



Case report

A case series describing common radiographic and pathologic patterns of hard metal pneumoconiosis



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ABSTRACT

Introduction: Hard metal pneumoconiosis is a rare but serious disease of the lungs associated with inhalational exposure to tungsten or cobalt dust. Little is known about the radiologic and pathologic characteristics of this disease and the efficacy of treating with immunosuppression.

Objective: We describe the largest cohort of patients with hard metal pneumoconiosis in the literature, including radiographic and pathologic patterns as well as treatment options.

Methods: We retrospectively identified patients from the University of Pittsburgh pathology registry between the years of 1985 and 2016. Experts in chest radiology and pulmonary pathology reviewed the cases for radiologic and pathologic patterns.

Results: We identified 23 patients with a pathologic pattern of hard metal pneumoconiosis. The most common radiographic findings were ground glass opacities (93%) and small nodules (64%). Of 20 surgical biopsies, 17 (85%) showed features of giant cell interstitial pneumonia. Most patients received systemic corticosteroids and/or steroid-sparing immunosuppression.

Conclusions: Hard metal pneumoconiosis is characterized predominately by radiographic ground glass opacities and giant cell interstitial pneumonia on histopathology. Systemic corticosteroids and steroid-sparing immunosuppression are common treatment options.

1. Introduction

Hard metal pneumoconiosis is a rare and serious occupational lung disease that occurs after inhalational exposure to the hard metals tungsten carbide and cobalt. The greatest exposures occur in mining processes, cemented tungsten-carbide industry, alloy production, and also the grinding and sharpening of steel tools with these hard metal abrasives. Individuals with more chronic inhalational exposure may develop interstitial lung disease and often present with worsening dyspnea, exercise intolerance, and a non-productive, bronchospastic cough [1,2].

Little is known about the spectrum of radiographic and pathologic

characteristics of hard metal pneumoconiosis. Prior literature is limited to case reports and very small case-series. The presence of giant cell interstitial pneumonia on histopathology is described as almost pathognomonic [3]. The most commonly reported radiographic findings include a reticulonodular pattern of opacities with ground glass mosaicism and traction bronchiectasis without radiographic honeycombing.

Furthermore, little is known about the prognosis and the effects of treatment. Previous case studies have suggested improvement with corticosteroids, but there is no clear, evidence-based treatment strategy. Long-term steroid use is not an ideal treatment strategy because of many dose-dependent side effects. To our knowledge, there are no prior

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studies that have examined the use of steroid-sparing immunosuppressive agents.

Here, we report the largest cohort of patients with hard metal pneumoconiosis. We describe the radiographic and histopathologic findings in these cases and describe our center's experience with systemic corticosteroids and steroid-sparing immunosuppression.

2. Methods

2.1. Patients

We retrospectively identified patients with a diagnosis of hard metal pneumoconiosis as described in the pathology registry cared for at the University of Pittsburgh between the years of 1985 and 2016. Patients were identified by searching the pathology database for the terms “giant interstitial pneumonia” or “hard metal pneumoconiosis” located in either the final pathology diagnosis or the pathology diagnosis comment section. Members of the study team (JC and LRT) reviewed the medical records of the patients identified through this search to confirm the diagnosis. This study was approved by the University of Pittsburgh Institutional Review Board with a waiver of informed consent (PRO16070398).

2.2. Data collected

For each case, we collected available basic demographic data including age at diagnosis, gender, and race as well as data on date of diagnosis, profession and occupational history, exposure, type of biopsy, steroid use and duration, and use and type of steroid-sparing immunosuppression. We collected data on comorbidities including chronic lung disease, chronic heart disease, gastroesophageal reflux disease, and cancer. We collected mortality data including time from diagnosis to death. We collected data on reported symptoms including dyspnea, cough with or without sputum production, and wheezing as well as prescriptions for inhaled corticosteroid. We collected pulmonary function test (PFT) data starting at the time of diagnosis and then at yearly follow-up for 2 years. PFT data includes the raw value and percent predicted forced vital capacity (FVC), forced expiratory volume over 1 second (FEV1), total lung capacity (TLC), diffusing capacity for carbon monoxide (DLCO). A study team expert in chest radiology (CRF) reviewed computed tomography (CT) scans for radiologic trends based on definitions in existing literature [4]. All but two CT scans were with sharp algorithm processing consistent with high resolution CT imaging. All scans were of good quality as determined by an expert in chest radiology (CRF). A study team expert in thoracic pathology (SAY) reviewed all biopsies for histologic trends. CT images do not correspond to the exact pathology sampling sites.

