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A Clinical Guide to Occupational and Environmental Lung Diseases

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Chapter 11
Hard Metal Lung Disease

Toshinori Takada and Hiroshi Moriyama

Abstract Hard metal lung disease is an occupational interstitial lung disease that affects people exposed to dust of tungsten carbide, a hard metal. The culprit is likely the cobalt used as a binder when tungsten and carbon are heated and combined. The disease can occur in workers engaged in the manufacture, utilization, or maintenance of tools composed of hard metal. The frequency of hard metal lung disease is usually less than 1% in those workers. Hard metal lung disease is diagnosed on the basis of occupational history, high-resolution computed tomography (HRCT) appearance of interstitial lung disease, bronchoalveolar lavage, and/or surgical lung biopsy. HRCT findings of hard metal lung disease may consist of bilateral ground-glass opacities, areas of consolidation, irregular linear densities, extensive reticular infiltrates, and traction bronchiectasis. Diffuse centriolobular micronodular opacities are characteristic. The pathologic findings of hard metal lung disease are a pattern of giant cell interstitial pneumonia (GIP). Features of GIP are bronchiolocentric fibrosing interstitial pneumonia with bronchiolar and peribronchiolar fibrosis and increased macrophages in the airspaces associated with multinucleated giant cells. Multinucleated giant cells in bronchoalveolar lavage (BAL) or lung specimens are diagnostic for hard metal lung disease, but the absence of the cells does not exclude the possibility of the disease. Elemental analysis of BAL or lung specimens shows the presence of increased amount of tungsten and/or cobalt. Hard metal lung disease may improve after removal from exposure and often responds to corticosteroids therapy; however, fatally progressive cases have also been documented. Prevention through a comprehensive respiratory protection by exposure avoidance and use of personal protective equipment is needed.

Keywords Hard metal lung disease • Giant cell interstitial pneumonia • Tungsten carbide • Cobalt • Electron probe microanalyzer

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Introduction

Hard metal was first developed in Germany in the early twentieth century. Several decades later, case reports with chest radiographic abnormalities consistent with pneumoconiosis in hard metal workers started to appear in the literature. Hard metal lung disease is now known as an occupational interstitial lung disease that affects primarily workers exposed to dust of tungsten carbide, a hard metal. The pathologic findings of hard metal lung disease are predominantly those of interstitial pneumonia and fibrosis with prominent multinucleated giant cells, resulting in a pattern of giant cell interstitial pneumonia (GIP) [1–3]. Liebow originally classified GIP as one of the idiopathic interstitial pneumonias [4], but it is now recognized that GIP is pathognomonic for hard metal lung disease [5]. Elemental analysis of bronchoalveolar lavage (BAL) or lung tissue reveals the presence of tungsten and/or cobalt that provides definitive diagnosis of the disease.

Epidemiology

The exact prevalence of hard metal lung disease is unknown, but is likely low. A cross-sectional study of 1,039 tungsten carbide production workers revealed that work-related wheeze occurred in 113 participants (10.9%) and interstitial lung disease in only 7 (0.7%) [6]. These findings suggest that only a small percentage of hard metal industry workers develop interstitial lung disease caused by hard metal exposure. Although the occurrence of hard metal lung disease in tungsten carbide workers is associated with elevated peak air concentrations of cobalt in excess of 500 $\mu g/m^3$, some cases have occurred following exposures of less than 50 $\mu g/m^3$ [7]. Individuals with increased susceptibility may develop hard metal lung disease after relatively short and low levels of exposure.

Exposure to Hard Metal

Hard metal, or tungsten carbide, is a synthetic compound that is produced by combining tungsten and carbon with cobalt used as a binder during the process. The proportion of cobalt varies between 5% and 25% by weight, depending on the hardness of the product. It has hardness nearly that of diamond and is used to make machine parts that require high temperature resistance, or to make tools used for drilling, cutting, machining, or grinding. The main occupational sources of exposure of hard metal consist of various stages in the production of hard metals, maintenance and resharpening of hard metal tools and blades, and the use of hard metal tools [8]. The component of hard metal that is responsible for the disease is most likely colbalt not tungsten. That the cobalt is the offending agent came from several lines of evidence. In animal studies, instillation of tungsten mixed with cobalt

produced toxic effects in the lung while tungsten alone did not [9, 10]. In diamond cutting industry, diamond tools are also used to cut stones, marble, glass, and to grind or polish various materials. Employees developed respiratory symptoms after working with diamond cutting disks made from the mixture of cobalt powder and microdiamonds. Workers in the manufacturing of diamond tools and those who use high-speed cobalt diamond disks in diamond polishing could develop the pathology of GIP similar to hard metal workers [11–13]. These diamond tools do not contain "hard metal" or tungsten.

