Occupational Lung Disease

4

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Occupational lung disease (OLD) refers to a variety of disorders that affect the lungs following inhalation of dusts or chemical antigens in the work setting. OLD is an important public health issue and responsible for approximately 70% of all deaths from occupational diseases [1]. Pneumoconioses comprise a subset of OLD that is defined as an interstitial lung disease caused by the inhalation of inorganic mineral dust. Other common work-related lung diseases include occupational asthma and hypersensitivity pneumonitis (see Chap. 3) secondary to the exposure to dusts or antigens from a growing list of inciting agents. Most pneumoconioses develop over the course of several decades and may have long latency periods between dust exposure and onset of disease. On the other hand, some individuals are more susceptible to occupational respiratory hazards because of differences in their genotype. For instance, the human leukocyte antigen (HLA)-DPB1 (E69) allele has been closely associated with sensitivity to beryllium, and individuals with such genotype are at increased risk to develop beryllium-induced disease among exposed workers [2]. Recognition of a causal relationship between dust exposure in the workplace and respiratory disease and subsequent implementation of effective workplace preventive measures has led to a major shift in the incidence and prevalence of respiratory disease over recent decades. For example, coal workers' pneumoconiosis associated with high-level coal mine dust exposure was once the most prevalent occupational lung disease, but increased automation in the coal mining industries and the implementation of efficient preventive exposure control measures have significantly reduced dust levels and thus the associated respiratory disease burden. Likewise, global consumption of asbestos has decreased following recognition of asbestos-related disease, and the incidence of asbestosis and malignant mesothelioma has since plateaued in developed countries although exposure to the fibers continues to be a threat during repair, maintenance, and demolition of asbestos-contaminated constructions [3]. Conversely, constant progress and technological developments in the work environment will lead to emerging new hazards for occupational respiratory disease requiring close monitoring to prevent adverse health effects [4]. OLD also includes lung diseases other than pneumoconioses. The histopathological characteristics of many of the pneumoconioses are quite characteristic allowing confident diagnosis in the presence of compatible occupational history and clinical features. Others, on the other hand show reaction patterns that are less specific and indistinguishable from non-occupational lung disease. In such cases, the diagnostic approach may require not only close correlation with vocational background and clinical presentation but also ancillary analytical methods. Correct interpretation of the disease process is particularly important not only for possible workers' compensation but also for prognosis and potential risk for development of neoplasia. Mineralogical analysis is not generally required in the diagnosis of most pneumoconioses as simple light microscopic observation and polarization is generally sufficient to characterize the particulate material. Analytical electron microscopy using a combination of electron microscopy and energy-dispersive spectrometry allows identification of particles in lung tissue that are too small to be identified by conventional light microscopy. Identification of the elemental composition of the dust is most often achieved with energy-dispersive X-ray analysis (EDXA). Newer methods, such as in-air microparticle-induced X-ray emission analysis, are also available but are currently only used in the research setting. A summary of the most pertinent findings of pneumoconioses is summarized in Table 4.1.

4.1 Silicosis

Silicosis is a fibrotic lung disease caused by the inhalation of crystalline silicon dioxide and is one of the most common occupational diseases worldwide [5]. The most important forms of silica in the workplace are quartz, tridymite, and cristobalite, and exposure to these particles occurs in many industries and occupations, including mining, quarrying, drilling, and tunneling operations, or among sandblasters,

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Table 4.1 Summary of pertinent findings in occupational lung diseases

Occupational lung disease	Inciting agent	Main pathological pattern	Imaging pattern	Additional features	Carcinogenic
Silicosis	Crystalline silica	*Acute silicosis:* alveolar proteinosis-like changes *Chronic silicosis:* silicotic nodule, progressive massive fibrosis	*Acute silicosis:* perihilar GGO and consolidation *Chronic silicosis:* small, well circumscribed centrilobular and perilymphatic nodules with upper lobe predominance; lymphadenopathy with eggshell calcification	Weak birefringent crystals	Yes (lung carcinoma)
Coal workers' pneumoconiosis	Coal dust	*Simple CWP:* coal dust macule, centriacinar emphysema; coal dust nodules (Medusa head) *Complicated CWP:* progressive massive fibrosis	*Simple CWP:* small, less well-defined centrilobular and perilymphatic nodules in mid and upper portions of lung; eggshell calcification uncommon *Complicated CWP:* large opacities with round or lentiform appearance	Mix of dim to bright birefringent crystals	Yes (lung carcinoma)
Asbestosis	Asbestos fibers	Paucicellular and collagenous interstitial fibrosis; bronchiolar wall fibrosis; asbestos bodies; honeycombing	Subpleural dot-like opacities and curvilinear lines; pleural-based irregular nodules; interstitial thickening; traction bronchiectasis; honeycombing	Asbestos bodies in lung tissue	Yes (mesothelioma, lung carcinoma)
Hard metal lung disease	Tungsten carbide/cobalt	Bronchiolitis obliterans; DIP-like reaction; GIP; collagenous fibrosis; honeycombing	Bilateral GGO; small centrilobular nodules; consolidation; reticulation; traction bronchiectasis; honeycombing	Emperiopoletic giant cells on BAL; urine or serum cobalt testing	No
Mixed dust pneumoconiosis	Crystalline silica and non-fibrogenic dusts (coal, iron, silicates)	Dust macules, mixed dust fibrotic lesions, silicotic nodules	Reticular, reticulolinear, or reticulonodular opacities; honeycombing; emphysema	Mix of dim to bright birefringent crystals	No
Beryllium lung disease	Beryllium	*Acute beryllium disease:* acute bronchitis, acute pneumonitis (diffuse alveolar damage) *Chronic berylliosis*: non-necrotizing granulomatous inflammation in bronchovascular distribution	*Acute beryllium disease:* airspace opacities *Chronic beryllium disease:* small parenchymal nodules in perilymphatic and septal distribution	Beryllium lymphocyte proliferation test on BAL	Yes (lung carcinoma)
Talcosis	Talc	*Inhaled form:* foreign body-type granulomatous response; progressive massive fibrosis; lower lobe emphysema *Injected form:* vascular and perivascular foreign body-type granulomas	Small centrilobular and subpleural nodules; GGO; irregular crescent-shaped large opacities; non-calcified pleural plaques; lymphadenopathy	Brightly birefringent needle-shaped crystals	No
Aluminosis	Aluminum	Dust-laden macrophages; UIP- or DIP-like patterns; non-necrotizing granulomas; alveolar proteinosis	Small rounded opacities with upper lobe predominance; thickening of interlobular septa; pulmonary fibrosis; honeycombing	Gray-black variably birefringent particles	No
Siderosis	Iron oxide	Dust-laden macrophages; DIP-like reaction; interstitial fibrosis; emphysema	Diffuse, ill-defined nodules; extensive GGO; emphysema; fibrosis; honeycombing; conglomerate masses	Ferritin levels in serum or BAL	No

Table 4.1 (continued)

Occupational lung disease	Inciting agent	Main pathological pattern	Imaging pattern	Additional features	Carcinogenic
Silicatosis	Silicon dioxide	Dust macules; progressive massive fibrosis; occasional multinucleate giant cells; emphysema; pleural fibrosis	Linear or nodular shadowing; diffuse irregular opacities; conglomerate masses	Brightly birefringent particles	No

GGO ground glass opacities, *CWP* coal workers' pneumoconiosis, *BAL* bronchoalveolar lavage, *UIP* usual interstitial pneumonitis, *DIP* desquamative interstitial pneumonitis, *GIP* giant cell pneumonitis

Table 4.2 Occupational activities with exposure to crystalline silica

Construction
Mining
Quarrying
Milling
Sandblasting
Agriculture
Ceramics and pottery
Shipbuilding
Foundry work
Arts, craft, and sculpture
Production of cement, plastics, and rubber
Stone masonry

Table 4.3 Disorders associated with exposure to silica

Silicosis
Infections (tuberculosis, atypical mycobacterial infection)
Neoplasia (lung carcinoma)
Chronic obstructive pulmonary disease (COPD)
Autoimmune diseases (rheumatoid arthritis, scleroderma)
Chronic renal disease

stonecutters, and foundry or brick workers [6–9] (Table 4.2). Although interstitial lung disease is the most common pathologic effect of silica, a number of other conditions may also be attributed to the mineral, including infectious disease (especially tuberculosis and atypical mycobacterial infection), small airway disease, autoimmune diseases, chronic renal disease, and lung cancer [6, 7] (Table 4.3). The development and severity of silicosis depends on the total amount, intensity, and duration of exposure to the agent and is usually associated with long duration (>10 years) and a dust content of 18–30% of crystalline silica [9]. Clinically, silicosis can be divided into several distinct forms, including *acute (silicoproteinosis)*, *accelerated*, and *chronic (or classic) silicosis*. The latter can be further subdivided into *simple* and *complicated* (or *massive progressive fibrosis*) variants according to the radiologic impression [6, 10–12] (Table 4.4). As with other occupational lung diseases, the diagnosis of silicosis relies on a history of substantial exposure to silica dusts together with corresponding radiological features and the results of lung biopsy in selected cases.

Table 4.4 Subtypes of silicosis

Acute silicosis (silicoproteinosis)
Accelerated silicosis
Chronic silicosis (classic silicosis) - *Simple silicosis and complicated silicosis (massive progressive fibrosis)*

4.1.1 Clinical Features

The presentation of patients with silicosis depends on the type of exposure to silica dust. In *acute silicosis*, individuals with heavy exposure to silica in enclosed spaces present with constitutional symptoms and rapidly progressive dyspnea which may result in respiratory failure and death [13, 14]. Patients with *accelerated silicosis* typically have suffered short but intense exposure (4–10 years); their clinical and radiographic presentation however is similar to patients with chronic silicosis [11]. Clinical presentation of patients with *chronic silicosis* can range from no symptoms in mild disease to cough and progressive dyspnea in advanced disease. The radiographic findings of *acute silicosis* consist of bilateral consolidation or ground glass opacities in a perihilar distribution, while high-resolution computed tomography (HRCT) scanning will show numerous bilateral nodular ground glass opacities in a centrilobular pattern as well as areas of consolidation [15, 16]. Radiographically, *simple silicosis* is characterized by multiple nodular opacities that are uniform and well circumscribed and range in size from 1 to 10 mm. These nodules are typically located in the upper posterior lungs and can show calcification in 10–20% of cases [10]. HRCT findings include the presence of multiple small nodules, 2–5 mm in diameter, in a centrilobular or perilymphatic distribution. These can be diffusely distributed throughout both lungs but tend to be more numerous in the upper lobes; calcification and subpleural clustering forming pleural pseudoplaques are common. Hilar and mediastinal lymphadenopathy is a frequent finding as are calcifications in an "eggshell pattern." Large symmetric bilateral opacities (>1 cm) as a result from coalescence of smaller nodules are characteristically seen in *complicated silicosis*. These are commonly observed in the middle lung zone or peripheral lung and often have irregular and ill-defined margins. Cavitation and calcifica-

tion may occur suggesting ischemic necrosis or superimposed tuberculosis. Paracicatricial emphysema is another common CT finding of *complicated silicosis* [10, 11]. *Acute silicosis* is a rapidly progressive disease that is frequently fatal within 1 year of the onset of symptoms due to cor pulmonale and respiratory failure despite medical therapy with corticosteroids [13, 17, 18]. Patients with *chronic silicosis* usually develop slowly progressive pulmonary fibrosis which can result in end-stage lung disease. Proven curative treatment currently does not exist for the chronic forms of the disease. Except for measures to avoid further exposure, the only other treatment consists of supportive therapy as other approaches, such as whole-lung lavage and corticosteroids, have failed to provide sustained improvement in lung function. Lung transplantation has been successfully performed in patients with end-stage lung disease [6, 8]. Of note, patients with silicosis are not only considered high risk for tuberculosis *(silicotuberculosis)* and other mycobacterial infections [6] but also have an increased risk for the development of lung cancer. Hence, tuberculin skin test and close radiological follow-up is indicated in all patients with silicosis [19].

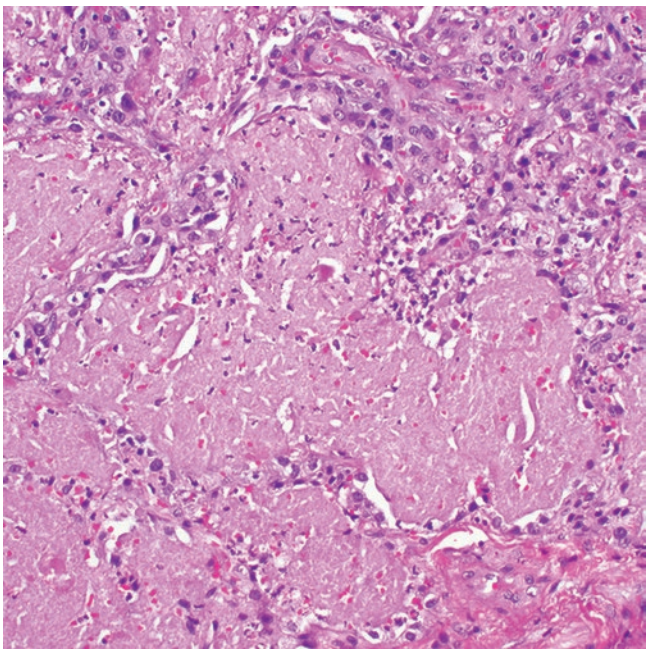

Fig. 4.1 Acute silicosis (silicoproteinosis) histologically characterized by granular lipoproteinaceous material within alveolar spaces

4.1.2 Pathological Features

Gross examination of lungs with simple silicosis typically shows discrete nodules that are very firm in consistency and gray-blue or black in color scattered in the lung parenchyma. In the complicated form, the lungs will demonstrate larger confluent nodules that are densely collagenous as well as areas of fibrosis. Histopathologic analysis of *acute silicosis (silicoproteinosis)* will display features reminiscent of primary alveolar proteinosis, i.e., granular lipoproteinaceous material filling the alveolar spaces along with severe alveolitis [15, 20] (Fig. 4.1). The histological hallmark of *chronic silicosis* is the silicotic nodule. Silicotic nodules are usually found in the respiratory bronchioles and are composed of concentric fibrotic and hyalinized laminar layers of collagen, fibroblasts, and lymphocytes surrounded by a peripheral zone of dust-laden macrophages [9, 21, 22] (Fig. 4.2a–c). Polarized light microscopy will usually reveal weakly birefringent silica crystals and more strongly birefringent silicate crystals measuring approximately 1–3 μm in length [23] (Fig. 4.3a, b). With continued exposure to the mineral, the small nodules of *simple silicosis* will enlarge and coalesce resulting in conglomerate fibrosis (progressive massive fibrosis) (Fig. 4.4). Focal necrosis may occur especially in the central portions of the lesion and may occasionally be associated with granulomatous inflammation or cavitation [9, 10, 24, 25].

4.1.3 Mineral Analysis

Scanning electron microscopy will reveal an angulated shape of the silica particles. Analytical electron microscopy with EDXA can be used to identify the composition of the inhaled dust.