3. Results

3.1. Cohort description

We identified 23 patients with a pathologic pattern on lung biopsy described in pathology reports as consistent with hard metal pneumoconiosis. The characteristics of each of these patients are detailed in Tables 1–3. Patients' median age at the time of diagnosis was 42 years. The vast majority were male (87%) and caucasian (100%). Tungsten carbide comprised 87% of the known exposures. Of the 17 patients with medical records available for review, all patients reported dyspnea, 13 reported cough 4 of which with sputum production, and 3 reported wheezing. The most prevalent comorbidity was gastroesophageal reflux disease, present in 8 patients. Of the 21 patients that have treatment data, 6 (29%) were prescribed inhaled corticosteroid and 18 (85%) received systemic immunosuppression. Sixteen patients (89%) received systemic corticosteroid or steroid-sparing immunosuppression. Fourteen of these sixteen patients (78%) received systemic corticosteroids.

Table 1
Cohort demographics.

	N	Result
Age, median (range)	23	42 (23–73)
Male	23	20 (87%)
White	22	22 (100%)
Related exposure	13	
Carbide/tungsten		11 (85%)
Cobalt		2 (15%)
Prescribed inhaled corticosteroid	21	6 (29%)
Steroid	18	
No		4 (22%)
Less than 6 months		7 (39%)
More than 6 months		7 (39%)
Immunosuppression	18	
No		8 (44%)
Cyclophosphamide		2 (11%)
Azathioprine		6 (33%)
Other		2 (11%)
Asthma	17	0
COPD	17	1 (6%)
Chronic heart disease	17	0
GERD	17	8 (47%)
Cancer	17	0
Death	23	5 (22%)
Age at death, median (range)	5	45 (37–74)
Years from diagnosis, median (range)	5	4.6 (1.0–5.4)

COPD – chronic obstructive pulmonary disease.

GERD – gastroesophageal reflux disease.

Ten of these patients received steroid-sparing immunosuppression, including 6 (38%) who received azathioprine and 2 (13%) who received cyclophosphamide. Mortality was 19% in this cohort and the median time from diagnosis to death was 4.6 years.

3.2. Pulmonary function testing

Of the 19 patients who had pulmonary function testing, 16 had a restrictive pattern, 2 were normal, and 1 was obstructed at the time of diagnosis. For the cohort as a whole, severely restrictive physiology with decreased DLCO was observed at baseline (Table 4). We also show individual patient trajectories for FVC and FEV1 (Fig. 1) over 2 years of follow up.

3.3. Radiology

Of the 23 cases, 14 CT chest studies were available for review. Radiographic honeycombing was present in 6/14 (43%) and traction bronchiectasis was seen in 8/14 (57%) (Fig. 2A). Ground glass opacities was the most frequently observed radiographic finding, present in 13/14 (93%) (Fig. 2B). Small nodules were common, found in 9/14 (64%) (Fig. 2C). Small cysts were uncommon and found in only 3/14 (21%) (Fig. 2D). None of our cohort exhibited perihilar conglomerate fibrosis, which is typical of other pneumoconioses. All images had more than one finding. The most common combination was small nodules and ground glass opacities, present in 50%.

3.4. Pathology

Of the 23 cases described as consistent with hard metal pneumoconiosis in biopsy reports, twenty surgical biopsy specimens were physically available for review. Seventeen biopsies showed features of giant cell interstitial pneumonia. Of the remaining three cases, two were consistent with usual interstitial pneumonia and one case was consistent with hypersensitivity pneumonitis. Injury was typically bronchiolocentric (15/20) with a lymphocytic bronchiolitis and with centrilobular airspace giant cells with leukoerythrophagocytosis (“cellular cannibalism”) in 17/20 cases. We identified prominent lymphoid

Table 2
Individual patients' description.