Patients with hard metal lung disease usually have a mean exposure duration of more than 10 years, ranging from 2.5 to 30 [14]. Hard metal lung disease may also occur after a shorter duration of exposure, which suggests that host susceptibility factors are also important in determining the development and the severity of the disease [15]. History of exposure to hard metal dust, however, may not be apparent in some cases. Office clerks working in a room next to a poorly air-conditioned hard metal factory may be exposed to hard metal dusts and develop hard metal lung disease. Some patients are unaware of such exposures, and others may have had no history of exposure. A case report from India demonstrated an office sweeper with GIP but no history of hard metal exposure [16]. Conversely, a 15-year-old boy with GIP was highly suspected of having been exposed to hard metal because both of his parents had occupational exposure to hard metal; however, a thorough metal analysis of his lung tissue was negative for tungsten or cobalt [17].

Clinical Presentation

Patients exposed to hard metal may develop three types of reactions: occupational asthma, a syndrome resembling hypersensitivity pneumonitis, and interstitial lung disease, which is generally recognized as hard metal lung disease [18]. The clinical presentation of hard metal lung disease is variable and there is usually no relationship between disease occurrence and the length of occupational exposure. Some patients develop acute disease with after relatively short exposure with rapidly progressive dyspnea. Others present more insidiously usually after long exposure with a radiological abnormality during routine screening.

Signs and Symptoms

In a typical case with hard metal lung disease, respiratory symptoms including dry cough and shortness of breath will appear within several months to years after exposure to hard metal. These symptoms may improve on holidays and exacerbate during workdays, similar to hypersensitivity pneumonia in some cases. Physical examination may show fine crackles during chest auscultation [19, 20]. In advanced

cases, clubbed fingers and weight loss are seen [1]. Patients with hard metal lung disease are sometimes complicated by pneumothorax [19, 21, 22], especially in advanced cases who developed honeycombing changes and multiple cysts.

Laboratory Tests

There are no specific blood tests for diagnosing patients with hard metal lung disease. The blood tests are usually performed to differentiate hypersensitivity pneumonitis, sarcoidosis, or neoplastic lung disease, or exclude secondary interstitial lung diseases, such as those associated with collagen vascular diseases. Patch testing, a method used to determine if a specific substance causes allergic inflammation of the skin, may be used to detect cobalt allergy, which is frequently accompanied by sensitivity to nickel [23, 24]. Three of four patients with hard metal lung disease were patch tested and were found to be positive for cobalt during the surveillance of Japanese hard metal workers (unpublished data). Other noninvasive methods such as urinary and blood concentrations of cobalt may also be used to identify the body burden of cobalt [25, 26].

Pulmonary Function

Pulmonary function tests typically show restrictive lung defect characterized by reduced total lung capacity, vital capacity, and lung diffusing capacity [17, 20]. In the early stages of the disease, the restrictive changes may improve after cessation of exposure and recur on returning to the workplace. In the advanced stages with pulmonary fibrosis, restrictive lung defects are frequently accompanied by impaired gas exchange with hypoxemia during exercises, or even at rest. Obstructive defect shown by a decrease in FEV1/FVC may occur at end stage when cystic changes predominate.

Chest Imaging

There are no pathognomonic radiographic features of hard metal lung disease. Although a patient with significant clinical and physiological impairment may sometimes have a normal chest radiograph, the chest radiograph typically shows a diffuse micronodular and reticular pattern predominantly in the lower lung zones (Fig. 11.1a). There are also nodular or diffuse reticulonodular infiltrates, and/or ground-glass opacities. In advanced disease, the lung volume decreases and small cystic lesions i.e. honeycombing may develop.