4.1.4 Differential Diagnosis

The differential diagnosis of silicosis includes other types of fibrotic lung disease. First and foremost, detailed clinical and occupational history usually allows for separation from other types of interstitial lung diseases, especially the idiopathic forms. Distinction from other forms of occupational lung disease may be achieved on the basis of a combination of occupational exposure, radiological appearance, and histopathological evaluation. For instance, asbestosis can be differentiated from silicosis by the presence of diffuse pulmonary fibrosis, pleural plaques, and the presence of asbestos bodies in bronchoalveolar lavage fluid or tissue specimens. In coal workers' pneumoconiosis, the parenchymal deposits consist of coal macules rather than silicotic nodules; the former are less well-defined and consist of coal dust-laden macrophages intermixed with collagen. Abundant free pigment, lack of eggshell calcifications in the lymph nodes, and more dot-like calcifications as opposed to diffuse

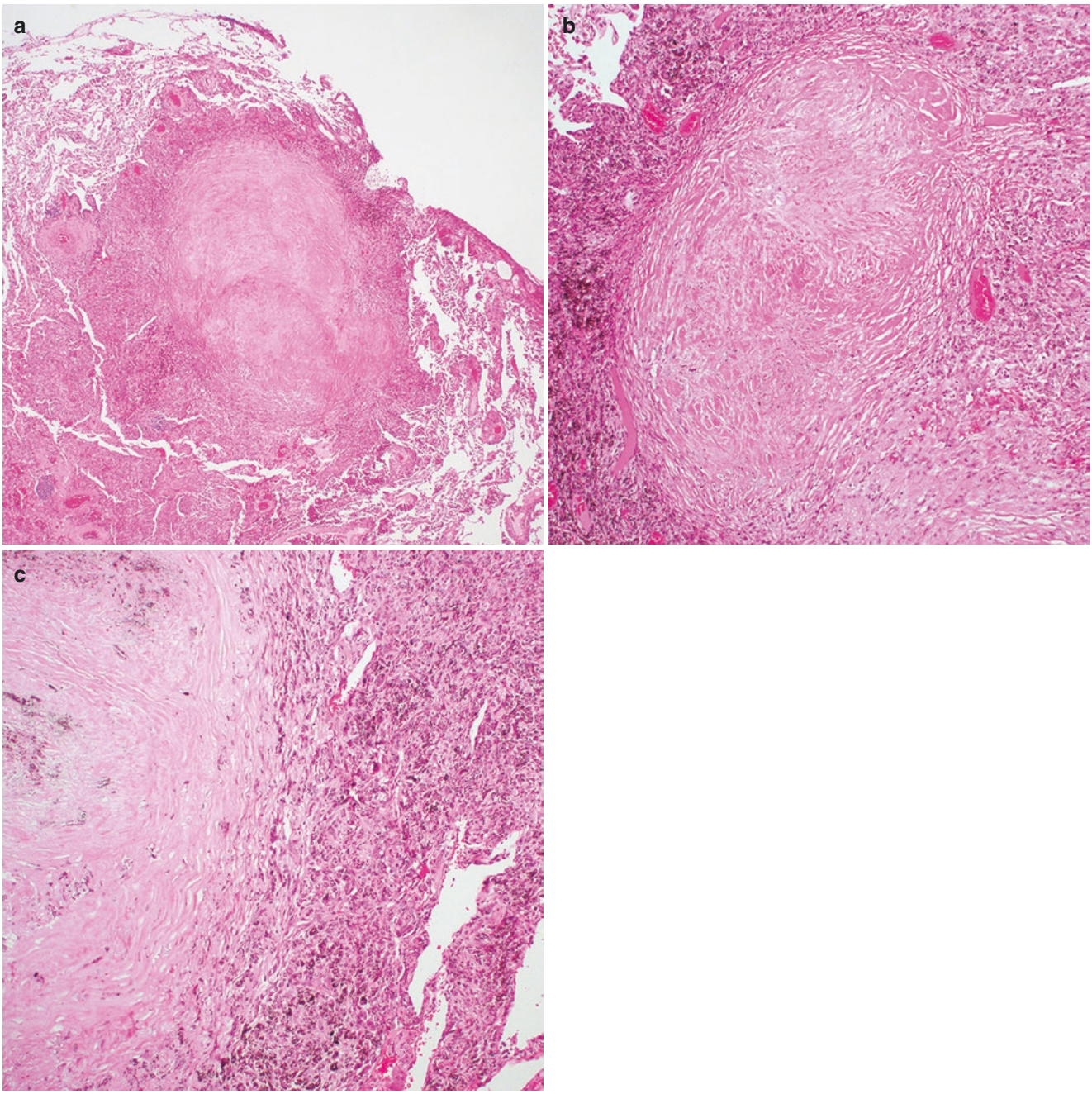

Fig. 4.2 (**a**) Low power view of a silicotic nodule located in the subpleural lung parenchyma; (**b**) silicotic nodules are composed of concentric layers of collagen; (**c**) the periphery of the nodules often contains a zone of dust-laden macrophages

calcifications within the parenchymal deposits in silicosis are other distinguishing features. On the other hand, the nodules in mixed dust pneumoconiosis often have a stellate-shaped appearance and a more linear arrangement of collagen fibers than silicotic nodules. *Silicotuberculosis* can be separated from pure silicosis by the presence of superimposed necrotizing granulomatous inflammation; such a finding should also prompt re-evaluation of the silicotic nodules in order to exclude the possibility of miliary tuberculosis.

4.2 Coal Workers' Pneumoconiosis

Coal workers' pneumoconiosis (CWP) develops in individuals exposed to washed coal or mixed dust containing coal, silica, kaolin, and mica [10], generally in the mining environment. The development of CWP usually requires an exposure time of more than 20 years and depends on several factors, including the concentration of the coal dust, type of coal, mine configuration, and personal protective measures

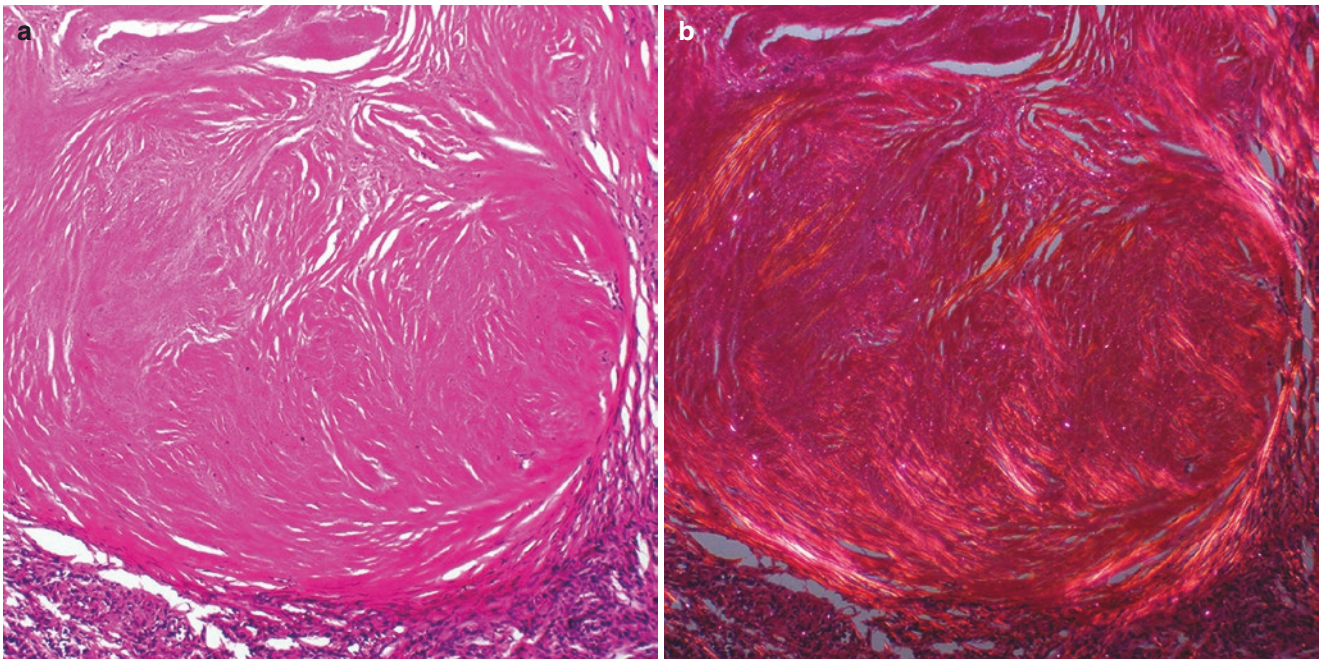

Fig. 4.3 (**a**) The hypocellular nodules in chronic silicosis contain (**b**) a mix of weakly and strongly birefringent crystals using polarized light microscopy. (Courtesy of Dr. K Syred, Plymouth, UK)

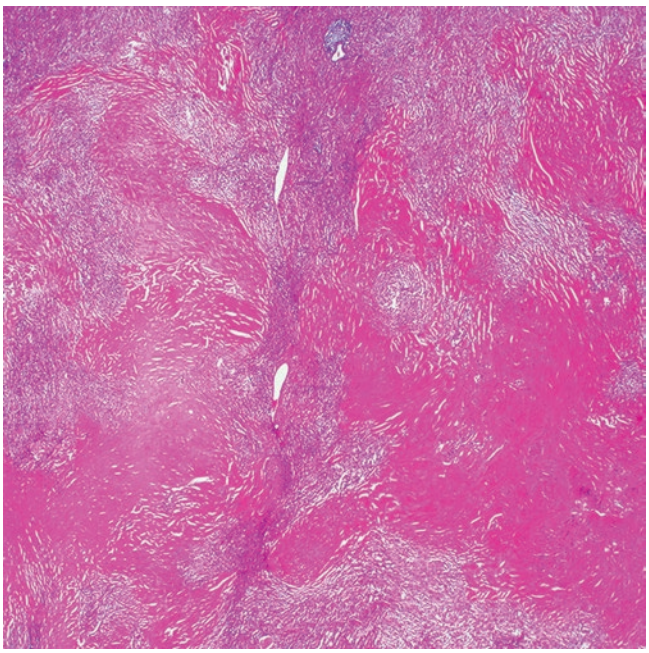

Fig. 4.4 Large confluent areas of fibrosis can be seen with progressive silicosis (progressive massive fibrosis). (Courtesy of Dr. K Syred, Plymouth, UK)

among which the inhaled quantity of coal dust particles appears to be the most important factor [26]. Like silicosis, CWP can be divided into simple and complicated forms, and imaging findings closely resemble those of silicosis. Interstitial fibrosis develops in less than 20% of at-risk coal miners, usually in the form of usual interstitial pneumonitis (UIP) or non-specific interstitial pneumonitis (NSIP) [27]. Implementation of the 1969 Federal Coal Mine Health and Safety Act [28] which introduced a limit of respirable dust in the air of US coal mines led to a significant decrease in the prevalence and severity of CWP; however, a considerable burden of disease remains in miners working entirely under the new standards, suggesting that further measures to reduce the dust burden in coal mines remain indicated [29].

4.2.1 Clinical Features

Coal workers with CWP may be entirely asymptomatic or present with slowly progressive dyspnea and decline in pulmonary function. Chronic bronchitis, emphysema, and chronic obstructive pulmonary disease (COPD) are other conditions associated with coal dust exposure, and emphysema rather than the nodular changes of CWP is more likely the major contributing factor to the decline in lung function in these patients [30]. Patients with complicated CWP may also report coughing up black sputum (melanoptysis). *Rheumatoid pneumoconiosis* or *Caplan syndrome* describes a characteristic imaging pattern in coal miners suffering from rheumatoid arthritis characterized by the presence of large and clustered nodules (0.5–5 cm) predominantly in the periphery of the lungs that appear very suddenly [31]. The imaging features of CWP are indistinguishable from silicosis and consist of small nodules in a perilymphatic or centrilob-

ular distribution in the mid and upper portions of the lungs in simple CWP. These nodules typically measure 1–5 mm in diameter and tend to be less well-defined than in silicosis. Pseudoplaques can result from aggregation of subpleural nodules, and calcification is present in up to 20% of patients. Notably, the characteristic "eggshell" pattern of calcification affecting mediastinal lymph nodes in silicosis is uncommon in CWP. HRCT of complicated CWP will display one or more large opacities (>1 cm) that typically arise in the lung periphery as round or lentiform nodules and that have a lateral border that parallels the chest wall. As these opacities enlarge, pericicatricial emphysema typically results. Like in silicosis, calcification and cavitation of the nodules may occur, either due to superimposed infection or ischemic changes [10, 11]. There is no effective specific treatment for CWP, and prevention and removal of the source of the inciting agent remains the best therapeutic option for patients with this disease [24]. Analogous to silicosis, patients with CWP have a higher incidence of mycobacterial infection and development of lung cancer than the normal population [32, 33].

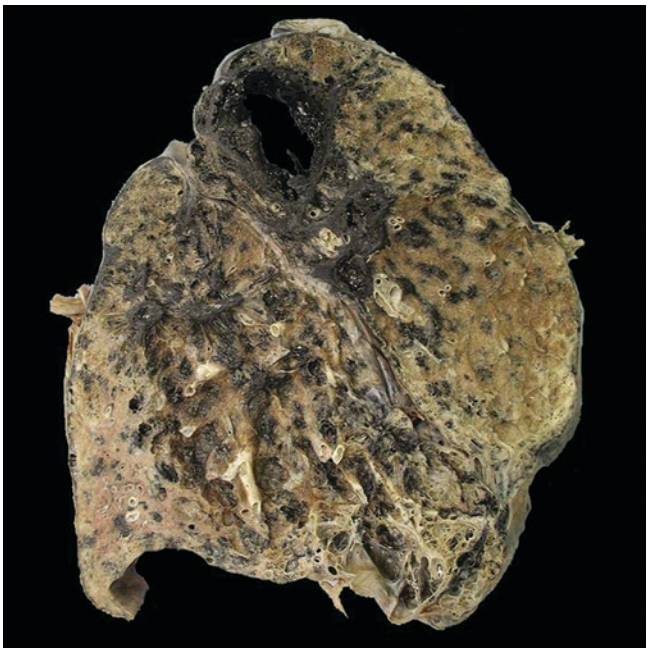

Fig. 4.5 Black macules are grossly apparent in this lung of a patient with coal workers' pneumoconiosis. Note the large cavitating pigmented lesion in the apex. (Courtesy of Dr. G Langman, Birmingham, UK)

4.2.2 Pathological Features

Although radiologically silicosis and CWP are often indistinguishable, the pathological findings are quite distinct. The most characteristic histological feature of *simple CWP* is the coal dust macule. Grossly, these macules can be identified as small foci of black pigmentation that predominantly involve the upper lobes and upper zones of the lower lobes (Fig. 4.5). Pigmentation of pleural lymphatics can also be noted and is one of the characteristic gross features of CWP. Microscopically, coal dust macules consist of small aggregates of dust-laden pigmented macrophages that vary in size from 1 to 5 mm and are often found in the walls of respiratory bronchioles and adjacent alveoli (Fig. 4.6). Associated collagen deposition is minimal; however, centriacinar emphysema is common and in fact required for pathologic diagnosis [29, 34–37]. Coal nodules are slightly larger than macules (up to 10 mm) and tend to occur in a background of CWP. These are fibrotic nodules consisting of mixed coal and fibrogenic dusts (often silica) and irregular collagen fibers (Fig. 4.7). Contrary to silicotic nodules, coal dust nodules often have irregular contours (*Medusa head*) and lack the hyalinized and laminated collagen core of the former (Fig. 4.8). In *complicated CWP*, gross examination of the lungs will show large confluent areas of pigmented fibrosis that are typically bilateral and upper zone predominant. Microscopically, complicated CWP is characterized by progressive massive fibrosis (PMF). This can take the form of uniform areas of pigmented fibrosis with irregular or whorled appearance or coalescence of coal nodules exceeding a diameter of 1 cm. The fibrosis typically destroys and replaces the underlying lung architecture. The large

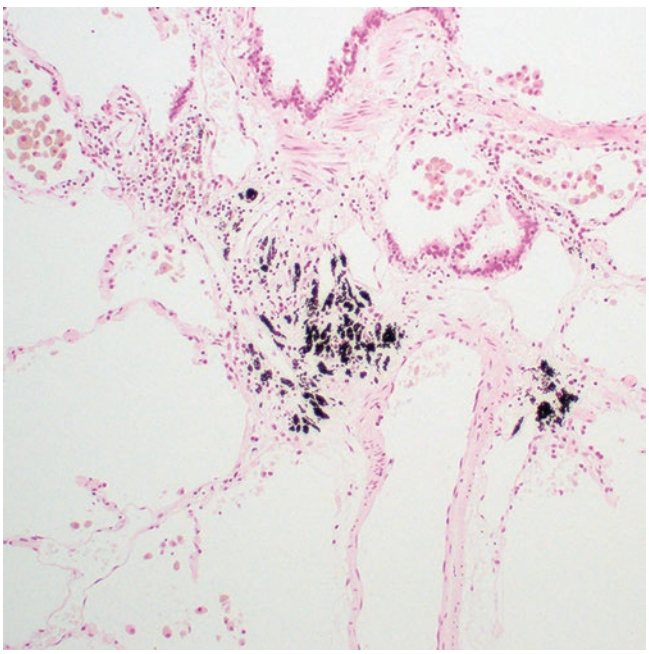

Fig. 4.6 Coal dust macules in coal workers' pneumoconiosis consisting of accumulations of dust-laden pigmented macrophages in the walls of respiratory bronchioles associated with little fibrosis

fibrotic lesions of complicated CWP may develop features of degeneration, such as liquefactive necrosis or cavitation; the latter should raise the suspicion for superimposed mycobacterial infection [35, 38–40]. Ferruginous bodies may be present and

