypoxemia of the arterial blood.

Histologically fibrosis and asbestos bodies are required for the diagnosis. Fibrosis starts in the alveolar walls, in peribronchiolar distribution. Fibrosis of the walls of the respiratory bronchioles and alveolar ducts may also be present.

- Grade I asbestosis is limited to the first layer of alveoli.
- When asbestosis progresses, fibrosis extends more to the periphery of the acinus, although in grade II asbestosis some unaffected alveoli between two bronchioles is seen.
- Grade III asbestosis is diagnosed when all alveoli between two adjacent bronchioles are fibrosed.

In advanced disease peribronchiolar pattern may no longer be evident. Different patterns are possible in such cases including usual interstitial pneumonia and non-specific interstitial pneumonia. Sometimes the pattern may not match any other form of pulmonary fibrosis.

On plain film (Fig. 6 on page 13), fibrotic changes appearing as ground glass, reticulations or honeycombing, "shaggy" heart, as well as blunted costophrenic angles and pleural plaques can be seen.

CT findings of asbestosis are variable. Changes are usually located in the subpleural distribution and start at the lower lobes, but can involve middle lobe and lingula or even upper lobes in advanced disease. One of the earliest CT findings is the presence of subpleural curvilinear lines (Fig. 7 on page 14). Small subpleural nodules corresponding to
peribronchiolar nodular fibrosis is another characteristic finding; these nodules together with small arteries can form “Y” shaped structures which do not reach pleura. If pleural plaques are located in the visceral layer, fibrotic lung changes might arise from them forming fibrotic bands radiating into the lung parenchyma. Pleural based interlobular septal thickening is another feature of pulmonary fibrosis. In advanced stages honeycombing and traction bronchiectasis can also develop (Fig. 8 on page 14, Fig. 9 on page 15). Ground glass opacification might be the sign of fine fibrosis when changes are too small for CT resolution. Asbestosis is usually related to pleural plaques, and absence of them should raise the suspicion for an alternative cause of pulmonary fibrosis. On the other hand features of asbestosis do not necessarily follow the distribution of pleural plaques. Asbestosis usually has slow course and does not progress quickly, this can help to differentiate from other fibrotic lung diseases (Fig. 10 on page 15).

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![Asbestosis](image)

Asbestosis

- Dose dependent, develops after prolonged exposure to high doses.
- Subpleural distribution, starts at the lower lobes.
- Can involve middle lobe and lingula or even upper lobes in advanced disease.
- Imaging findings:
  1. Sub-pleural curvilinear lines.
  2. Small subpleural nodules corresponding to peribronchiolar nodular fibrosis.
  3. Fibrotic bands radiating into the lung parenchyma.
  4. Pleural based interlobular septal thickening.
  5. Honeycombing and traction bronchiectasis in advanced stages.
  6. Ground glass might be the sign of fine fibrosis.

Fig. 11: Asbestosis

References: MD Laima Tamkeviciute

Mesothelioma is a malignant tumor originating from pleura which is highly related with asbestos exposure. Chest wall radiation, mineral erionite and cancerogenic simian virus 40 are another precursors. The latency period after asbestos exposure is long and counts 30-40 years. Although early detection can lead to more favourable outcomes, overall prognosis is poor. Mesotheliomas should be classified according to TNM 8 classification as a widely accepted standard.
Mesothelioma can arise from either parietal or visceral layers. Based on gross anatomy mesothelioma can be diffuse or localised. Histologically it can be epithelioid (most often type), sarcomatoid, desmoplastic and biphasic.

 Clinically mesothelioma manifests as chest pain and breathlessness. The pain is usually dull and unilateral, but sometimes can become neuropathic or pleuritic. At early stages breathlessness is due to pleural effusion, but in advanced disease it is caused by lung entrapment and reduced lung function.