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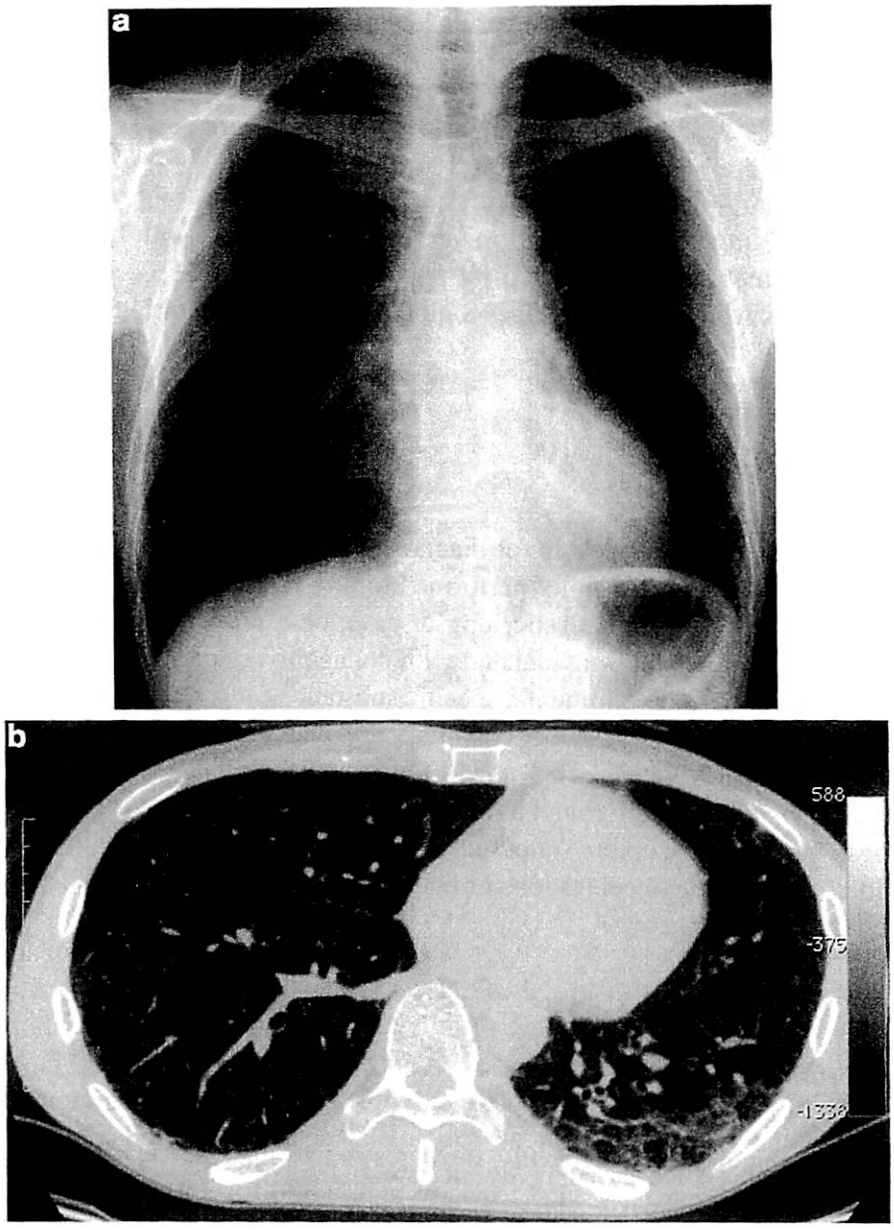

Fig. 11.1 A 53-year-old Japanese man presented with dry cough and exertional dyspnea. He had a history of exposure to hard metal for 30 months. A chest radiograph demonstrates fine reticular opacities mainly in the left lower lung with mild volume reduction (**a**). HRTC demonstrates diffuse centriolobular micronodular opacities and irregular linear opacities in the subpleural zone of the left lower lobe (**b**).

High-resolution computed tomography (HRCT) has become an essential diagnostic tool in diffuse parenchymal lung disease, in particular interstitial lung disease. Figure 11.1b shows the characteristic radiologic appearance of HRCT in a mild case with hard metal lung disease; it shows diffuse centriolobular micronodular opacities in the middle and lower lung fields and subpleural curvilinear densities

with ground-glass attenuation in the left lower lobe. Centriolobular micronodular opacities pathologically correspond to centrilobular fibrosis and giant cell accumulation within the alveolar space. HRCT findings of hard metal lung disease may also consist of areas of consolidation, irregular linear opacities, extensive reticular opacities, and traction bronchiectasis [27, 28].