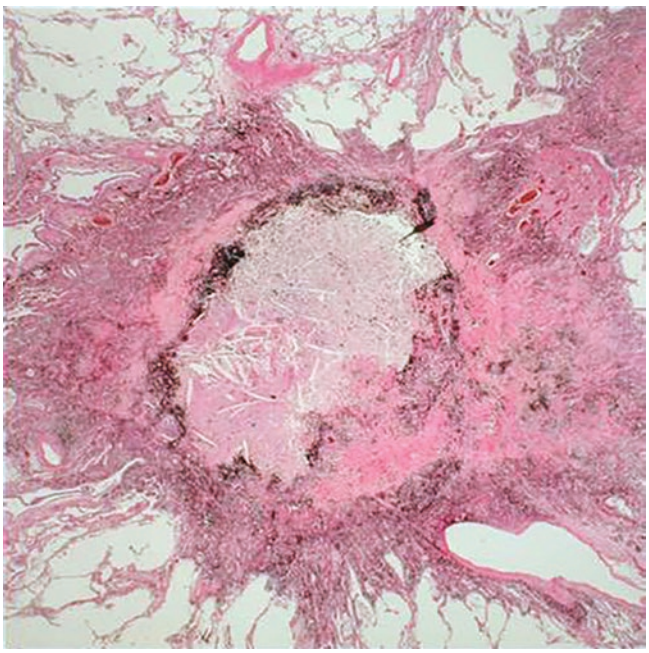

Fig. 4.7 Coal dust nodules are larger than macules and composed of collagen mixed with coal and fibrogenic dusts. (Courtesy of Dr. G Langman, Birmingham, UK)

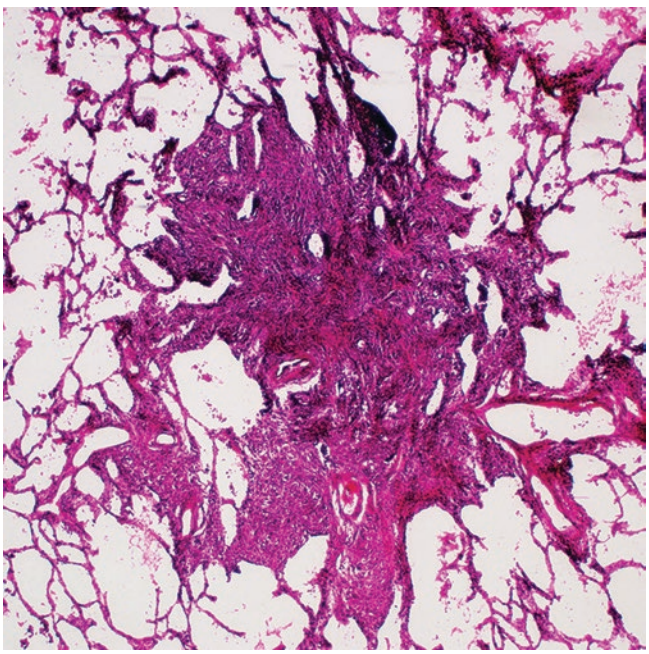

Fig. 4.8 Coal dust nodules often have a Medusa head appearance with irregular extensions into the surrounding parenchyma

will usually be found within alveolar spaces. Contrary to true asbestos bodies, these are typically composed of a straight black core fiber. Examination under polarized light shows a range of dim to brightly birefringent crystals representing the mixed character of the dust (Fig. 4.9). Other forms of diffuse interstitial lung

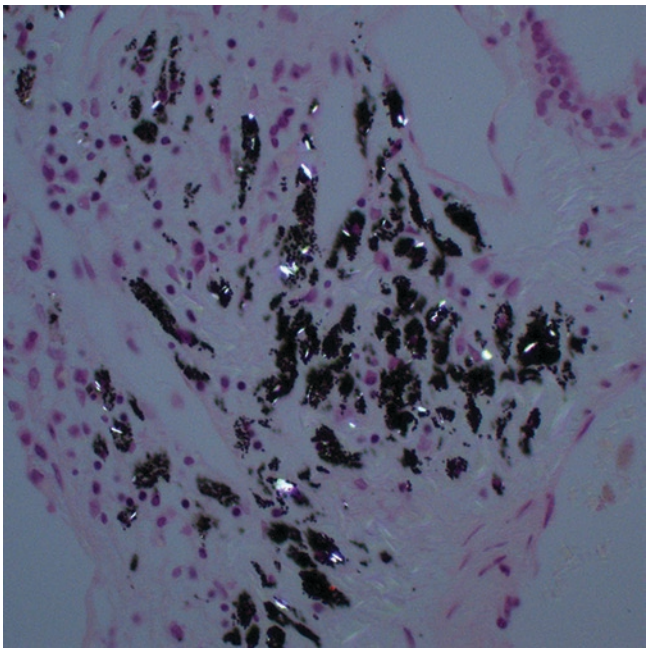

Fig. 4.9 A mix of dim to brightly birefringent crystals is a characteristic finding in coal dust macules and nodules under polarized light

disease can develop in approximately 20% of patients, usually in the form of UIP or NSIP [27]. Moreover, the presence of classic silicotic nodules is not an uncommon finding in CWP due to the common occurrence of silica among the inhaled coal dust. The nodules of *rheumatoid pneumoconiosis* (*Caplan syndrome*) closely resemble the rheumatoid nodules of rheumatoid arthritis [31]. These are typically of larger size (up to 5 cm or more), mostly found in a subpleural location, and composed of a core of fibrinoid necrosis surrounded by a layer of fibroblasts, palisading histiocytes, and inflammatory cells, including lymphocytes, plasma cells, eosinophils, and giant cells. Rings of coal dust can often be appreciated in the periphery of these nodules. Since the nodules can closely mimic infectious granulomas, close correlation with clinical history, serologic, and culture studies is necessary before a diagnosis of rheumatoid pneumoconiosis can be confirmed [40].

4.2.3 Mineral Analysis

Coal dust is usually composed of a mixture of carbon, silicates, and silica. Although mineral analysis is not generally required, analytical methods, such as analytical electron microscopy or EDXA, may be used to support the diagnosis.

4.2.4 Differential Diagnosis

The pathologic differential diagnosis of CWP primarily includes silicosis, infectious lung disease, or involvement

of the lung by rheumatoid arthritis. Silicotic lung disease often produces clinical and radiological signs and symptoms that are indistinguishable from CWP. At a histological level, however, coal dust macules or nodules differ from silicotic nodules based on their irregular borders and irregular arrangement of collagen fibers, whereas in silicotic nodules the contours are usually well-defined and the collagen bundles are concentrically arranged. Use of polarized light microscopy may identify crystalline silica or silicate minerals in the latter. Infectious granulomas may pose a diagnostic difficulty, especially if associated with pigmentation and after special stains have failed to identify any infectious organism. In this scenario, close attention should be paid to the more random distribution of the lesions in infectious disease and an absence of any other identifying features of coal dust exposure, such as coal dust macules. Rheumatoid nodules of the lung unrelated to occupational lung disease typically lack the ring-like dust deposition of nodules in rheumatoid pneumoconiosis.

4.3 Asbestosis and Benign Asbestos-Related Lung Disease

Asbestos-related lung disease (ARLD) continues to be a significant health burden despite the ban of asbestos use in most developed countries. The long latency between asbestos exposure and manifestation of disease is the reason why the incidence of ARLD keeps increasing worldwide. Along with the malignant conditions linked to asbestos exposure – malignant mesothelioma and lung carcinoma (discussed in chapters 22 and 12, respectively) – inhalation of the fibers can result in benign pleuropulmonary disease, including pleural effusions, pleural plaques, rounded atelectasis, diffuse pleural thickening (DPT), and diffuse pulmonary fibrosis (*asbestosis)* (Table 4.5). Collectively, the term asbestos refers to a group of naturally occurring fibrous silicates with high durability, tensile strength, and heat resistance. Based on these qualities, asbestos has been used in many industries, such as shipyards, construction and electrical industry, thermal insulation, and car manufacturing among others. Asbestos can be grouped into two different categories, amphiboles and serpentines depending on their mineralogical properties. The amphibole group incorporates the commercially exploited crocidolite (blue asbestos) and amosite (brown asbestos) along with other non-commercial forms. The serpentine group only consists of a single variety, chrysotile or white asbestos, which represents >90% of the asbestos used worldwide [41] (Table 4.6). Epidemiologic studies have demonstrated that the risk of developing ARLD is not only dependent on the cumulative asbestos dose [42] but also on the fiber type and its aerodynamic properties. As such, the curly and short fibers of the serpentine chrysotile have been shown to be less fibrogenic and tumorigenic than the straight and long fibers of the amphiboles crocidolite and amosite [43–46]. Despite the ban of asbestos use in most developed countries, the effects of occupational exposure in the 1960s–1980s are manifesting themselves today, and many countries are currently experiencing a peak of ARLD. Despite its well-known adverse health effects, asbestos mining and processing still continues in developing countries, among which Russia and China now belong to the leading producers and consumers [41]. Consequently,

Table 4.5 Asbestos-related lung disease

Asbestos-related lung disease	Latency period	Radiology	Pathology	Prognosis
Benign pleural effusion	5–10 years	Unilateral pleural effusion	Serosanguinous exudate	Benign, usually asymptomatic
Pleural plaques	20–30 years	Pleural plaques along basolateral chest wall and diaphragm	Hyalinized fibrous tissue +/− calcification	Benign, usually asymptomatic
Rounded atelectasis	20–40 years	Subpleural lung mass with comet tail sign	Atelectasis; pleural fibrosis; pleural invagination	Benign, usually asymptomatic
Diffuse pleural thickening	15 years	Irregular pleural shadowing with blunting of costophrenic angles	Pleural fibrosis +/− lymphoid aggregates	Benign
Asbestosis	20–40 years	Subpleural dot-like opacities and curvilinear lines; pleural-based irregular nodules; interstitial thickening; traction bronchiectasis; honeycombing	Paucicellular and collagenous interstitial fibrosis; bronchiolar wall fibrosis; asbestos bodies; honeycombing	May lead to respiratory failure or malignant asbestos-related lung disease
Mesothelioma/ lung carcinoma	20–40 years	Pleural effusion; diffuse nodular pleural thickening; solitary lung lesion	*Mesothelioma:* epithelioid, sarcomatoid, or biphasic malignancy *Lung carcinoma:* usually non-small cell lung carcinoma (NSCLC)	Malignant; usually fatal

Table 4.6 Mineralogic types of asbestos

Amphiboles	*Serpentine*
Commercial: Amosite (brown asbestos), crocidolite (blue asbestos) *Non-commercial:* Tremolite, actinolite, anthophyllite	Chrysotile (white asbestos)
<10%	>90%
Long thin fibers	Short curved fibers
Stable in lung	Unstable in lung
Highly fibrogenic and carcinogenic	Less fibrogenic and carcinogenic

an increase in the incidence and prevalence of ARLD is expected in these countries in the next few decades.

4.3.1 Clinical Features

ARLD primarily affects patients with direct occupational exposure to raw asbestos or asbestos products such as miners, shipyard workers, electricians, construction or industrial workers, and firefighters among others. Indirect exposure is attributed to exposure to asbestos that occurs through contamination of the worker's clothing or hair and most often affects members of the same household that come into contact with the fibers [47–49]. Another non-occupational source of asbestos exposure has been identified in relation to home renovation or car maintenance practices with increasing rates of ARLD among occupants or renovators of buildings that contain asbestos [50]. All types of ARLD typically develop after a long latency period from time of initial exposure to clinical onset of the disease, which is usually in excess of 20 years. Pleural effusion on the other hand is often the first thoracic manifestation of asbestos exposure and typically occurs after a latency period of 5–10 years [51]. *Benign pleural effusions* occur in approximately 0.7% of workers exposed to asbestos [52]. The diagnosis can only be made after careful exclusion of other causes of pleural effusion as the clinical signs and symptoms are indistinguishable from other underlying etiologies. The effusion is typically asymptomatic; more rarely patients present acutely with fever, pleuritic chest pain, and elevated inflammatory markers in the serum [53]. The process is mostly unilateral and resolves after 3–4 months, although recurrent effusions can be seen in 30–40% of cases, and in half of the patients, progression to DPT will ensue [54]. *Pleural plaques* are the most common manifestation of asbestos-related pleural disease (up to 80% of exposed workers) occurring 20–30 years after exposure [55]. They usually do not cause any symptoms and are typically an incidental finding on imaging procedures performed for unrelated reasons. In contrast to DPT, pleural plaques are only infrequently associated with respiratory impairment. *Rounded atelectasis* is caused by invagination of an area of visceral pleural thickening into the underlying parenchyma causing atelectasis of that portion of the lung. Rounded atelectasis can also occur secondary to other benign causes of pleural thickening and is not specific to ARLD; however, it should be noted that in isolated cases, the process may be seen in association with mesothelioma [56]. *DPT* affects 2–6% of asbestos-exposed patients and is often a sequel of recurrent pleural effusions [57]. The process often affects the visceral pleura, especially along the lung bases and often is bilateral in distribution. Breathlessness on exertion and pleuritic chest pain are the most common clinical findings along with a restrictive ventilator defect. Like most other manifestations of ARLD, DPT is not necessarily asbestos-induced but can be seen in many other conditions, such as empyema, tuberculosis, connective tissue diseases, or drugs among others. *Asbestosis*, defined as a diffuse interstitial pulmonary fibrosis due to inhalation of excess asbestos fibers, has a latent period of more than 20 years and primarily occurs in workers with heavy and prolonged exposure to asbestos [58, 59]. Progressive dyspnea and dry cough are the most common presenting symptoms of the disease, and finger clubbing may be seen in severe cases. Lung function tests will show a restrictive ventilatory pattern and reduced gas transfer [60]. The diagnosis of asbestosis often relies on clinical history, exposure history, and radiological findings and only rarely requires lung biopsy; however, if the disease is subclinical or if clinical and radiological features are atypical or non-diagnostic, lung biopsy may be helpful to resolve other diagnostic considerations. Radiologic imaging of pleural effusions in ARLD will most often demonstrate a unilateral effusion with a left-sided predominance and possible residual blunting of the costophrenic angle [54]. Pleural plaques are more easily detectable on high-resolution computed tomography (HRCT) scans of the chest than chest X-ray and most commonly develop along the posterolateral chest wall between the sixth and tenth ribs and along the diaphragm [61]. The HRCT signs of rounded atelectasis include the presence of a peripheral lung mass that abuts the pleura and that has a characteristic curving tail of invaginated bronchovascular structures spiraling into the mass ("comet tail sign") [55, 62]. On chest radiographs, DPT presents with irregular pleural shadowing that extends to both chest walls and can result in blunting of the costophrenic angles. According to Lynch et al. [63], DPT is defined on HRCT as a contiguous sheet of pleural thickening 3 mm thick and more than 5 cm wide on traverse images and 8 cm or greater in craniocaudal extent. HRCT findings of asbestosis include subpleural curvilinear opacities, ground glass opacities, subpleural poorly defined centrilobular nodules, thickening of the interlobular septa, parenchymal bands, traction bronchiectasis, and honeycombing [10, 55, 62, 64]; especially, the presence of pleural disease in combination with subpleural centrilobular nodules is indicative of asbestosis rather than other forms of

pulmonary fibrosis [10, 64]. The treatment of the group of benign ARLD is non-specific and largely limited to supportive or symptomatic care. Drainage of pleural effusion or decortication of DPT may be helpful in some patients. For patients with asbestosis, no effective therapy currently exists, and management usually follows the guidelines for patients with other interstitial lung diseases with focus on surveillance, prevention, and symptom abatement. Aside from malignant mesothelioma, asbestos exposure also predisposes affected individuals to develop lung cancer with asbestos-related lung cancer accounting for 5–10% of all lung cancer cases [65]. The risk of developing lung cancer not only appears to depend on cumulative asbestos exposure (≥25 fibers/ml-years) [65] but also on the smoking status of the patient, as tobacco use has been associated with a multiplicative synergistic effect on the incidence of lung cancer [66, 67]. For this reason, smoking cessation plays a major role in the surveillance and treatment of individuals with a past history of asbestos exposure.