Chest x-ray usually is the first imaging modality. The earliest sign may be pleural effusion, which can be loculated. Later, irregular pleural thickening with involvement of interlobar fissures can be seen (Fig. 13 on page 16). Pleural plaques can also be noted and should suggest asbestos exposure if the clinical history is unclear. Although chest x-ray films can provide important information, it is neither sensitive nor specific modality.
According to British Thoracic Society guidelines, CT thorax with contrast, optimised for pleural evaluation, should be the initial cross-sectional imaging modality in the evaluation of patients with suspected pleural mesothelioma. In diffuse forms lobulated or smooth pleural thickening is the main feature, followed by loculated pleural effusion. In advanced disease lung becomes retracted with reduced volume. CT is very important for staging, because mesothelioma is very likely to invade adjacent structures directly. Invasion of the lung parenchyma (Fig. 15 on page 16), mediastinum (Fig. 16 on page 17, Fig. 17 on page 17, Fig. 18 on page 18), chest wall (Fig. 19 on page 18), contralateral pleura, diaphragm, abdominal organs and peritoneum, as well as spread to lymph nodes can be evaluated on contrast enhanced CT. If T stage remains unclear and differentiation of the affected structures is important for management, then dedicated MRI should be considered. Hematogenic metastases are quite common, but usually reported late or in autopsy. FDG PET-CT should be considered if excluding distant metastases could change management, but this modality should be avoided for patients who have had prior talc pleurodesis. Due to potential false positive interpretations, FDG PET-CT should be performed with a caution for population with a high prevalence of tuberculosis.

Thoracocentesis, biopsy and biomarkers also play an essential role to differentiate mesothelioma from benign and other malignant pleural disease. The most common differential diagnosis is pleural metastasis (Fig. 20 on page 19), benign diffuse pleural thickening and empyema (in a relevant clinical setting)(Fig. 21 on page 19).
Asbestos is also related with increased risk for **lung cancer** especially when combined with smoking history. In those cases clinically and radiologically lung cancer manifests in its usual manner (Fig. 22 on page 20).
**Fig. 1:** Diffuse pleural thickening with round atelectasis and pleural effusion

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**Pleural plaques.** Plain film (A) shows bilateral calcified opacities (black arrows). CT chest axial images in lung (B, D, C) and soft tissue (E) windows show bilateral calcified pleural plaques (white arrows) on paracostal, paramediastinal and diaphragmatic surfaces.

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Pleural plaques mimicking mesothelioma. Plain film (A) shows right-sided pleural thickening (black arrow) and irregular opacity in the right lower lobe (black arrowhead). Arterial phase CT chest sagittal reconstruction (B) and axial image (C) in soft tissue window show right sided calcified pleural thickening (white arrows), extending to mediastinal surface. Mesothelioma was suspected and FDG PET/CT scan was performed: axial image (D) shows moderate avidity (white arrowheads). No mesothelial cells were found histologically after biopsy.

Fig. 4: Pleural plaques mimicking mesothelioma

Asbestosis in 76 years old patient with history of asbestos exposure. Plain film (A) shows extensive bilateral pulmonary fibrosis with typical for asbestosis “shaggy heart” sign (black arrows). CT chest axial images (B, C) show subpleural fibrosis with multiple traction bronchiectases (white arrows); bronchiolectases forming honeycombing are seen at the level of the pleural plaques (arrowheads).

Fig. 6: Asbestosis
Fig. 7: Asbestosis

Asbestosis in a patient with history of working in asbestos mines. CT chest axial image (A) and coronal reconstruction (B) show bilateral subpleural bands, typical for asbestosis.

Fig. 8: Asbestosis

Asbestosis in patient with known occupational asbestos exposure. CT chest axial images in soft tissue window (A, B, C) show calcified pleural plaques (white arrows) and pericardial calcification (dotted arrows). Axial images in lung window (D, E, F) show subpleural predominant pulmonary fibrosis with traction bronchiectases (black arrows) and subpleural bands, typical for asbestosis (arrowheads).
Progressive asbestosis in 76 years old patient with known asbestos exposure. CT chest coronal (A,D) and axial (B-C, E-F) images in lung window show calcified pleural plaques, subpleural predominant pulmonary fibrosis with subpleural curvilinear lines and honeycombing, which progressed over 3 years (D-F).

**Fig. 9:** Progressing asbestosis
**Fig. 10:** Drug toxicity: fibrotic lung disease in extrathoracic primary tumour treated by chemotherapy

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Mixed sarcomatous and epithelioid mesothelioma in 75 years old ex-heating engineer. T3N2M0. Plain film (A) shows widened right superior mediastinum (black arrows) as well as a small right sided pleural effusion with extension to the pleural fissure (black arrowheads). Contrast enhanced CT chest coronal reconstruction (B) and axial images (C, D, E) in soft tissue window show nodular thickening of the pleura (white arrows) with invasion of mediastinal fat (white arrowheads), enlarged right sided hilar and subcarinal lymph nodes (circles) and loculated right-sided pleural effusion (asterisk).