Bronchoscopy and BAL

BAL findings from case series and case reports of patients with hard metal lung disease show increased total cell counts, increased lymphocytes and eosinophils, and decreased CD4/CD8 ratio [1, 17, 20, 29]. Reduced CD4/8 ratio suggests that immunologic pathogenesis of the lung disease may be similar to that of hypersensitivity pneumonitis [30]. The presence of bizarre multinucleated giant cells in BAL is diagnostic for hard metal lung disease [31]. Elemental analysis of macrophages in BAL could detect inorganic dust particles and reveal the increased amount of tungsten [32]. Lung biopsy usually is not needed if these BAL findings are present.

Pathology

The histologic pattern of GIP is characteristic of hard metal lung disease [5, 33]. Transbronchial biopsies (TBBs) are too small for the pathologists to make an accurate pathologic diagnosis of GIP. Features of GIP are bronchiolocentric fibrosing interstitial pneumonia with bronchiolar and peribronchiolar fibrosis and increased macrophages in the airspaces associated with multinucleated giant cells (Fig. 11.2). The characteristic distribution of fibrosis in GIP suggests that the inflammation in the centrilobular area is initiated by hard metal detected by elemental analysis. Other less characteristic cases may resemble usual interstitial pneumonia or desquamative interstitial pneumonia with or without honeycombing.

Multinucleated giant cells are morphologically classified into Langhans-type cells and foreign body-type cells. Langhans-type cells showing a circular peripheral arrangement of nuclei are often seen in many infectious granulomatous disorders or in unknown pathological inflammatory granulomatous disorders such as sarcoidosis. Foreign-body-type cells, which have the nuclei scattered in an irregular fashion throughout the cell, are characteristic in foreign body granulomas. Multinucleated giant cells in GIP do not resemble either Langhans-type cells or foreign-body-type cells. They distinctively show cannibalism containing phagocyted cellular material (Fig. 11.2b). The phagocytized cells are mostly macrophages or neutrophils. Giant cells are also found in other diseases such as sarcoidosis and viral pneumonia, especially pneumonia due to measles. GIP by measles is differentiated from hard metal

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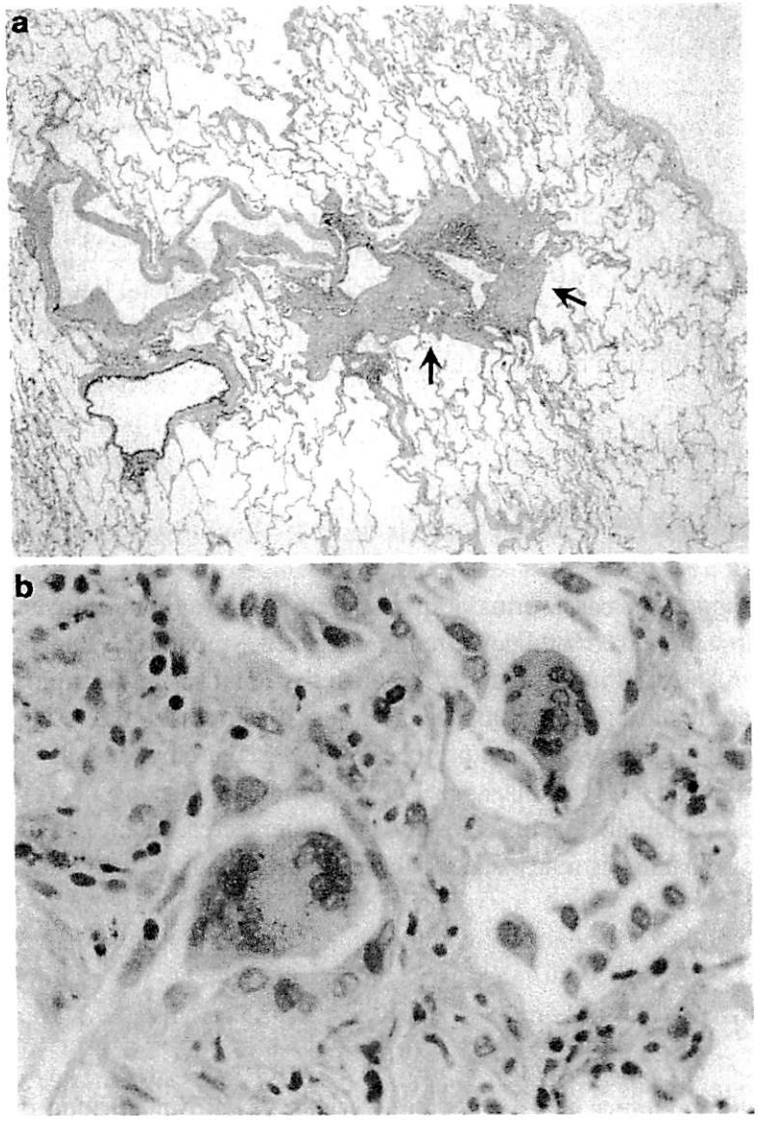