4.3.2 Pathological Features

Benign pleural effusions associated with asbestos exposure are composed of a sterile serosanguinous exudate, and pleural biopsy may show normal histological findings or an acute fibrinous pleuritis. Fibrotic pleural changes may develop with recurrent disease [66]. *Pleural plaques* can vary in size and number and are pale yellow or white in appearance and usually found on the posterolateral chest wall, dome of the diaphragm, and mediastinal pleura (Fig. 4.10a, b). They are sharply demarcated from the surrounding pleura and subpleural tissue and have a tendency to calcify. Microscopically, they are hypocellular lesions composed of hyalinized fibrous tissue with collagen bundles arranged in a "basket weave" pattern [62, 66, 68, 69] (Fig. 4.11a, b). *Rounded atelectasis* grossly shows an ill-defined area of atelectasis with a deeply invaginated pleural fold; microscopically, it is characterized by a combination of atelectasis, pleural fibrosis, and pleural invagination [70]. Unlike pleural plaques, DPT is characterized by a diffuse process involving the pleural surfaces, mainly at the lung bases and often bilateral in distribution. Involvement of the fissures is commonly seen. Light microscopy will show a basket weave type of fibrosis with occasional lymphoid aggregates [71]. The macroscopic features of *asbestosis* are variable and may range from grossly unremarkable lungs to small and fibrotic lungs in advanced stages of the disease. Honeycomb change in the form of subpleural cystic spaces may be seen (Fig. 4.12). These findings are generally more common in the lower lobes and the periphery of the lungs. Fibrotic changes can be seen as areas of firm gray tissue with accentuation of secondary lobular septa. Although the airways are typically unremarkable, areas of traction bronchiectasis can be noted in advanced cases.

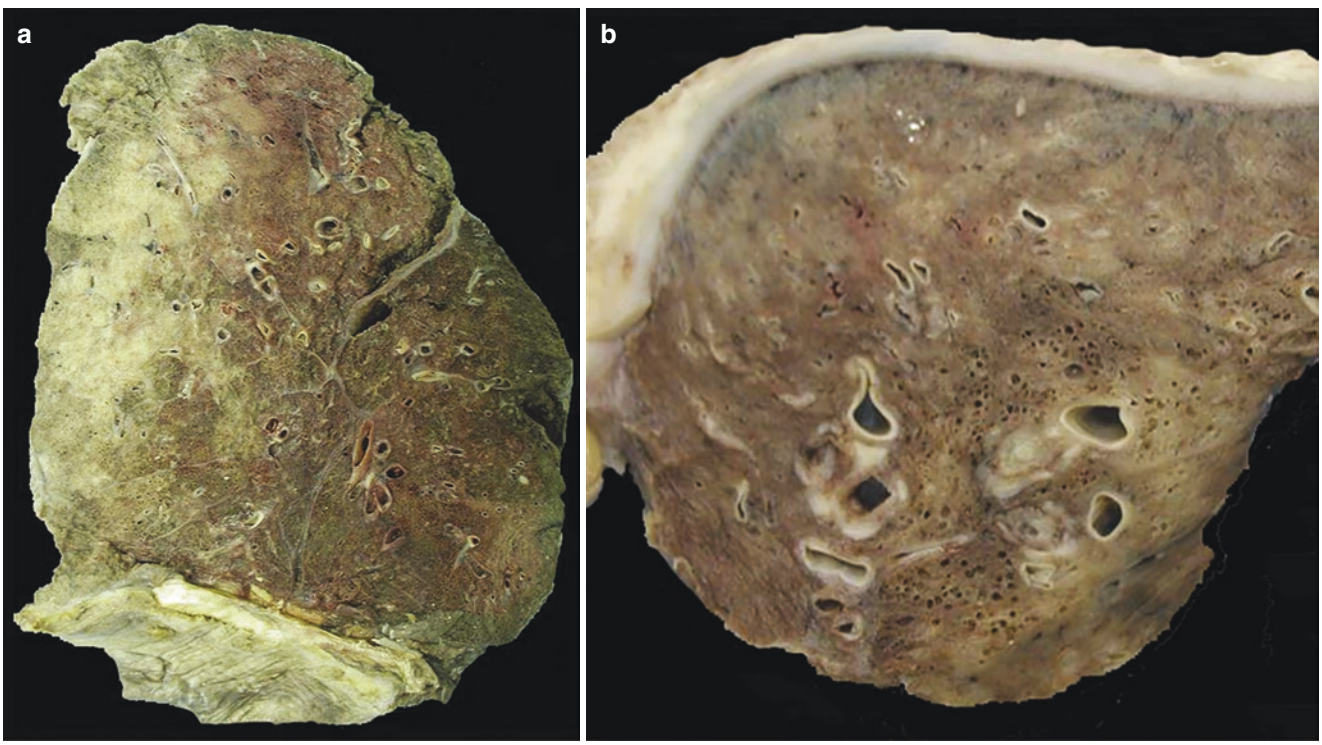

Fig. 4.10 (**a**) A calcified pleural plaque is apparent on the inferior surface of the right lung. (Coutesy of Dr. G Langman, Birmingham, UK); (**b**) prominent pleural fibrosis with plaque formation on the surface of the lung forming a pleural rind. (Courtesy of Dr. G Langman, Birmingham, UK)

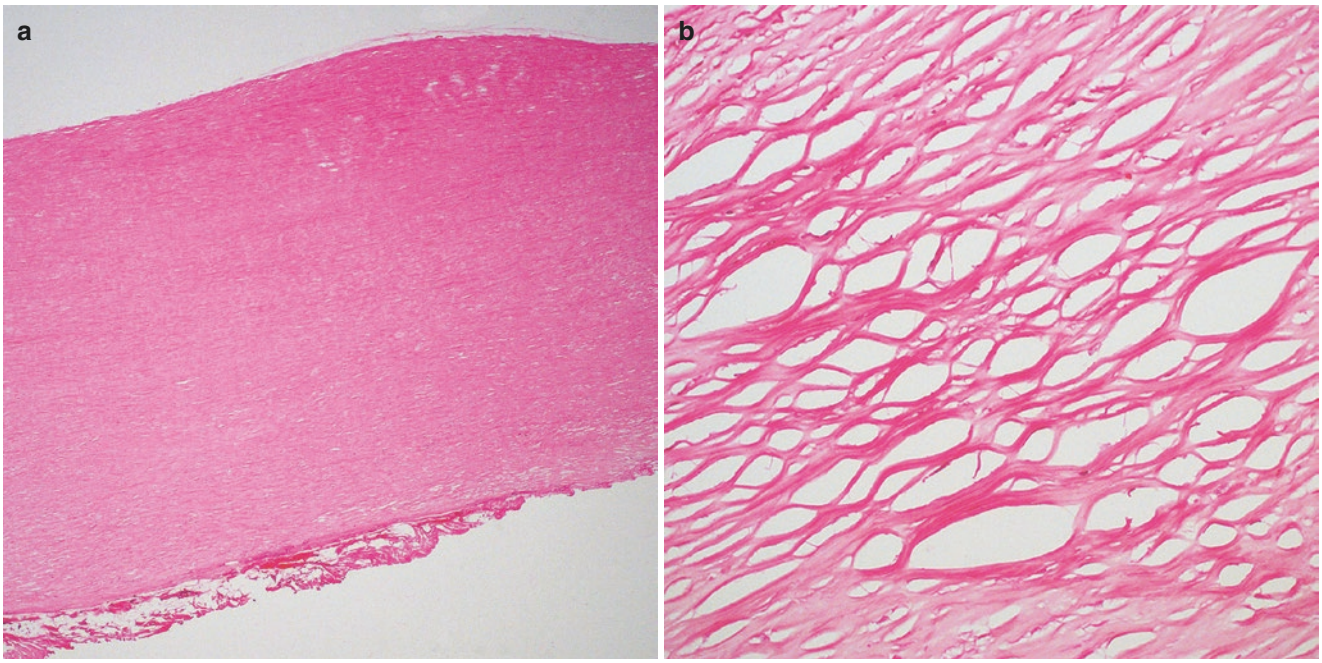

Fig. 4.11 (**a**) Microscopically, pleural plaques are hypocellular fibrous lesions with (**b**) basket-weave appearance of the collagen

Fig. 4.12 Subpleural areas of fibrosis and honeycomb change with sparing of more central portions of the lung are grossly noted in this case of asbestosis. (Courtesy of Dr. G Langman, Birmingham, UK)

Parietal pleural plaques are present in most cases of asbestosis. All cases of suspected asbestosis require thorough tissue sampling, and current guidelines recommend sections from central and peripheral lung parenchyma from each lobe in autopsy cases (10 blocks minimum). Likewise, for pneumonectomy or lobectomy specimens, sampling should include central and peripheral sections from each lobe [66, 67]. Microscopically, the diagnosis of asbestosis requires recognition of an appropriate pattern of interstitial fibrosis and the presence of asbestos bodies (either as seen by light microscopy or as counted by mineral dust analysis). Early asbestosis is characterized by fibrosis limited to the alveolar septa immediately adjacent to bronchioles. With disease progression, the fibrotic process extends outward to eventually include adjacent bronchioles largely obscuring the initial peribronchiolar changes. In later stages of the disease, the fibrosis can assume variable patterns and can closely resemble usual interstitial pneumonitis (UIP) (Fig. 4.13) or nonspecific interstitial pneumonitis (NSIP) or other forms of interstitial fibrosis (Fig. 4.14). Contrary to UIP though, fibroblastic foci are uncommon in asbestosis, and honeycombing is not as severe as in UIP. In general, the fibrosis in asbestosis is always paucicellular and collagenous, lacking any significant inflammation or fibroblastic response (Fig. 4.15a–c). In some cases, asbestos exposure may elicit a fibrotic response limited to the respiratory bronchioles and alveolar ducts without any interstitial involvement (bronchiolar wall fibrosis). Bronchiolar wall fibrosis in the presence of asbestos bodies has recently been termed *asbestos airway disease* rather than asbestosis after recognizing that similar changes may be seen in the lungs of elderly smokers who have no history of occupational exposure [66, 67] (Fig. 4.16). In addition to the changes described above, there are several other histologic changes, albeit non-specific, that can be seen in asbestosis, including type II pneumocyte hyperplasia,

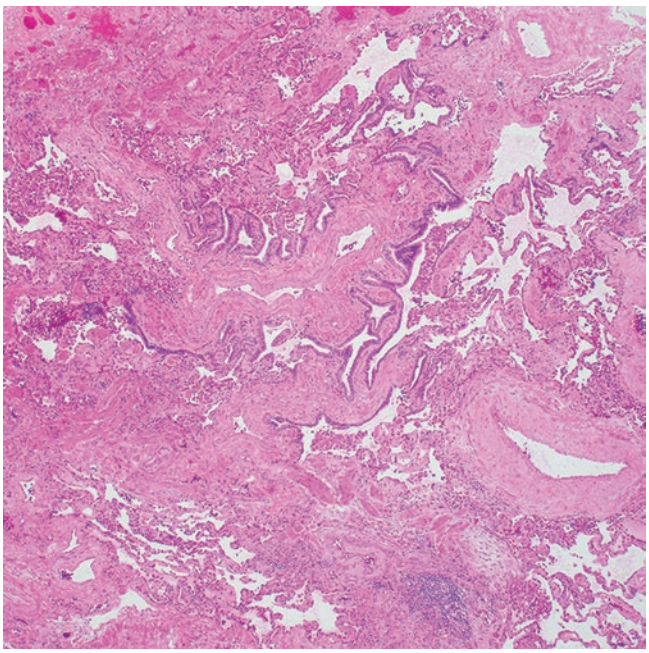

Fig. 4.13 The histological appearance of asbestosis can vary significantly. In this case, the lung shows fibrotic changes similar to those seen in usual interstitial pneumonitis (UIP)

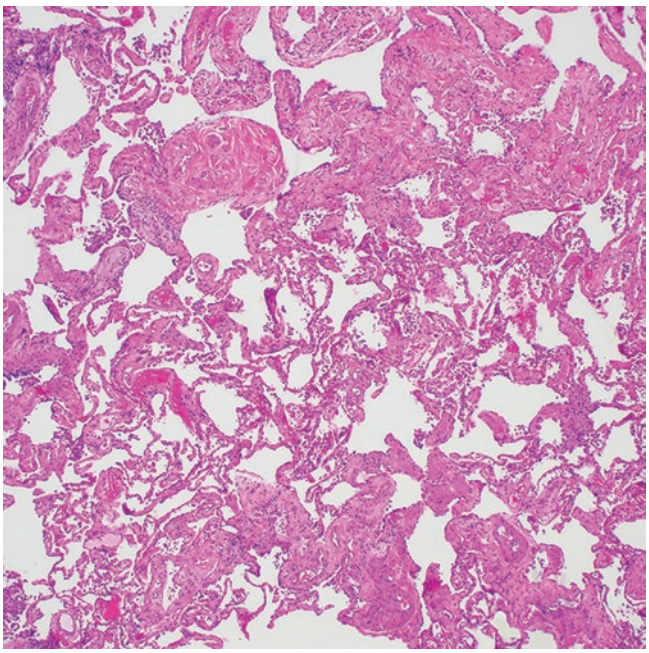

Fig. 4.14 In other cases of pulmonary asbestosis, the changes can be more non-specific, such as in this case that is characterized by irregular thickening of the alveolar walls

small bony spicules, variable numbers of alveolar macrophages, laminated concretions (pulmonary blue bodies), and perivascular fibrosis. Several grading schemes have been presented for grading the extent and severity of asbestosis [72, 73] of which a modified version has recently been proposed by the Asbestosis Committee of the College of American Pathologists and Pulmonary Pathology Society (CAP-PPS) [67] (Table 4.7). Identification of asbestos bodies can be achieved by using routine hematoxylin- and eosin-stained sections (Fig. 4.17), Perl's iron stain (Fig. 4.18) or unstained thick sections (20–25 μm) (Fig. 4.19). Asbestos bodies are golden-brown, beaded linear structures with a thin translucent core that are formed after deposition of an iron coating on the surface of inhaled asbestos fibers. Based on CAP-PPS criteria, a minimum of two asbestos bodies per cm^2 of lung tissue is required in addition to diffuse interstitial fibrosis for a reliable diagnosis of asbestosis [67]. Of note, the presence of asbestos bodies alone only indicates asbestos exposure and in isolation is insufficient for a diagnosis of asbestosis.

4.3.3 Mineral Analysis

Fiber analysis provides an opportunity to measure the cumulative mineral fiber burden in lung tissue and can be used as an adjunct technique in the assessment of asbestosis, especially in cases where asbestos bodies cannot be identified in tissue sections by conventional light microscopy or to exclude a diagnosis of asbestosis in individuals with pulmonary fibrosis and history of asbestos exposure who lack the required diagnostic criteria [74, 75]. Various methods for mineral fiber analysis exist, including phase contrast light microscopic, electron microscopic, and ashing analytical techniques [76–78]. Optimal samples for mineral analysis consist of 2 cm^3 blocks from three different anatomic sites from apical upper, apical lower, and basal segments of the lung; these samples should not contain tumor or large areas of pleural fibrosis [67]. Of note, reference values for the interpretation of results may vary depending on the method and laboratory used. Within these limits, concentrations exceeding 1 asbestos body/ml bronchoalveolar lavage (BAL), 1000 asbestos bodies/g dry lung tissue, 1×10^6 amphibole fibers (>1 μm)/g dry lung tissue, and 0.1×10^6 amphibole fibers (>5 μm)/g dry lung tissue are levels considered as non-trivial asbestos exposure [79].