**Fig. 13:** Mixed sarcomatous and epithelioid mesothelioma T3N2M0.

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**Fig. 15:** Mesothelioma T2N1M0

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Mesothelioma T2N1M0. Contrast enhanced CT chest coronal reconstruction (A) and axial images (B, C) in soft tissue window show irregular thickening of the pleura (arrows) with invasion of diaphragm muscle (arrowhead) and irregular contour of collapsed right lower lobe, suggesting lung parenchyma invasion (white dotted arrow). Enlarged lymph nodes were seen in the mediastinum.

**Fig. 16:** Mesothelioma T4N1M0

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Mesothelioma T4N1M0. Plain film (A) shows diffuse left sided pleural thickening (black arrows) with a small pneumothorax (black dotted arrow) and fibrotic changes in the left hemithorax. Contrast enhanced CT chest axial images in soft tissue windows (B, C) and axial image in lung window (D) show diffuse partially calcified pleural masses, which extend to pleural fissure (white dotted arrow). Masses invade mediastinal fat tissue (asterisk), aortic wall (arrowhead) and endothoracic fascia (white arrow).
**Fig. 17:** Mesothelioma T4N2Mx

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**Mesothelioma T4N2Mx.** Contrast enhanced CT chest axial (A - D) images and coronal reconstructions (E, F) in soft tissue window show pleural masses in the right hemithorax (white arrows), which extend to pleural fissure (blue dotted arrow). Masses invade mediastinal fat tissue (asterisk), azygos vein (yellow arrowhead), endothoracic fascia and chest wall (yellow arrow), diaphragm and possibly liver parenchyma (black arrowhead). Right upper paratracheal (white circle) and right sided supraclavicular lymph nodes (yellow circle) are enlarged. Imaging for distant metastases was not yet performed.

**Fig. 18:** Mesothelioma T4N1M0

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**Mesothelioma (T4N1M0)** in 76 years old patient. CT chest axial images in soft tissue window (A, B) demonstrate irregular left sided pleural thickening (black arrows) with invasion of mediastinal fat (black dotted arrows) and pericardial nodular thickening (white arrows). Loss of subepicardial fat layer at the level of basal lateral left ventricle wall (white dotted arrows) on horizontal long axis (E) and short axis (D) reconstructions are noted suggest transmural pericardial invasion, stage T4. Consequently round atelectasis (circle) developed secondary to pleural changes (F). Enlarged ipsilateral hilar lymph nodes are not shown here. Note dilated left ventricle and thrombus in an apical aneurysm (arrowheads).
**Fig. 19:** Mesothelioma T4N1Mx

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**Mesothelioma T4N1Mx.** Contrast enhanced CT chest coronal reconstruction (A) and axial images (B, C) in soft tissue window show pleural masses in the right hemithorax (arrows) and encapsulated effusion (asterisk). Masses invade chest wall (dotted arrows). Note the enlarged lymph node in the right hilum (circle). Imaging for distant metastases was not yet performed.

**Fig. 20:** Adenocarcinoma with pleural metastases mimicking mesothelioma

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**Differential diagnosis. Adenocarcinoma with pleural metastases mimicking mesothelioma.** Contrast enhanced CT chest coronal reconstructions (A), axial image (B) and FDG PET CT axial images (C) and coronal reconstructions (D) show enhancing and FDG avid mass in the left upper lobe (circle), multiple pleural nodules (arrowheads) and lymphadenopathy (arrows).
**Differential diagnosis. Pyothorax in febrile parient with elevated inflammatory markers.** Contrast enhanced CT chest image in soft tissue window (A) shows loculated pleural effusion (white asterisk) with compressive changes of the adjacent lung segments. *Candida glabrata* was detected microbiologically. Two weeks after fluconazole therapy induction (B) pyothorax is partially resolved (black asterisks), but residual diffusely thickened pleural layers are seen (arrows).

**Fig. 21:** Pyothorax

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**Asbestosis and lung adenocarcinoma in 80 years old male with known asbestos exposure and smoking history.** CT chest axial images in lung (A, B) and soft tissue (C) windows show pleural plaques (arrow) and fibrotic changes (arrow head) suggesting asbestosis. The tumour in the right lung (asterisk) was histologically proven to be pulmonary adenocarcinoma.

**Fig. 22:** Asbestosis and lung adenocarcinoma

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Conclusion

Asbestos can cause a wide variety of diseases including asbestosis and malignant tumors. Knowledge of the natural history of diseases and imaging findings are important for timely diagnosis.
References


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