Fig. 11.2 Surgical lung biopsy specimens demonstrating giant cell interstitial pneumonia (GIP). Low magnification of lung biopsy from a 53-year-old Japanese hard metal manufacturer shows centrilobular inflammation and fibrosing lesions (*arrows*) (**a**, ×4). Higher magnification shows irregular multinuclear giant cells in the alveolar spaces (**b**, ×80).

lung disease by the presence of interstitial edema, pneumocyte hyperplasia, and hyaline membranes characteristic of diffuse alveolar damage [34]. Giant cells in the granuloma of sarcoidosis are conglomeration of epithelioid cells sharing the same cytoplasm and having multiple nuclei. They may contain cytoplasmic inclusions such as asteroid bodies and Schaumann bodies [35] and are morphologically different from those in hard metal lung disease.

Table 11.1 Techniques of elemental analysis of human tissues

Liquid analysis
Atomic absorption spectrometry
Plasma optical emission mass spectrometry
Ionic-coupled plasma emission spectrometry
Solid analysis
EPMA-EDS
EPMA-WDS

EPMA electron probe microanalyzer; *EDS* energy dispersive spectrometer; *WDS* wave length dispersive spectrometer

Elemental Analysis

Various techniques of elemental analysis for detection of hard metal elements have been described (Table 11.1). Liquid analysis includes atomic absorption spectrometry, plasma optical emission mass spectrometry, and ionic-coupled plasma emission spectrometry [16, 28]. These techniques can be used to detect elements in dissolved tissue solution but cannot correlate the anatomical relationship between elements and the characteristic centrilobular fibrosis with giant cell accumulation within alveolar space in GIP because the lung architecture is generally destroyed by digestion or ashing.

In contrast, solid analysis uses thick or thin section of specimens without tissue destruction. It has been mainly used to identify the constituents of hard metal in the lung tissue. Electron probe microanalyzers (EPMA) irradiate specimens with a finely focused electron beam. When combined with energy dispersive spectrometers (EDS), EPMA can simultaneously analyze all elements and map chemical elements in lung tissue of hard metal lung disease with very high resolution [2, 5, 36]. Using this technique (EPMA-EDS), Abraham et al. reported that 30 of the 31 cases with GIP were amongst the 50 cases with the highest tungsten concentrations. In addition, the top 27 cases all displayed GIP and the 30 GIP cases had been employed in the tungsten carbide industry [5].

EPMA with a wavelength dispersive spectrometer (WDS) also has been widely used in the field of material sciences to obtain element distribution in small samples with a spatial resolution in the order of 1 μm. WDS is almost ten times more sensitive than EDS for all elements under optimized operating conditions [37]. When EPMA-WDS is applied to a tissue section, however, intense beam to detect trace amount of elements may also burn the tissue sample because of high temperature. Watanabe et al. has developed an improved EPMA-WDS technique that can be used to analyze metal elements in tissue sections of 2-μm thickness [38].

Moriyama et al., applying EPMA-WDS to biopsy lung tissue of hard metal lung disease, demonstrated that tungsten was distributed in a relatively high concentration almost throughout the peribronchiolar fibrosis in the centrilobular lesion. Qualitative analysis of a selected area (10×10 μm area) in a fibrosing lesion of GIP showed the presence of Al, Si, Ti, Cr, Fe, and Ta, in addition to tungsten.

Cobalt, which is always present in hard metal and is thought to be critical in the pathogenesis of GIP, is not always detectable because biosoluble cobalt rapidly disappears from the lung. In patients with hard metal lung disease, cobalt is only detected in approximately 10% of lung tissue samples by EPMA-EDS [5] and in 24% by the more sensitive EPMA-WDS [14]. Lung tissues from TBBs may also be used for elemental analysis. The distribution of mineral dust in the lung is usually uneven [39]. TBBs usually contain the peribronchial connective tissues, which are a common repository for inhaled dust [40]. Thus, if TBBs are used for elemental analysis, detection of tungsten or cobalt may be falsely negative due to the smaller samples and uneven distribution of the deposited dust. Larger surgical lung biopsy samples are preferred for exact mapping of hard metal elements in lung tissue.