4.3.4 Differential Diagnosis

Pleural effusions, rounded atelectasis, and DPT are conditions that are not necessarily asbestos-induced and often the result of other benign or malignant processes, most often fibroinflammatory in nature. In this context, close attention to clinical and occupational history as well as laboratory parameters is crucial to elicit the underlying etiology. Pleural plaques on the other hand almost always develop

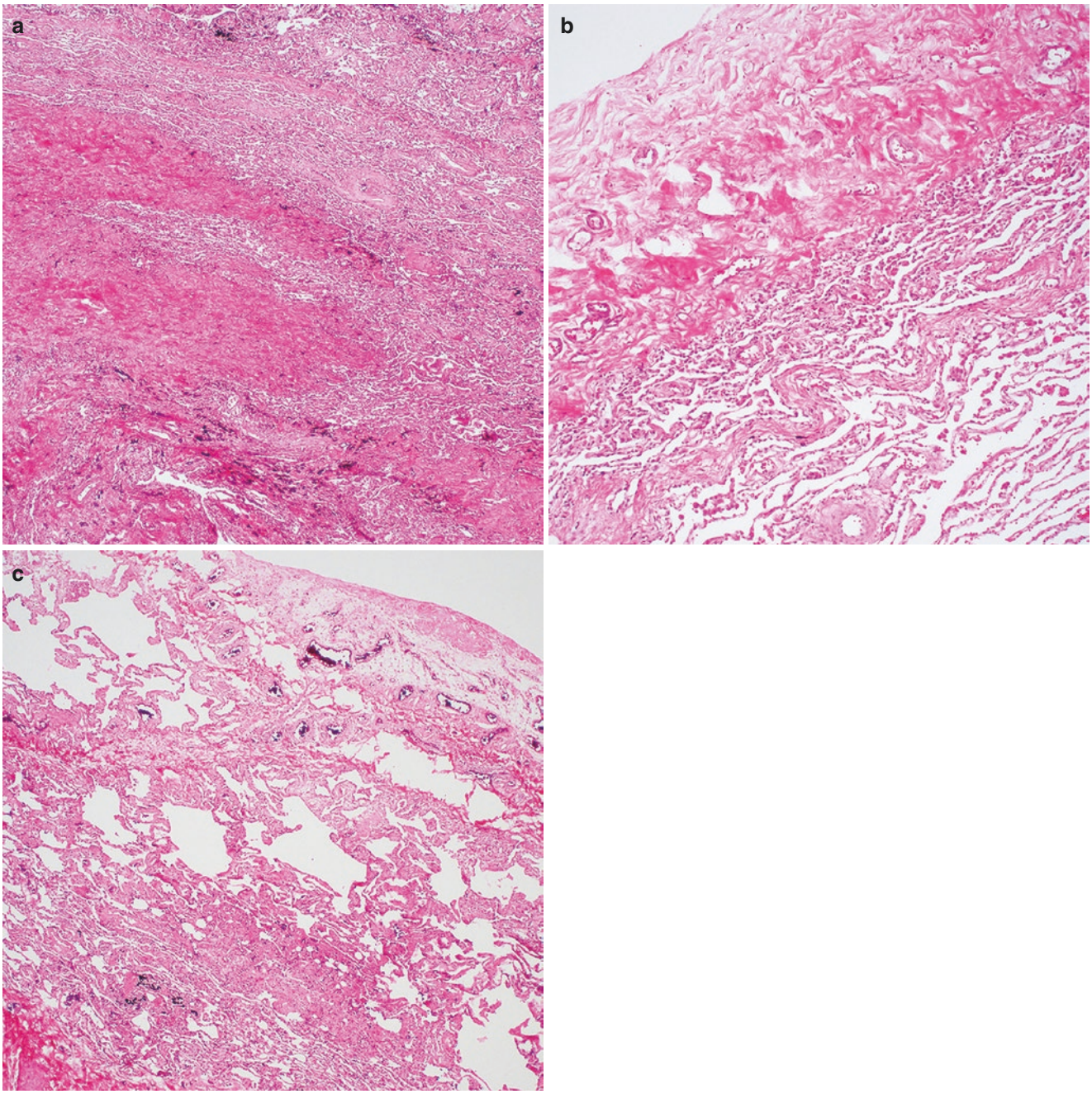

Fig. 4.15 (**a**) The fibrosis in asbestosis is generally hypocellular without a significant infiltrate of inflammatory cells; (**b**) pleural and subpleural fibrosis in asbestosis without cellular infiltration; (**c**) irregular interstitial fibrosis lacking a corresponding inflammatory reaction

secondary to prior asbestos exposure, and the likelihood increases even more if multiple and bilateral pleural plaques are identified. Other rare causes for pleural plaques include trauma to the chest wall, empyema, and hemothorax [66]. Asbestosis needs to be distinguished from idiopathic forms of pulmonary fibrosis as well as from other occupational lung diseases, such as silicosis or mixed dust pneumoconiosis. Especially in cases of advanced fibrosis, asbestosis may be difficult to distinguish from idiopathic pulmonary fibrosis, most commonly UIP. Clinically, apart from history of asbestos exposure, patients with UIP typically progress more rapidly, whereas the clinical course of asbestosis is

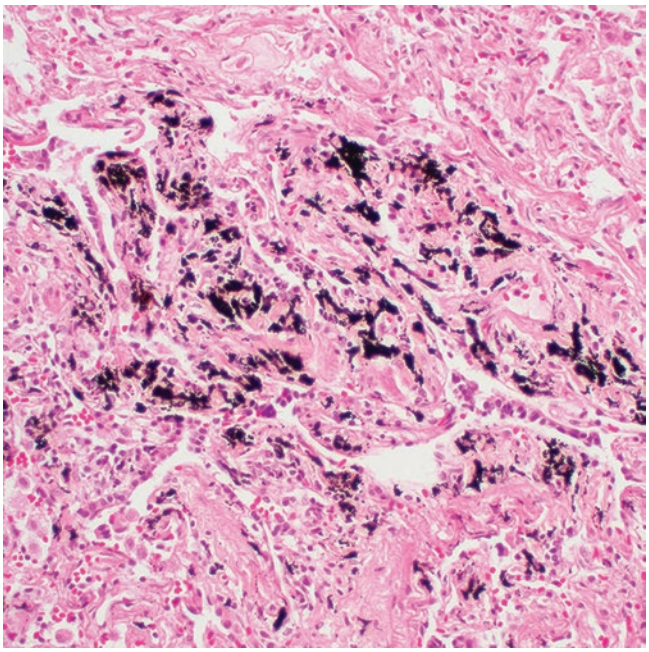

Fig. 4.16 Asbestos airway disease is histologically characterized by dust-laden macrophages surrounding distal bronchioles. In some cases, asbestos bodies may be identified within the macrophage infiltrate

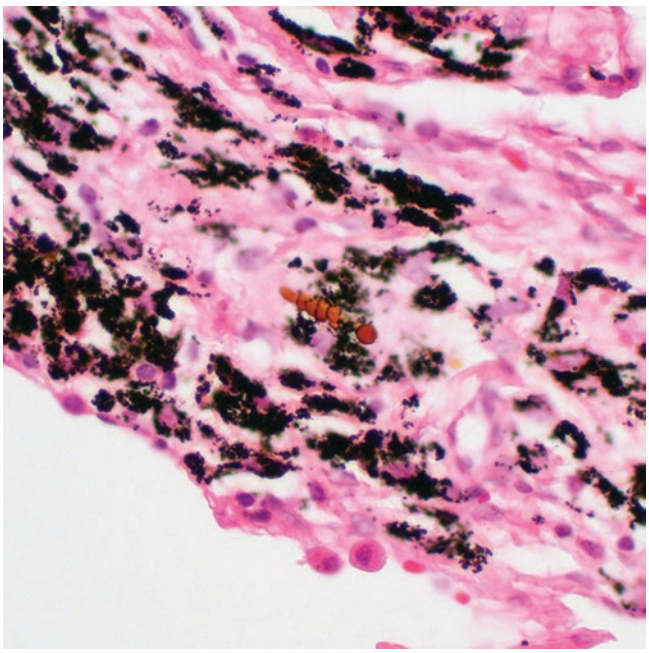

Fig. 4.17 Asbestos bodies are golden-brown, beaded, linear structures located in the lung parenchyma in routine hematoxylin-eosin section

Table 4.7 Histologic grading for asbestosis

Grade	Histology
0	No peribronchiolar fibrosis *or* fibrosis confined to bronchiolar walls
1	Fibrosis confined to the walls of respiratory bronchioles and first tier of adjacent alveoli
2	Extension of fibrosis to involve alveolar ducts and/or ≥2 tiers of alveoli adjacent to the respiratory bronchiole with sparing of at least some alveoli between adjacent bronchioles
3	Fibrotic thickening of the walls of all alveoli between ≥2 adjacent respiratory bronchioles
4	Honeycomb changes

From Roggli et al. [67], with permission

more protracted and usually occurs over decades. In addition, lung tissue from patients with advanced asbestosis characteristically contains numerous asbestosis bodies, which allow distinction from other forms of interstitial lung disease. On the other hand, the fibroblastic foci often seen in UIP should be rare in asbestosis and if present in greater numbers provide evidence against a diagnosis of asbestosis [66, 67]. Silicosis is a disease process consisting of multiple small hyalinized collagenous nodules that tend to affect the upper lobes, whereas asbestosis predominantly affects the lung bases [72]. Mixed dust pneumoconiosis is characterized by an irregular bronchiolocentric interstitial fibrosis associated with dust particles; identification of asbestos bodies and a more diffuse fibrotic process are features that can distinguish asbestosis from mixed dust pneumoconiosis [80].

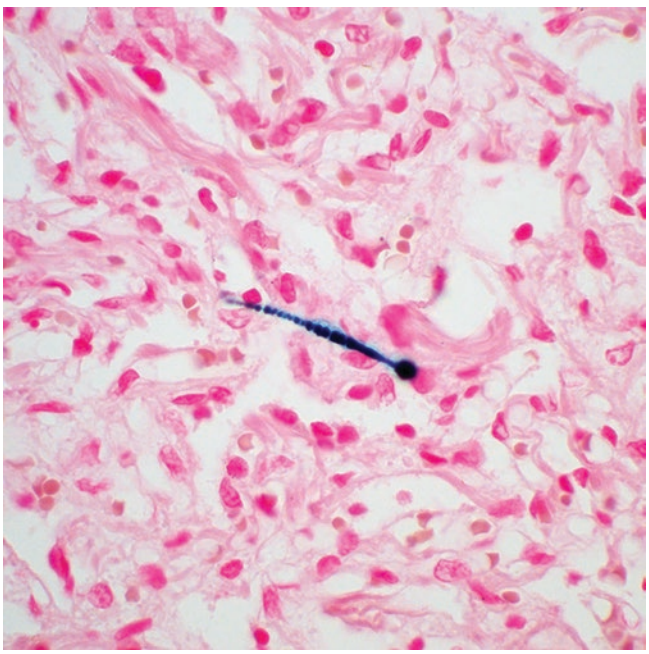

Fig. 4.18 Deposition of an iron coating around the surface of the structures can be highlighted using histochemical stains for iron (Perl's stain)

4.4 Hard Metal Lung Disease

Hard metal lung disease is a form of interstitial lung disease caused by the inhalation of tungsten carbide dust. Hard metal is an alloy of tungsten carbide (80–95%), cobalt (5–20%),

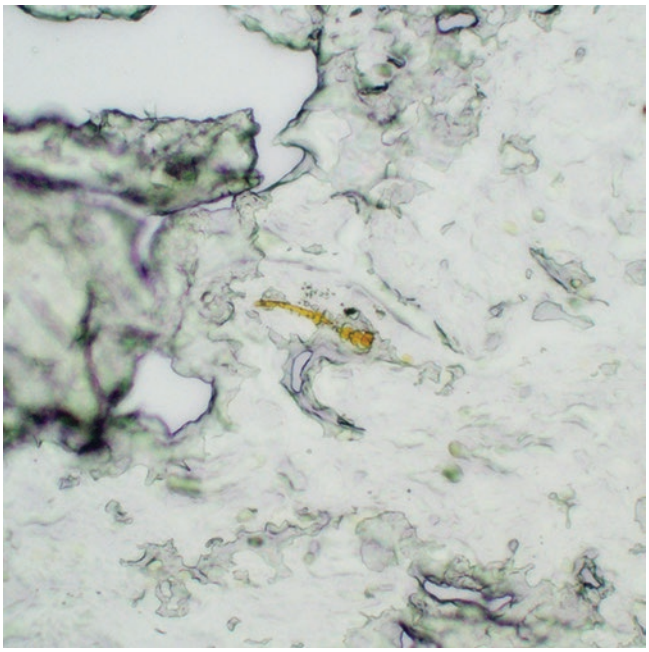

Fig. 4.19 Asbestos bodies can also be identified in thick unstained sections

and occasionally minor amounts of other metals, such as tantalum, titanium, and vanadium oxides [81–83]. The metal generated is characterized by its resistance to high temperatures and extreme hardness equivalent to 90–95% of that of diamonds. As such, hard metal is used in the production of tools designed to machine, grind, or cut metals or in drilling technologies [84, 85]. Hard metal lung disease occurs in workers exposed to hard metal dust through the manufacturing or use of tools created by the process of powder metallurgy or the formation of materials from the metal powders [84, 86–88]. The causative agent for hard metal lung disease appears to be cobalt rather than tungsten carbide, and the condition has been variously referred to in the medical literature as *cobalt lung*, *giant cell interstitial pneumonitis*, *hard metal pneumoconiosis*, and *hard metal lung disease* [87]. The underlying mechanism of hard metal lung disease appears to be an immunologic one and depends on whether an individual activates an adaptive immune response to cobalt which can lead to active inflammation and pulmonary fibrosis [89]. Clinically, cobalt exposure can present in two forms, as occupational asthma or as interstitial lung disease [81, 90–95], although the term hard metal lung disease is usually reserved for the latter. Giant cell interstitial pneumonitis (GIP) is the most common and characteristic histopathological finding in the condition and was first described by Liebow in 1969 [96] as a form of idiopathic interstitial fibrosis until the association with hard metal dust led to the exclusion of giant cell interstitial pneumonitis from the classification of interstitial pneumonias [97]. According to several authors, the diagnosis of hard metal lung disease requires the following criteria: (a) a history of exposure to hard metal dust, (b) clinical features characteristic of the disease, (c) radiological findings of interstitial lung disease, (d) histological findings of interstitial fibrosis, and (e) identification of hard metal dust in the lung tissue [81, 98].

4.4.1 Clinical Features

Hard metal lung disease can present in a subacute or chronic manner [84]. Dyspnea, cough, fever, chills, and weight loss characterize the subacute form and typically occur during or months to years after exposure and usually improve with cessation of the inciting agent [84, 99, 100]. Allergic manifestations, such as allergic rhinitis and wheezing, may coexist [86]. The chronic form often presents with shortness of breath, dyspnea on exertion, and cough; in long-standing cases, cyanosis, weight loss, and clubbing may occur [84]. In contrast to the subacute form, removal from exposure fails to alleviate symptoms in chronic hard metal lung disease [84]. The occupational histories reveal individuals that work in grinding, cutting, shaping, or repairing hard metals or diamond polishing [101]. As opposed to other occupational lung diseases, hard metal lung disease shows no distinct relationship between the duration of occupational exposure and severity of the disease supporting a role for hypersensitivity and individual susceptibility in the pathogenesis in the condition. Pulmonary function tests often show a restrictive pattern [101, 102]. Results of chest radiographs can range from normal to bilateral reticulonodular infiltrates and end-stage interstitial fibrosis [10]. HRCT findings include bilateral ground glass opacities, areas of consolidation, reticular opacities, and traction bronchiectasis. In advanced disease, parenchymal distortion and honeycombing may be identified [103, 104]. The management of hard metal lung disease primarily consists of removal from exposure [89]. This can lead to improvement or remission in patients with the subacute type of the disease, while in patients with chronic hard metal lung disease, remission may be more difficult to achieve and patients may progress to end-stage pulmonary fibrosis and death [105, 106]. In addition to cessation of exposure, treatment with inhaled or systemic steroids has proved successful in several cases [106, 107]. Lung transplantation may be indicated for advanced disease; however, disease recurrence in the transplanted lung has also been reported [108].

4.4.2 Pathological Features

Histopathologically, the spectrum of hard metal lung disease ranges from bronchiolitis obliterans to interstitial mononuclear infiltrates with desquamation of mononuclear or giant

cells into the alveolar spaces to diffuse interstitial fibrosis. Bronchiolitis obliterans is usually the earliest manifestation of the disease and is characterized by organizing fibroblastic tissue filling up the alveolar spaces and ducts. Desquamative interstitial pneumonitis (DIP)-like features with desquamation of mononuclear cells into the alveolar lumina in a peribronchial distribution can also be noted. The pathological hallmark of hard metal lung disease, however, is GIP in which air spaces are expanded by mononuclear or multinucleate giant cells demonstrating cellular cannibalism, i.e., engulfment of up to three macrophages or neutrophils in the cytoplasm of the giant cell. Particulate material may also be identified in these cells. Overall, the process is often patchy in distribution and temporally heterogeneous with alternating areas of interstitial injury, old fibrosis, active interstitial organization, interstitial inflammation, and areas of normal lung. In some instances, type II pneumocytes may appear hyperplastic and become detached; however, these are rarely multinucleated and fail to show any engulfment of cells or particulate matter within their cytoplasm. Interstitial inflammation in the form of lymphocytes and plasma cells and scant eosinophils or neutrophils may also be appreciated. In advanced lesions, there is patchy distribution of dense collagenous fibrosis and honeycombing with or without any underlying areas characteristic for hard metal lung disease and closely resembling the changes typically attributed to usual interstitial pneumonia (UIP). Additional histopathologic changes include paucicellular granulomas, alveolar damage, occasional fibroblastic foci, and diffuse lymphoid hyperplasia with reactive germinal centers. These components however should not be the predominant histological features [85, 92, 101].