	Age at diagnosis	Gender	Race	Cough	Biopsy	Steroid Use	Steroid use over 6 months	Steroid-sparing drug	PFT pattern at diagnosis	Outcome
1	42	male	C	no	VATS	yes	yes	Azathioprine	restrictive	alive
2	49	male	C		TBBx					alive
3	33	male	C	yes	VATS	yes	no		restrictive	died
4	25	male	C	yes	VATS	no		Azathioprine	restrictive	alive
5	36	male	C	yes	VATS	no		Azathioprine	restrictive	alive
6	31	male	C	yes	VATS	yes	no	Azathioprine	restrictive	alive
7	65	male	C	yes	VATS	no			restrictive	alive
8	74	male	C		VATS					died
9	51	female	C	yes	VATS	yes	no	Interferon	restrictive	died
10	59	female	C	no	VATS	yes	no	Azathioprine	restrictive	alive
11	56	male	C	yes	VATS	yes	yes		restrictive	alive
12	38	male	C	yes	VATS	yes	no		restrictive	alive
13	32	male	C		autopsy				restrictive	transplant/died
14	28	male	C	no	VATS	yes	yes		restrictive	alive
15	30	male	C	no	VATS	yes	yes	leflunomide	normal	alive
16	27	male	C		VATS	yes	yes			alive
17	58	male	C	yes	explant	yes	no	cyclophosphamide	restrictive	transplant/alive
18	56	male	C	yes	VATS	yes	yes	cyclophosphamide	restrictive	alive
19	44	male	C		VATS					alive
20	49	male	C	yes	VATS	yes	no	azathioprine	restrictive	alive
21	44	male	C		VATS				restrictive	died
22	23	male	C	no	VATS	yes	yes		normal	alive
23	42	female	C	yes	VATS	no			obstructive	alive

TBBx – transbronchial biopsy.

VATS – video-assisted thoracoscopic surgery.

PFT - pulmonary function testing.

aggregates and eosinophils in 7 cases each. Honeycomb change was rare, seen in only 4/20 cases, although we identified pleuroparenchymal scarring in 7/20 cases. Fig. 2 shows pathology that correlates with the above mentioned radiographic descriptions.

4. Discussion

We report the largest cohort of patients with hard metal pneumoconiosis in the literature. Description of this disease is limited by small numbers and reliance on case studies or small case series. The disease is associated with a broad age range, where clinical manifestations can range from normal to severe. It is notable that the mean age of those who died was 46.8 years, suggesting that this is a disease of young people. Those who work with tungsten or cobalt are at increased risk of

Table 4
Baseline pulmonary function testing for the cohort.

	N	Median (IQR)
FVC % predicted	19	52 (48–60)
FEV1% predicted	19	58 (53–83)
FEV1/FVC	19	0.85 (0.76–0.89)
TLC % predicted	13	63 (51–75)
DLCO % predicted	17	48 (31–60)

developing hard metal pneumoconiosis. We found that hard metal pneumoconiosis is characterized predominately by radiographic ground glass opacities and small nodules. The most common histopathology associated with hard metal pneumoconiosis is giant cell interstitial

Table 3
Occupational and exposure history.

1	Worked in manufacturing for 5 years prior to symptoms. Exposed to tungsten carbide dust. Wore a simple fiber mask for 5 years then forced airflow mask.
2	Not available
3	Worked as a factory press operator for 4 years prior to developing symptoms. Exposed to carbide.
4	Worked as a furnace technician. Exposed to cobalt and other hard metal fumes.
5	Worked at a cemented carbide plant for 15 years prior to presentation.
6	Worked as a machinist and used high frequency device to polish metal- tungsten carbide. Developed symptoms after 9 years at which time he began using a respirator. Stopped work 2 years later.
7	Worked in grinding room of a tungsten carbide plant for 18 years prior to presentation. Did not use any personal protective equipment.
8	Not available
9	Worked as a millright exposed to metal grinding.
10	Worked as a nurse. No clear exposure history to explain diagnosis.
11	Worked in a fiberglass factory exposed to calcium sulfate. No known hard metal exposure.
12	Worked in a tool and dye shop and exposed to tungsten carbide with surface grinding.
13	Not available
14	Worked in carbide factor with many exposures including heavy metals.
15	Worked as a “powder processor” mixing and loading mixtures of cobalt, nickel, and tungsten wax. Wore a paper mask.
16	Processed cemented carbide for 7 years prior to presentation
17	Worked in a carbide dye factory as engineering supervisor with exposure to tungsten and carbide. Also formed his own tool and dye business one year prior to diagnosis.
18	Worked in furniture factory, did asphalt work, firefighter, and drove a garbage truck. No clear hard metal exposure.
19	Not available
20	Worked making metal bearings exposed to grinding of tungsten carbide.
21	Not available
22	Not available
23	No known exposures.