Readers interested in elemental analysis of lung tissue by EPMA-WDS are referred to the following web site for more information: http://www.med.niigata-u.ac.jp/in2/.

Diagnostic Evaluation

The following four elements are required for the diagnosis of hard metal lung disease (see Fig. 11.3):

1. A history of hard metal exposure; in particular, engagement in hard metal industry. As with any occupational disease, a comprehensive and detailed work history is a key element for the diagnosis. Note that history of exposure to hard metal dust is sometimes not apparent.
2. Chest HRCT showing opacities consistent with hard metal lung disease; in particular, centriolobular micronodular opacities.
3. Giant cells in BAL and/or a pathological diagnosis of GIP in surgical lung biopsy. Multinucleated giant cells in BAL or lung specimens are diagnostic for hard metal lung disease, but the absence of the cells does not exclude the possibility of the disease.
4. Tungsten and/or cobalt detected by elemental analysis in giant cells or lung specimens. Note that cobalt is only detected in some lung tissue samples because of its biosolubility.

For the differential diagnosis, all other types of interstitial pneumonia, in particular, hypersensitivity pneumonitis, sarcoidosis, neoplastic lung disease, or secondary interstitial lung disease such as collagen vascular disease associated lung fibrosis should be excluded. Elemental analysis of BAL or lung specimens shows the presence of increased amount of tungsten and/or cobalt for a definite diagnosis of hard metal lung disease. Although the finding of GIP is almost pathognomonic of hard metal lung disease, Moriyama et al. reported two patients whose biopsies exhibited features of GIP but no tungsten or cobalt was detected, and neither had a history of work in the hard metal industry [14]. Screening of lung tissue from patients with suspected occupational lung diseases by EPMA-WDS sometimes yields elements

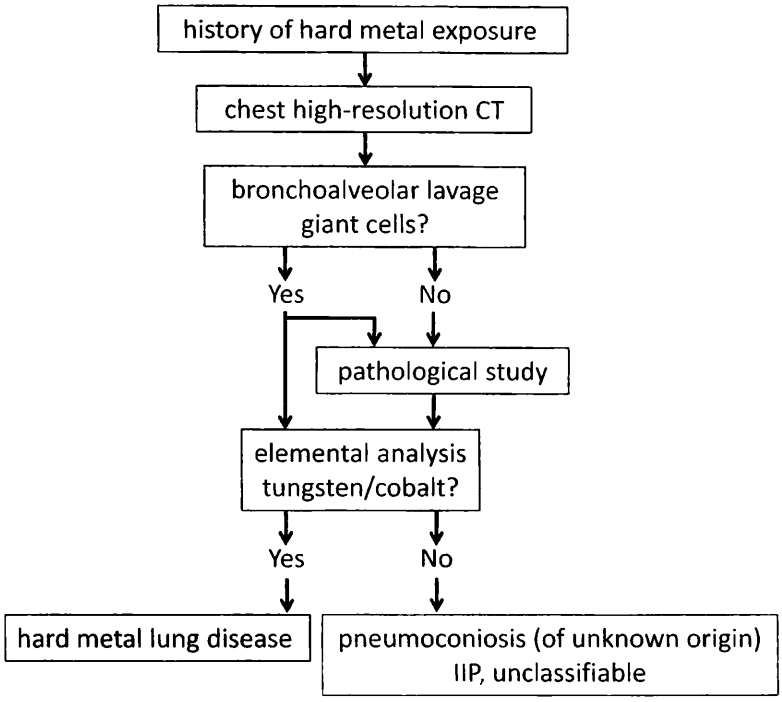

Fig. 11.3 Proposed diagnostic algorithm for hard metal lung disease. A patient with respiratory symptoms with occupational history in hard metal industry should proceed to chest HRCT. If interstitial lung disease is detected by HRCT, the patient should be further investigated by BAL and/or surgical lung biopsy. Giant cells in BAL or giant cell interstitial pneumonia are pathognomonic for hard metal lung disease. Hard metal elements, tungsten and/or cobalt, detected by elemental analysis are the definitive findings for diagnosis of the disease. *IIP* idiopathic interstitial pneumonia.

that have not been thought to cause lung injury, including indium, vanadium, and niobium, etc. Extrinsic elements that are difficult to detect with current techniques may cause non-hard metal lung disease or "idiopathic" GIP [41].