4.4.3 Mineral Analysis

If an occupational history is difficult to obtain, several laboratory investigations may be used to confirm ongoing exposure to cobalt, such as serum or urine testing [109]. Bronchoalveolar lavage may reveal multinucleated giant cells showing emperipolesis, and in the right context, this finding is diagnostic of cobalt-induced lung disease [110, 111]. Tungsten, cobalt, and other minerals of the hard metal group can also be identified using scanning electron microscopy or spectroscopic analysis, although these techniques are often reserved for research purposes [85, 112].

4.4.4 Differential Diagnosis

Pathologically, hard metal lung disease needs to be differentiated from other conditions that can present with giant cell pneumonitis. Among these, several viruses can produce a pneumonic process characterized by giant cells, including measles, respiratory syncytial, and parainfluenza virus [113, 114]. In contrast to hard metal lung disease, the virus-induced giant cell pneumonias contain giant cells that are smaller and show less emperipolesis than the ones in hard metal lung disease. In addition, the giant cells in viral giant cell pneumonias will characteristically contain viral inclusions within their nuclei. In cases of doubt, serologic studies, tissue cultures, or histochemical/immunohistochemical analysis may be used to distinguish these entities [101]. In cases, in which paucicellular granulomas are identified within the interstitium, hypersensitivity pneumonitis may enter the differential diagnosis; in such cases, serology, occupational, and environmental history becomes crucial. In advanced cases of hard metal lung disease, the histological changes may be indistinguishable from UIP. Identification of additional areas characteristic of hard metal lung disease may aid in the differential diagnosis; if such features are not identified, a combination of occupational history, clinical features, and identification of hard metal dust in lung tissue may confirm the diagnosis [81, 98].

4.5 Mixed Dust Pneumoconiosis

Mixed dust pneumoconiosis (MDP) is generically defined as a pneumoconiosis caused by simultaneous exposure to crystalline silica and various non-fibrogenic dusts, such as coal, iron, or silicates [80]. The diagnosis requires documentation of occupational history of exposure to mixed dust and exclusion of other forms of occupational lung disease. Occupations associated with MDP include quarry workers, foundry workers, metal miners, pottery workers, ceramics workers, and stonemasons [80]. The clinical course of MDP is slower than that of silicosis, which is attributed to the modifying effect of the non-fibrogenic dusts on the strong fibrogenic potential of the crystalline silica. Early reports of MDP had described the condition as *siderosilicosis* [115] or *anthrasilicosis* [116, 117] depending on the composition of the lesions before the more unifying term *Mischstaubpneumokoniose* (*mixed dust pneumoconiosis*) was introduced in 1946 [118].

4.5.1 Clinical Features

Like most other occupational lung diseases, patients with MDP present with non-specific respiratory symptoms, such as cough and dyspnea [80] requiring thorough knowledge of patients' occupation and history of dust exposure to raise the suspicion of MDP. Pulmonary function tests may show variable patterns, including restrictive, obstructive, mixed, or even normal patterns. On chest radiographs, MDP presents with a mixture of small rounded and irregular opacities; if

ill-defined opacities predominate, as opposed to the small round lesions of silicosis, a diagnosis of MDP becomes more likely especially in the presence of occupational history to mixed dust [119]. HRCT will demonstrate reticular, reticulolinear, and reticulonodular opacities; honeycombing and areas of emphysema may also be seen [119]. The prognosis for MDP is generally better than for silicosis or asbestosis; however, diffuse interstitial fibrosis resembling UIP may also be encountered in some cases [80]. As with other occupational lung diseases, removal from exposure to dust is the most important step in management.

4.5.2 Pathological Features

The pathological features of MDP typically include a mixture of dust macules, mixed-dust fibrotic lesions, and silicotic nodules [17]. Macules are collections of dust-laden macrophages in the interstitium usually in a peribronchial or perivascular distribution and without any significant fibrosis (Fig. 4.20). Mixed-dust fibrotic lesions are stellate-shaped nodules with a central collagenous core surrounded by linear or radial collagen fibers admixed with dust-laden macrophages (Fig. 4.21). Both, macules and mixed-dust fibrotic lesions are often associated with centrilobular emphysematous changes which may be so prominent as to obscure any other features of MDP (Fig. 4.22). As described above, silicotic nodules are well circumscribed, small round firm nodules consisting of whorled hyalinized collagen. When viewed under polarized light, the lesions of MDP often contain numerous birefringent crystals due to the high number of silicates [17] (Fig. 4.23a, b). Larger lesions resembling progressive massive fibrosis or superimposed patterns of UIP may also be observed. According to the definition by Honma

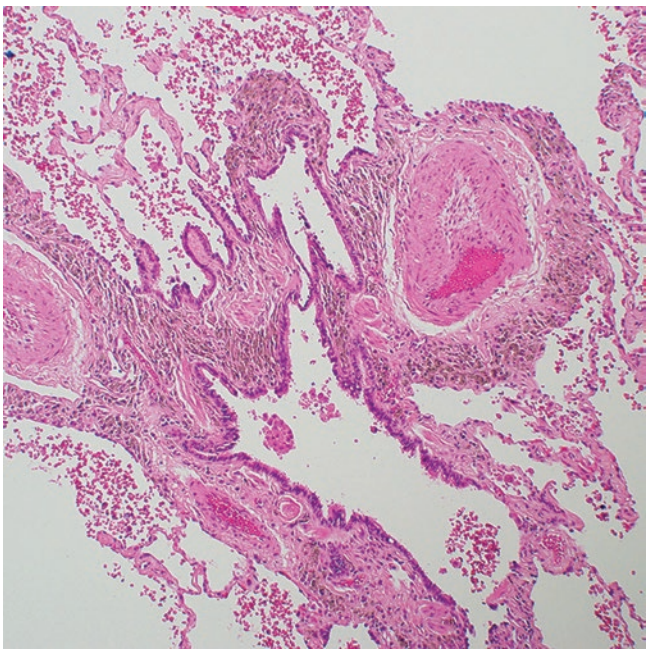

Fig. 4.20 Dust-laden macrophages in a peribronchial or perivascular distribution forming macules is characteristic of mixed dust pneumoconiosis

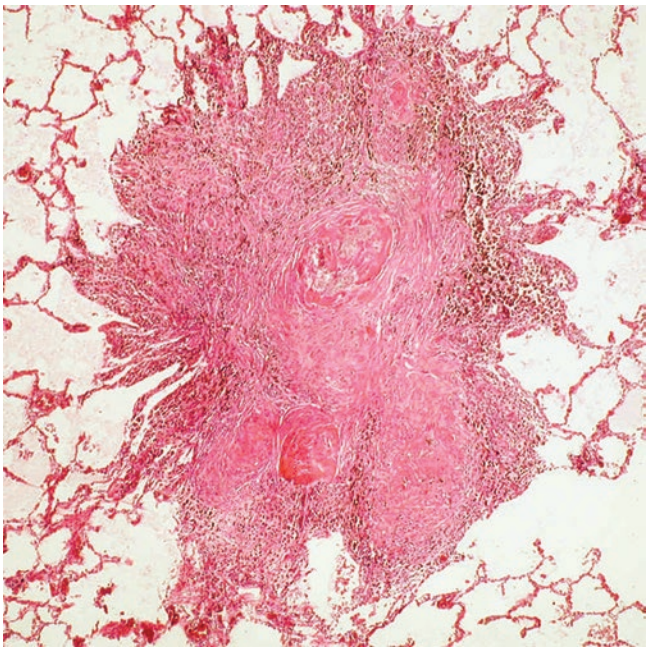

Fig. 4.21 Mixed dust fibrotic lesions have a nodular shape and consist of a central collagenous core surrounded by collagen fibers admixed with dust-laden macrophages. (Courtesy of Dr. G Langman, Birmingham, UK)

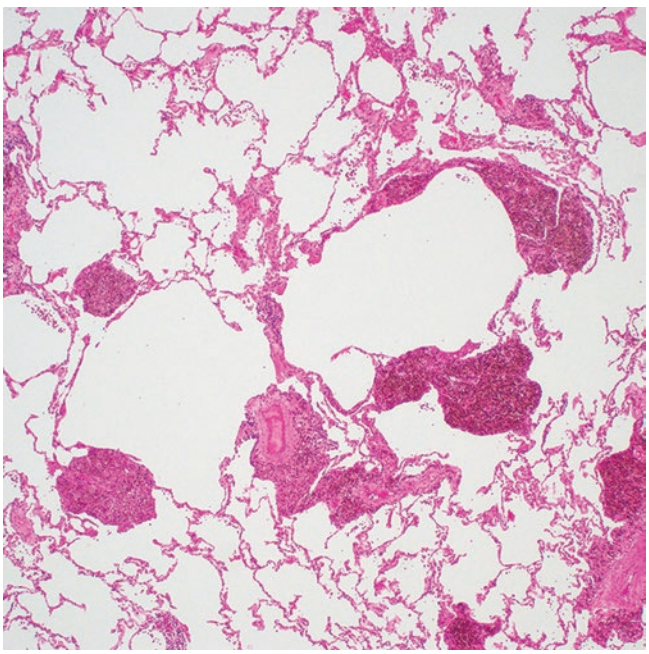

Fig. 4.22 Emphysematous changes associated with the macules or fibrotic lesions are not uncommon in mixed dust pneumoconiosis

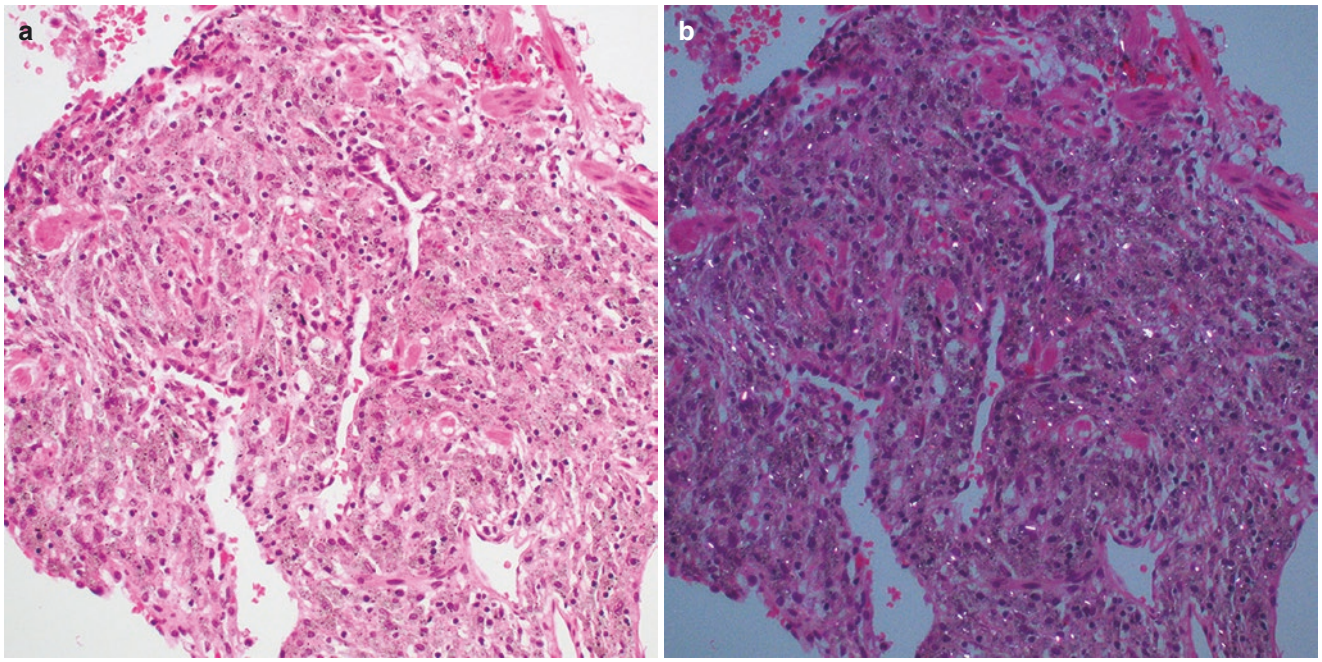

Fig. 4.23 (**a**) The lesions of mixed dust pneumoconiosis often show (**b**) strongly birefringent crystals when viewed under polarized light

et al. [80], if silicotic nodules are present, these should be outnumbered by the macules and mixed-dust fibrotic lesions; if silicotic nodules predominate, the more appropriate diagnosis would be silicosis.

4.5.3 Mineral Analysis

Confirmation of the diagnosis can be achieved using mineral dust analysis. Several methods can be used to detect the presence of silica, silicates, and various metal particles, each requiring different amounts and types of tissue specimens. These include techniques such as tissue ashing, X-ray diffraction analysis, and analytical electron microscopy [120–122].

4.5.4 Differential Diagnosis

There are several other occupational and non-occupational lung diseases that enter the differential diagnosis of MDP, including silicosis, coal workers' pneumoconiosis, and UIP. Pure silicosis is composed of small round densely hyalinized nodules only and will lack a significant number of macules or mixed-dust fibrotic lesions. In a similar manner, coal workers' pneumoconiosis is characterized by coal dust macules and nodules but will lack the silicotic nodules that would indicate a diagnosis of MDP. UIP-type changes can on occasion be superimposed and replace the underlying mixture of nodules in MDP. In this instance, close attention should be paid to areas unaffected by the diffuse fibrosis to identify the nodular deposits typical for MDP. As with all other occupational lung disease, thorough knowledge of occupation and dust exposure will help confirm the diagnosis; mineral dust analysis can support the diagnosis in cases where clinical findings are inconclusive or exposure history is not convincing.

4.6 Beryllium Lung Disease

Beryllium is a metal that is known for its lightness, high rigidity, high melting point, and good conductivity for heat and electricity [123]. Due to these properties, beryllium has become an important component in the manufacture of aerospace, military, nuclear power, and electronics industries [124]. Inhalation of beryllium particles, dust or fumes – usually in the workplace – can cause adverse pulmonary effects, including an acute chemical pneumonitis or chronic beryllium disease (CBD) [125–127]. Acute chemical pneumonitis is usually the result of inhalation of high concentrations of beryllium particles and is caused by direct toxicity of the metal on the respiratory tract [128]. The incidence of this type of injury has been markedly reduced by implementation of workplace measures and establishment of permissible exposure limits [129]. However, beryllium is still being used for many applications, and it is estimated that between 200,000 and 800,000 individuals are at risk of exposure in the USA alone [130]. Lung injury in CBD is characterized by non-necrotizing granulomatous inflammation that is

thought to be the result of an antigen-driven, delayed-type hypersensitivity reaction [124, 131, 132]. This is supported by the fact that only a small proportion of individuals (1–15%) exposed to beryllium actually develop the disease and that amount and length of exposure do not correlate with the incidence and severity of the disease [133, 134]. CBD may also occur in individuals with minimal exposure, such as staff not directly in contact with the metal, those living in the vicinity of beryllium factories, or household contacts [135]. Clinically, histologically and radiologically, CBD can show striking similarity to sarcoidosis often requiring the use of additional testing, including tissue beryllium levels or beryllium lymphocyte proliferation testing to establish the final diagnosis. Although the lung is the primary organ of involvement, the granulomatous reaction can also involve other organs, such as the skin, lymph nodes, salivary glands, liver, spleen, kidney, and bone [127].

4.6.1 Clinical Features

Exposure to beryllium primarily occurs in the workplace environment, such as in the aerospace, nuclear, military, automotive, metal, electronics, and telecommunications industries. Beryllium-associated disease can also be contracted through indirect contact, such as by workers and staff not directly working with the metal. Patients with acute beryllium disease, induced by inhalation of high concentrations of the metal dust, typically present with dyspnea, cough, and chest pain of rapid onset approximately 1–3 weeks after exposure [128]. In contrast, development of CBD requires very little cumulative exposure for sensitization and depends on individual susceptibility. The latency period between sensitization and CBD is highly variable and can range from 3 months to more than 30 years [136]. Signs and symptoms of CBD include insidious onset of dyspnea on exertion, cough, chest pain, fatigue, weight loss, and anorexia [137, 138]. Lung function tests may be normal or show restrictive, obstructive, or abnormal gas exchange patterns [139]. Widespread air space opacities are the main radiological feature in acute berylliosis, while HRCT findings of CBD are similar to those of other granulomatous diseases. Common findings include parenchymal small nodules, predominantly located along bronchovascular bundles or interlobular septa. Other findings include interlobular septal thickening, ground glass opacities, conglomerate masses, and honeycombing. Hilar or mediastinal lymphadenopathy may also be observed [140, 141]. The clinical course of acute berylliosis ranges from self-limited to rapidly progressive and fatal; some cases can progress to CBD [138]. The treatment of CBD usually involves prolonged administration of corticosteroids with excellent results; however, cases that progress to end-stage lung disease do occur. In such cases, progression to cor pulmonale portends a grave prognosis. Like silicosis and asbestosis, a well-recognized association with beryllium exposure is the occurrence of lung carcinoma, especially in cases following acute berylliosis [142, 143].