Treatment and Prognosis

Hard metal lung disease may improve with only removal from exposure and often responds to corticosteroid therapy. Accurate diagnosis is therefore essential to patient management. However, fatally progressive cases have also been documented [42].

Exposure Cessation

Hard metal lung disease progresses with continuation of the exposure. Thus, patients with the disease should be removed from further exposure to hard metal dust.

The complete cessation of exposure may bring improvement and even complete remission in the early forms of the disease. Interruption of the exposure by improved hygiene at work and exhaust ventilation produced good symptomatic and clinical improvement in diamond polisher's lung [11]. However, the disease may recur in subjects who return to work after being successfully treated by removal from exposure and corticosteroid therapy. Furthermore, the continued exposure can cause rapid progression of the disease and fatal outcome in the subjects [22, 42]. Twelve of 19 cases with hard metal lung disease surveyed in Japan were removed from further exposure by job change, retirement, and reshuffle at workplace, and four cases improved by only exposure cessation (unpublished data). Two cases managed only by strict wearing of protective mask or working in areas with better exhaust ventilation without job change did not show improvement. This suggests that complete removal from exposure is necessary for clinical improvement.

Medical Treatment

Although no controlled studies exist, corticosteroid therapy is reported to produce clinical, functional, and radiologic improvement [1, 2, 11, 43, 44]. In our institute, 13 of 19 cases with hard metal lung disease in Japan were initially treated by oral prednisolone 40–60 mg/day and one third also treated by intravenous methylprednisolone (1 g/day for 3 days) (unpublished data). Most improved and only three cases died of respiratory failure. Exposure cessation and glucocorticoids may not be sufficient in some cases and, in this situation, addition of a second agent should be considered.

A second immunosuppressive agent may be added to glucocorticoid therapy for either its glucocorticoid-sparing effect or progressive lung disease not responsive to corticosteroid therapy alone. The choice of a specific agent is dependent on the experience of the treating clinician, but cyclophosphamide, azathioprine, or cyclosporin was most commonly used [45]. One case report showed that a 31-year-old woman with severe pulmonary fibrosis secondary to hard metal disease was treated with glucocorticoid and cyclophosphamide, which resulted in stabilization of her pulmonary function. She underwent a successful term pregnancy subsequently [46].

Lung Transplantation

Lung transplantation has been used as the last resort for patients with hard metal lung disease [22, 47]. There is also a report that documented recurrence of the disease in the transplanted lung [47]. Although autopsy confirmed the presence of numerous giant cells characteristic of GIP with associated fibrosis throughout the transplanted lung, there was no evidence of tungsten particles in the transplanted lungs in that case, indicating GIP might develop in the transplanted lung via immune mechanisms.

Prevention

Hard metal lung disease is a preventable disease. Primary prevention is through exposure control by better industrial hygiene practices, i.e., mask wearing and maintenance of better exhaust ventilation and workplace monitoring. The current Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for cobalt is 0.1 mg/m^3 of air as an 8 h time weighted average (TWA) concentration, but this may be still too high as hard metal lung disease has been reported in workers exposed to very low level of cobalt dust [26]. Regular chest radiographs and spirometry screening may be useful in identification of early disease, especially in employees working in poor hygiene conditions. Patch test for cobalt may also be useful in detecting the disease at an earlier stage.

Summary and Recommendations

1. Workers in hard metal manufacture, maintenance of hard metal tools, and diamond tooling are exposed to hard metal elements, in particular, cobalt, and thus are at risk for developing hard metal lung disease.
2. Hard metal lung disease appears 2.5–30 years after exposure, but history of exposure to hard metal dust may be obscure.
3. The diagnosis of hard metal lung disease is usually based on a good exposure history, giant cells in BAL and/or a pathological diagnosis of GIP in surgical lung biopsy. The presence of increased amount of tungsten by elemental analysis confirms diagnosis.
4. Complete cessation of exposure with or without corticosteroids is the most acceptable treatment for hard metal lung disease. Prevention through a comprehensive exposure control strategy in the workplace by the use of personal protective equipment and better ventilation systems should decrease the prevalence of hard metal lung disease.

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