4.6.2 Pathological Features

The histopathological correlate of acute beryllium disease is characterized by an acute bronchitis and pneumonitis. The latter shows alveolar septa that are widened by interstitial edema accompanied by an inflammatory infiltrate of lymphocytes and plasma cells. Type II pneumocyte hyperplasia, foamy macrophages in alveolar spaces, and hyaline membranes can be observed (acute alveolar damage). Focal areas of organization, vascular congestion, and occasional multinucleate giant cells are further findings [127, 144]. Grossly, the lung parenchyma in CBD shows a gray and nodular cut surface and rubbery consistency. The hallmark of CBD on microscopic examination is the presence of non-necrotizing granulomatous inflammation that tends to involve the interstitium with preferential distribution along the bronchovascular bundles and occasionally also the pleura (Fig. 4.24). The granulomas are composed of epithelioid histiocytes, multinucleate Langhans-type giant cells, and lymphocytes (Fig. 4.25). Inclusions resembling asteroid or Schaumann bodies are also a frequent finding. In some cases, clearly defined granulomas are not always present, and histiocytes are rather scattered diffusely throughout the interstitial spaces. Interstitial fibrosis, areas

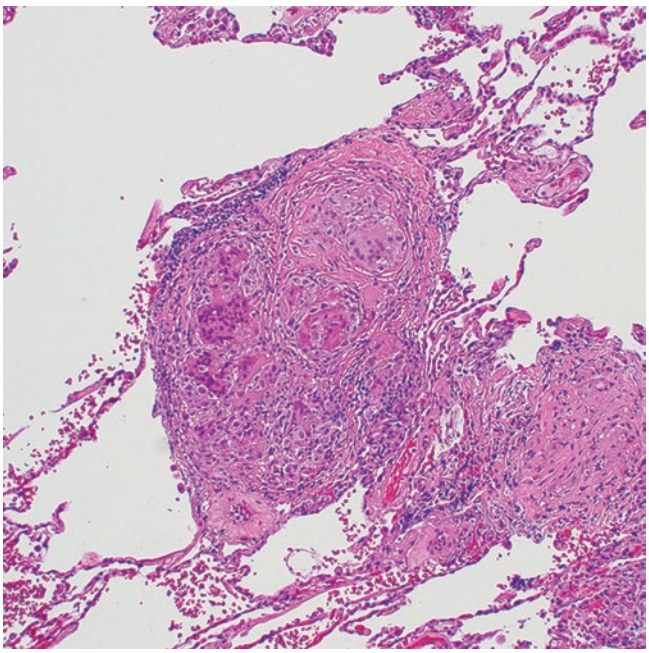

Fig. 4.24 The lesions in chronic beryllium lung disease consist of non-necrotizing granulomas, histologically indistinguishable from those of sarcoidosis

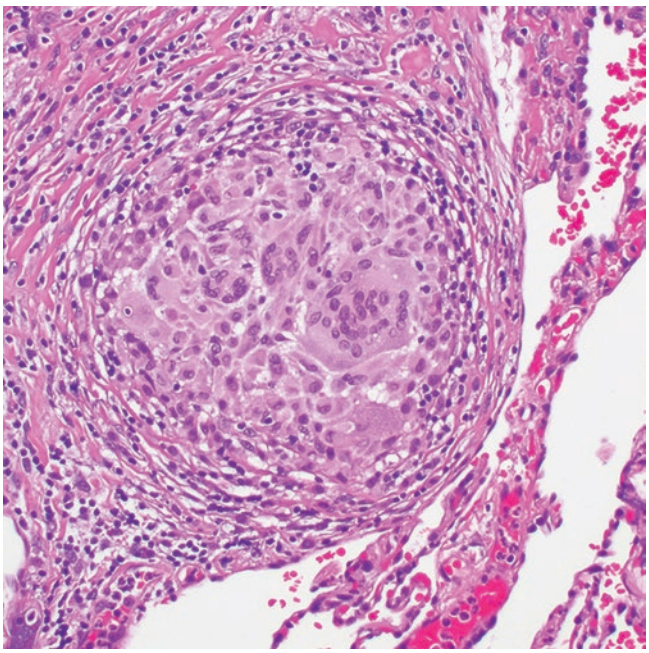

Fig. 4.25 High power view of a non-necrotizing granuloma in chronic beryllium lung disease shows an accumulation of Langhans-type giant cells and epithelioid histiocytes

of honeycomb change, and cystic changes are found in lungs that have progressed to end-stage lung disease [127, 144]. Examination with polarized light microscopy may demonstrate small round birefringent particles within the granulomas [145].

4.6.3 Mineral Analysis

Several techniques for detecting beryllium in tissue sections or beryllium-specific immunologic responses are currently available and can be used in support of a diagnosis of beryllium-associated lung disease. Beryllium patch test or beryllium lymphocyte proliferation testing on lymphocytes from blood and bronchoalveolar lavage are currently the preferred methods and assess the immune response of a patient suspected to be sensitized to beryllium [146]. Alternative approaches include spectrographic or fluorometric analyses of beryllium in lung tissue. More recently, energy-dispersive X-ray analysis has been shown to be a reliable tool for detecting the metal in lung tissue, with the added benefit of using routine paraffin sections [145].

4.6.4 Differential Diagnosis

The main differential diagnosis for CBD is sarcoidosis which clinically and histologically can be virtually indistinguishable. Ultimate diagnosis will therefore often have to rely on careful environmental and occupational history as well as additional analyses, such as sensitization tests to beryllium or lung tissue analysis for the metal. As such, a combination of history of exposure, granulomatous inflammation on lung biopsy, and positive lymphocyte proliferation test makes a diagnosis of CBD most likely [127]. Another condition causing a similar granulomatous response is hypersensitivity pneumonitis. In the latter, however, the granulomas are not well-defined and accompanied by bronchiolocentric interstitial pneumonia and chronic bronchitis. In cases of doubt, once again close attention should be paid to the patient's occupation or environmental exposure accompanied by the results of clinical or laboratory testing as specified above.

4.7 Talcosis

Talc is a hydrous magnesium silicate that is widely used in milling, paper, plastics, rubber, ceramic, paint, and cosmetic industries [147, 148]. Talc is not always used in its pure form but more often also contain various other minerals accounting for a heterogeneous mineral composition [149]. Therefore, the pulmonary changes attributed to talc inhalation are often caused by contaminants or other minerals, such as silica or asbestos. Pulmonary disease induced by inhalation of talc dust can take three different forms: (1) *talcosilicosis*, caused by talc mixed with high silica content; (2) *talcoasbestosis*, due to inhalation of talc containing asbestos fibers; and (3) *talcosis (talc pneumoconiosis)*, secondary to pure talc exposure. The clinical, radiologic, and pathological abnormalities of *talcosilicosis* and *talcoasbestosis* are virtually identical to silicosis and asbestosis, respectively. A fourth form of pulmonary disease is seen in drug users who administer crushed drug tablets containing talc as a filler or binding agent intravenously [150, 151]. Talc is also frequently used for pleurodesis to treat recurrent pleural effusions due to different causes. As such, talc deposits are often seen in decortication or extrapleural pneumonectomy specimens in patients with mesothelioma.

4.7.1 Clinical Features

Talcosis most commonly affects male patients between the 4th and 6th decade of life [148, 152, 153]. For talcosis to develop, a relatively short but strong exposure to talc dust may be necessary [154]. Accidental massive inhalation of talc dusting powder (baby powder) has been reported in several infants and children, with development of acute respiratory distress syndrome and fatal outcome [155]. Patients with occupational exposure can be asymptomatic or present with non-specific symptoms, such as exertional dyspnea, cough, night sweats, and weight loss [156, 157]. Late complications include chronic respiratory failure, pulmonary arterial hypertension, and cor pulmonale [148, 152, 153,

157]. Pulmonary disease in intravenous drug abusers presents with progressive dyspnea, fever, and signs and symptoms of obstructive lung disease due to the development of emphysema [152, 158, 159]. The HRCT findings of pulmonary talcosis include diffuse well-defined centrilobular nodules or ground glass opacities. During disease progression, the nodules can become confluent and form large heterogeneous conglomerate masses. The intravenous form of the disease will show very similar findings on HRCT with the addition of lower lobe emphysema [160, 161]. Aside from avoidance of exposure to talc dust, there is no definitive treatment for talcosis. Corticosteroids and immunosuppressants have been used with variable success but no clear benefits. Lung transplantation can be considered for treatment of end-stage lung disease. Overall, the prognosis is poor with progressive decline of pulmonary function [154, 156, 162].

4.7.2 Pathological Features

Grossly, macules and nodules can be identified in the pulmonary parenchyma in cases of talcosis. Additionally, fibrotic areas as well as foci of honeycombing may be present. Lesions resembling progressive massive fibrosis (>1 cm in diameter) may be observed in some cases. Microscopically, a granulomatous response dominates the picture in the inhaled and injected forms of the disease. In talcosis induced by inhalation, multiple small foreign body-type granulomas are identified predominantly in the alveolar septa and air spaces (Fig. 4.26). These consist of multinucleated giant cells containing brightly birefringent needle-shaped crystals when examined under polarized light (Fig. 4.27a, b). These granulomas can merge producing fibrotic lesions resembling progressive massive fibrosis. In the injected form of talcosis,

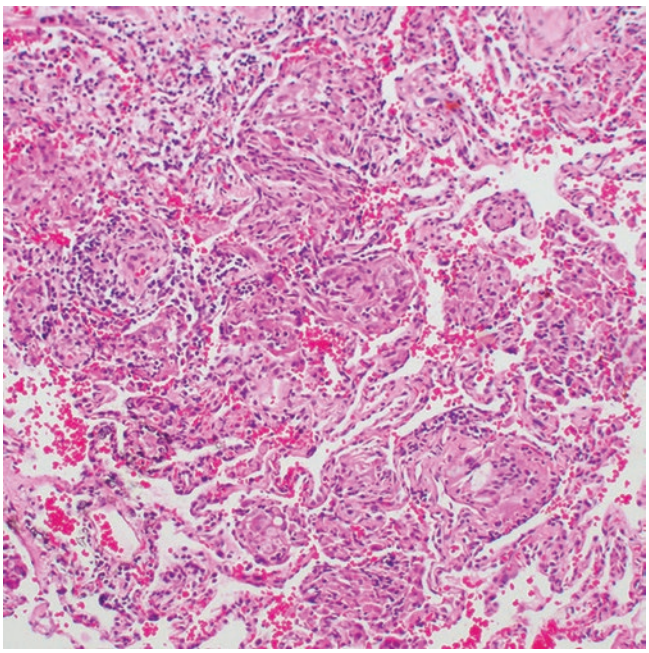

Fig. 4.26 In inhalation talcosis, multiple foreign body-type granulomas are scattered in the lung parenchyma, mainly along alveolar septa and air spaces

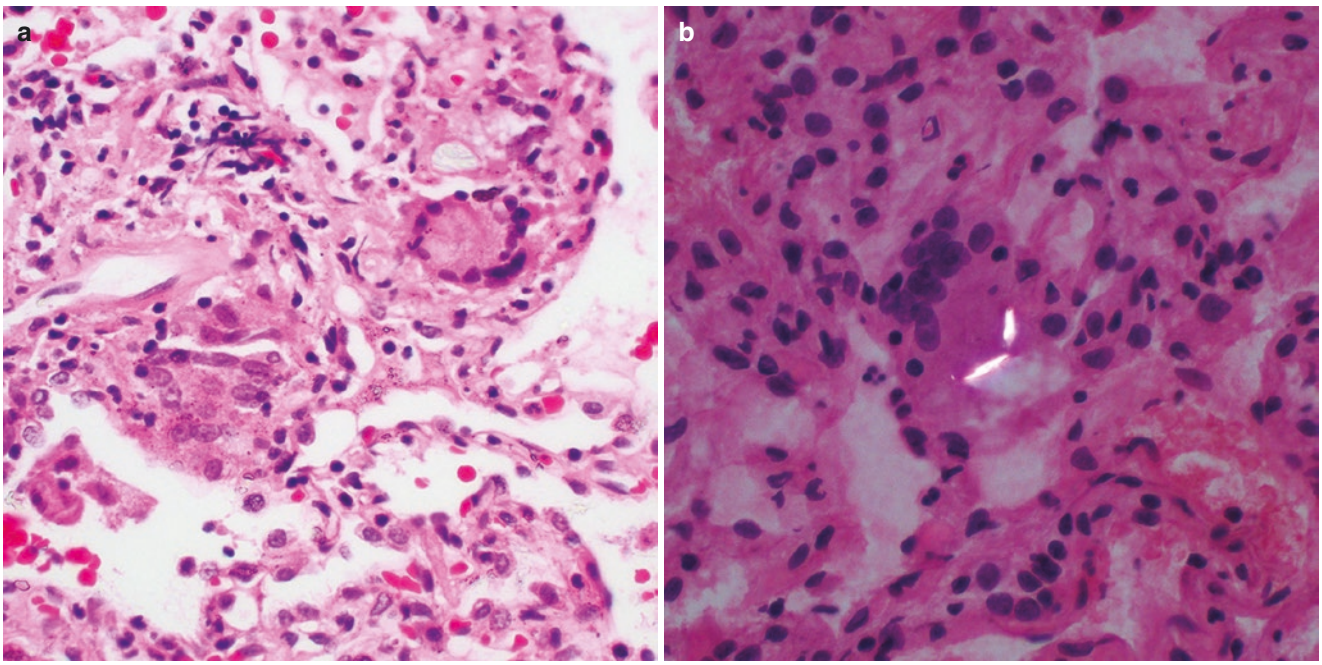

Fig. 4.27 (**a**) Higher magnification of the foreign body-type granulomas in inhalation talcosis shows the presence of (**b**) refractile material under polarized light

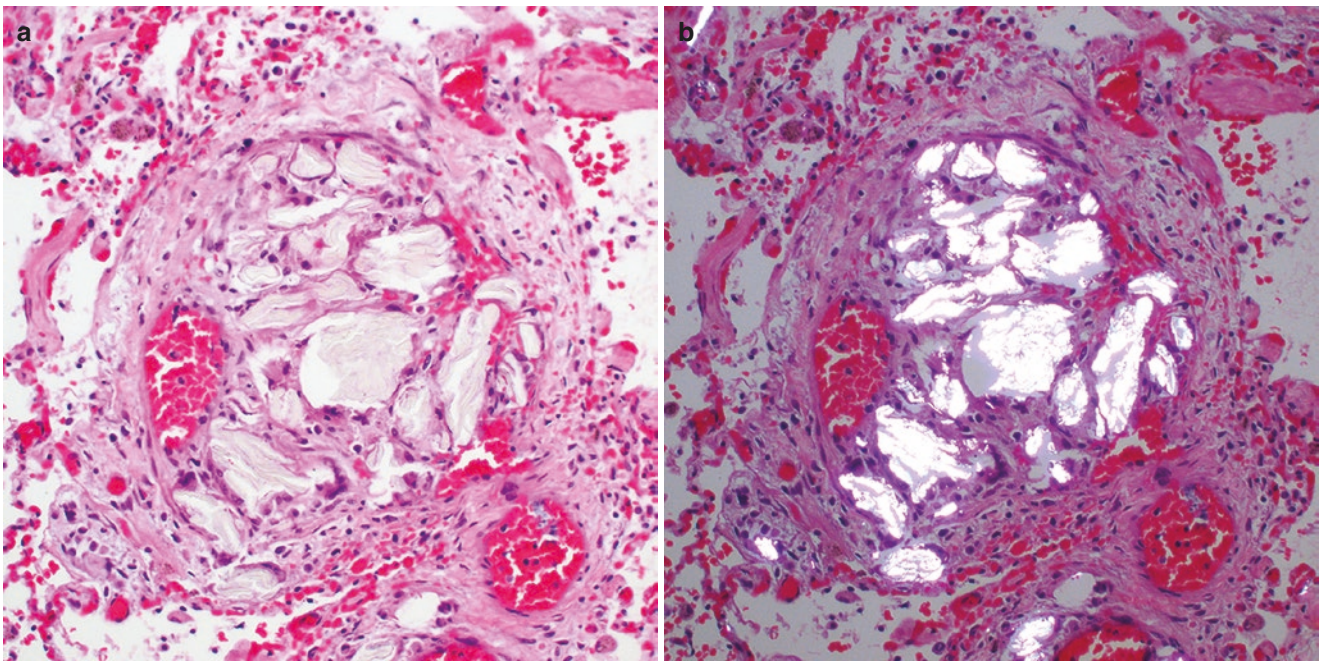

Fig. 4.28 (**a**) The injected form of talcosis demonstrates foreign body material eliciting a granulomatous response in the lumina and walls of the pulmonary vasculature; (**b**) the material is strongly birefringent under polarized light

the granulomatous response is largely centered on the vessels and perivascular tissues with subsequent development of pulmonary arterial hypertension (Fig. 4.28a, b). Emphysematous changes, primarily affecting the lower lobes, are another typical finding of this disease form. Of note, talc particles in the vascular form of pulmonary talcosis are usually larger (>10 μm) than their inhaled counterparts (<5 μm) [149]. In long-standing cases of either form, areas of interstitial fibrosis and honeycombing may develop [148, 150, 153, 160].

4.7.3 Mineral Analysis

Although the histopathological picture of pulmonary talcosis is quite characteristic, mineral dust analysis can be used to confirm the diagnosis in equivocal cases or to assess the different components of inhaled dust. Such analysis can be performed with a combination of analytical transmission electron microscopy and X-ray diffraction, scanning electron microscopy, or X-ray microanalytic techniques [148, 150].

4.7.4 Differential Diagnosis

Pulmonary talcosis must be distinguished from other non-necrotizing granulomatous diseases, most importantly sarcoidosis. The granulomatous response in talcosis as compared to sarcoidosis is of foreign body cell type and contains numerous bright needle-shaped crystals as opposed to the rare and small crystalline calcium carbonate inclusions sometimes identified in sarcoidosis. Although rarely required, analytical mineral dust analysis can help support the diagnosis in difficult cases. As with all occupational lung diseases, pertinent history relating to all possible environmental, occupational, or recreational exposures in every patient is very important and should be performed thoroughly.

4.8 Aluminosis

Lung damage caused by exposure to aluminum has been known since the 1930s when the first such cases were reported in Germany [163]. Pulmonary aluminosis is a very rare disease compared to other occupational lung diseases. As use of aluminum in the industries continues to rise, lung damage should be monitored and prevented. The exact pathogenesis of aluminum-induced lung is still under investigation, in particular which forms of aluminum can cause lung disease. Potential influencing factors that are thought to contribute to antigenicity include the existence of fibrous particles of alpha aluminum oxide [164], role of aluminum oxides and their low-temperature transitional forms [164, 165], the impact of additives and lubricants in the processing of aluminum powder [166], and aluminum particle size [167]. More recent debate has focused on a possible contribution of genetic predisposition and individual susceptibility

in the development of aluminum-induced lung disease [168]. Inhalation of aluminum or its compounds occurs primarily during processes in bauxite smelting, use of fine aluminum powder in the manufacture of explosives, aluminum welding or grinding, and polishing of aluminum materials [169–171].

4.8.1 Clinical Features

Patients with aluminosis present with exertional dyspnea and dry non-productive cough. Restrictive or obstructive ventilatory defects and decreased diffusion capacity often accompany these symptoms [167, 169, 170, 172]. Radiographic findings include nodular, slightly irregular opacities that may merge into larger nodular lesions with predominance in the upper lung fields. Subpleural bullous emphysema, spontaneous pneumothorax, pulmonary fibrosis, and honeycombing are other possible findings [165, 167, 169, 171–175]. Small rounded opacities (up to 3 mm), mainly in the upper lobes, and thickening of interlobular septa are typical findings on HRCT [171]. As for other pneumoconiosis, no effective therapy exists for the treatment of aluminosis. Therefore, avoidance of exposure and supportive treatment along with preventative measures in the workplace are recommended.

4.8.2 Pathological Features

Grossly, the lungs in aluminosis often show cobblestoning of the pleura and fibrotic changes or areas of honeycombing involving the lung parenchyma, preferentially in the upper zones [164, 173]. Histologic examination of the lungs in aluminosis shows highly variable changes. Perivascular and peribronchial accumulation of dust-laden macrophages is one of the earliest findings microscopically. The dust is gray-black and variably birefringent when examined under polarized light. Diffuse interstitial fibrosis resembling usual interstitial pneumonitis (UIP), a non-necrotizing granulomatous process, alveolar proteinosis, and desquamative interstitial pneumonitis-like changes are patterns associated with pulmonary aluminosis [164, 169, 173, 176].

4.8.3 Mineral Analysis

Energy-dispersive X-ray spectroscopy and tissue digestion methods are available for the analysis of particle classification in aluminosis [164, 173]. More recently, irradiation with a proton microbeam (in-air microparticle-induced X-ray emission analysis) was successfully used for elemental analysis in a case of aluminosis; however, this method is currently mainly restricted to the research setting [177].

4.8.4 Differential Diagnosis

The range of histopathologic changes in pulmonary aluminosis raises the possibility of other disease processes. The non-specific features of the interstitial fibrosis can be indistinguishable from those of idiopathic pulmonary fibrosis (UIP). In the latter, however, the lung damage is predominantly found in the lower lobes, while the changes in aluminum-associated lung disease are upper zone predominant. The granulomatous form of aluminosis may closely resemble tuberculosis, fungal infection or sarcoidosis. The former often show a necrotizing process, and special stains or tissue cultures should be able to rule out an infectious process. Sarcoidosis on the other hand may be more difficult to exclude; however, crystalline inclusions in sarcoidosis are rare while dominant in aluminosis. Definitive diagnosis may require analytical methods to exclude or confirm the presence of aluminum particles in tissue specimens as well as close correlation with occupational history.

4.9 Siderosis (Arc Welder Pneumoconiosis)

Siderosis is caused by inhalation of dust or fumes of metallic iron oxide that is encountered in various industries, such as iron and steel rolling mills, steel grinding, mining and crushing iron ore, or silver polishing [178–180]. The condition is most commonly seen in workers exposed to metal fumes during welding, and the disease is therefore also known as *welder siderosis* or *arc welder pneumoconiosis*. Siderosis was initially believed to be an asymptomatic non-fibrogenic pneumoconiosis without functional impairment, unless inhaled simultaneously with silica in which case a *silicosiderosis* with fibrosis and disability can develop [181, 182]. However, experimental studies have shown that pulmonary fibrosis can develop in lungs with ongoing welding fume exposure and in the absence of concomitant crystalline silica or asbestos fibers [183–185].

4.9.1 Clinical Features

Symptoms of patients with siderosis can range from asymptomatic to dyspnea and persistent cough [186]. Likewise, pulmonary function tests can show normal, restrictive, obstructive, or mixed patterns. HRCT is characterized by widespread small ill-defined centrilobular nodules and less commonly patchy ground glass opacities, mild reticulation, and emphysematous changes [10, 187]. Other than cessation of exposure, no specific treatment exists for patients with siderosis. In contrast to silicosis, radiographic changes may almost completely resolve with time as the iron dust is cleared from the lungs.

4.9.2 Pathological Features

Grossly, siderotic lungs contain numerous brown- or black-colored macules, 1 mm to 4 mm in diameter and evenly distributed [188]. Microscopic analysis reveals that these lesions consist of aggregations of pigmented iron oxide particles within macrophages involving respiratory bronchioles and alveolar ducts. Along with the interstitial accumulation, dust-laden macrophages may also be found in alveolar spaces, generating a desquamative interstitial pneumonitis (DIP)-like pattern. Histochemical stains for iron usually display a diffuse and intense reaction with Prussian blue. High exposure to welding fumes over a prolonged period of time may also lead to variable degrees of fibrosis, affecting the interstitial, peribronchial, and perivascular tissues. Emphysema may be present and is usually associated with current or prior smoking history. Other particulate material, such as silica or asbestos fibers, may show respective superimposed changes [180, 183, 186].

4.9.3 Mineral Analysis

The diagnosis of pulmonary siderosis is usually easily accomplished on the basis of occupational history, radiological findings, and results of lung biopsy. Aside from iron histochemical stains which may be useful to confirm the nature of the pigment, analytical energy-dispersive X-ray spectroscopy may identify the element in question in difficult cases [178]. In addition, elevated ferritin levels in serum and bronchoalveolar lavage fluid have been described in patients with siderosis compared to a control group [179].

4.9.4 Differential Diagnosis

The histopathological findings of siderosis by itself usually do not cause significant diagnostic difficulties, especially if occupational history, clinical presentation, and radiological findings are taken into account. Occasionally, however, siderosis may be accompanied by other particulates which may modify the histologic changes. In this context, siderosis is often seen as part of a mixed dust pneumoconiosis requiring close attention to morphologic detail.

4.10 Silicatosis (Silicate Pneumoconiosis)

Silicates are a group of minerals which consist of silicon dioxide combined with other elements, such as aluminum, magnesium, or calcium [189]. Silicates are some of the most common minerals in the earth crust, and exposure typically occurs in the mining and quarrying industries or in agriculture [190]. This group of minerals includes mica, kaolin, vermiculite, feldspar, bentonite, fuller's earth, and talc (see Sect. 4.7) [191–195]. Exposure to silicates is often associated with exposure to other minerals, such as silica and asbestos, however, clinically significant pneumoconioses have also been associated with exposure to pure silicates. The development of silicatosis appears to be directly related to intensity and years of exposure, although the prevalence of the disease is generally low [190–195].

4.10.1 Clinical Features

Development of clinical disease requires chronic exposure and long latency. In mild disease, patients can be asymptomatic but demonstrate abnormalities on chest radiograph. In more severe cases, patients typically present with increasing dyspnea, cough, and wheezing and a restrictive pattern on pulmonary function tests [190–195]. Radiologic abnormalities can range from fine linear or nodular shadows to diffuse small irregular opacities and large conglomerate masses [190–195]. Silicate pneumoconiosis is generally a slowly progressive disease but may occasionally result in end-stage lung disease with progressive massive fibrosis. Cessation of dust exposure is the mainstay of therapy in the absence of more specific treatment. In isolated cases, corticosteroid therapy has been attempted [190–195].

4.10.2 Pathological Features

Gross examination of the lungs in silicatosis shows small ill-defined gray-brown nodular lesions within the lung parenchyma that are often more pronounced in the lower lobes and widespread fine fibrosis. Larger masses of firm and rubbery consistency may also be seen replacing the normal lung. Focal emphysematous changes are not uncommon [191, 193]. Microscopic findings include macules, nodules, and large confluent masses and variable degrees of collagen deposition, primarily in a peribronchiolar or perivascular distribution. The macules consist of aggregates of golden-brown dust-laden macrophages, and particle-filled macrophages can be seen extending into and expanding the interstitium (Fig. 4.29). Nodules and large confluent masses (progressive massive fibrosis) consist of fibrosis intermixed with mineral dust. Occasional multinucleate giant cells may be present, but granulomas are not typically seen. Brightly birefringent particles within the macrophages and fibrotic lesions can be identified with the use of polarizing microscopy (Fig. 4.30a, b). Emphysema, pleural thickening, and

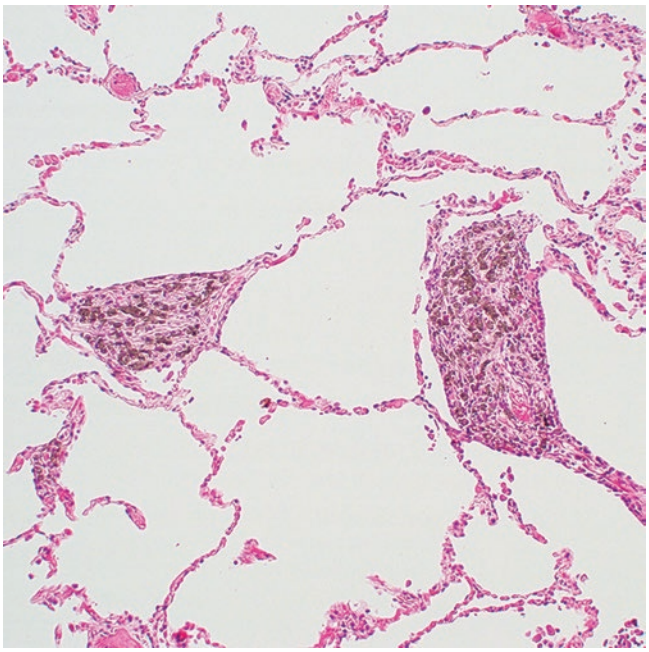

Fig. 4.29 Pulmonary silicatosis shows aggregates of golden-brown dust-laden macrophages forming macules in the pulmonary interstitium

pleural fibrosis are other findings that can be seen in pulmonary silicatosis [190–195].

4.10.3 Mineral Analysis

Analytical electron microscopy reveals single or stacked sheets of crystalline material [189]. Energy-dispersive spectroscopy can be used to identify the exact elemental composition of the silicate [195].

4.10.4 Differential Diagnosis

The diagnosis of silicatosis can usually be established by a combination of occupational exposure and clinical and pathological findings. Since silicates are often admixed with other minerals, such as silica and asbestos, a diagnosis of mixed dust pneumoconiosis should be excluded. In such cases, close attention should be paid to the added presence of silicotic nodules or diffuse fibrosis that are typically associated with silica or asbestos exposure, respectively.

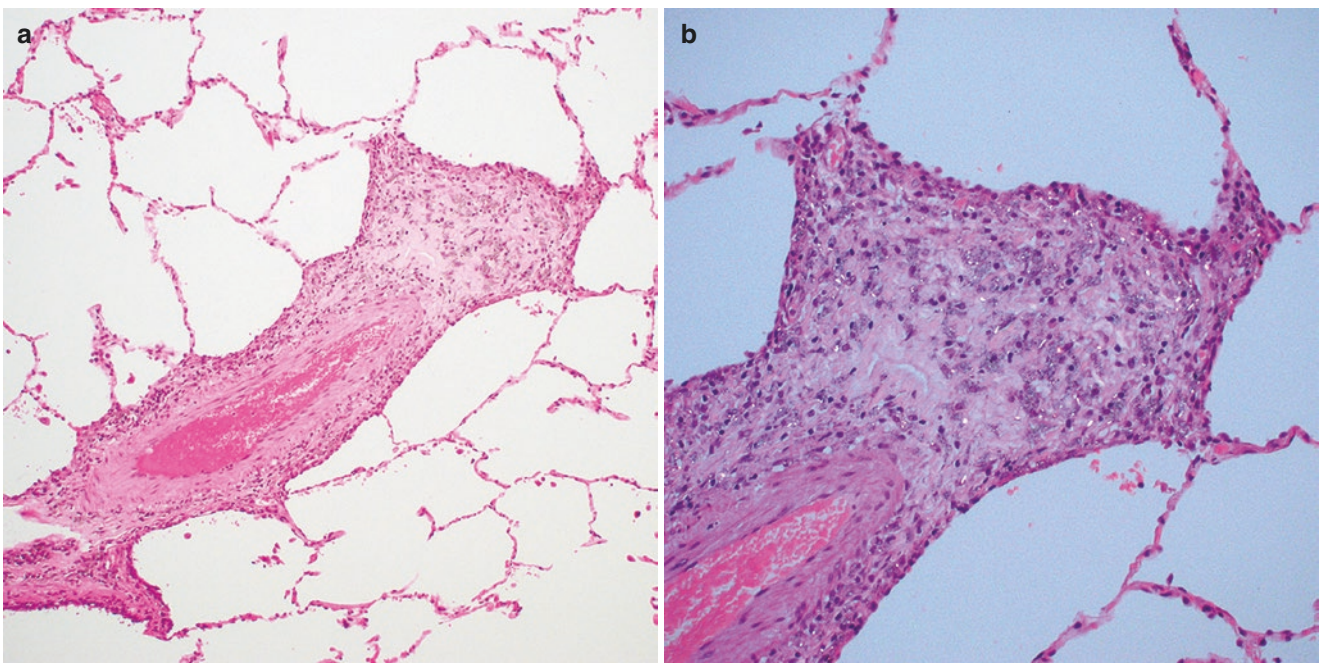

Fig. 4.30 (**a**) Perivascular macule in silicatosis containing (**b**) birefringent particles when viewed under polarized light

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