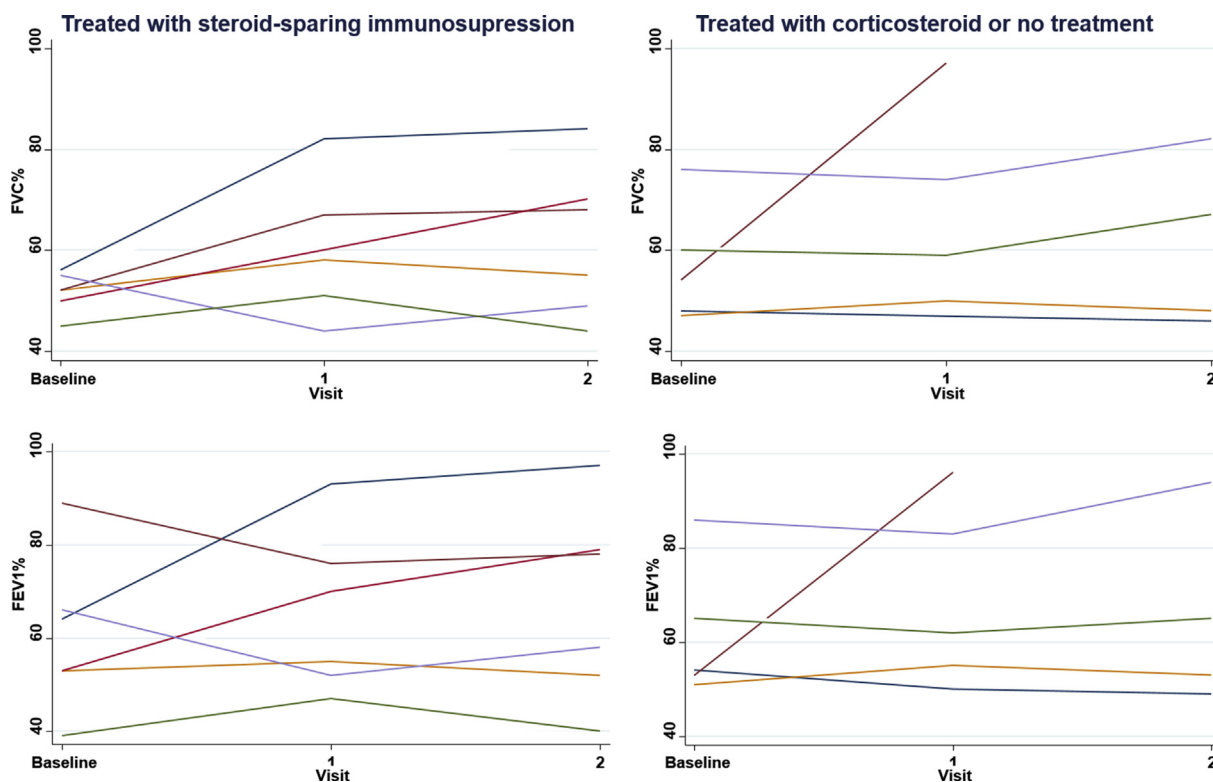


Fig. 1. Individual patient trends in FVC and FEV1.

pneumonia. And the most frequently used steroid-sparing immunosuppressive agent was azathioprine.

We found that hard metal pneumoconiosis has a variety of radiographic findings. All patients' chest imaging in this cohort had more than one radiographic pattern. Though most patients had ground glass opacities and small nodules, we also commonly observed honeycombing and traction bronchiectasis-patterns that are reported as rare in existing literature [5,6]. Small cysts have been reported as common in the literature but were rare in this cohort [7]. Importantly, none of this cohort had typical perihilar conglomerate fibrosis, which occurs with other inhalational lung disease such as silicosis and coal workers' pneumoconiosis.

Hard metal pneumoconiosis histopathology is more predictable. We find that almost all cases show giant cell interstitial pneumonia characterized by a bronchioleentric injury pattern with centrilobular air-space giant cells with leukoerythrophagocytosis. This is consistent with existing literature showing a majority of hard metal pneumoconiosis pathology demonstrates giant cell interstitial pneumonia [8–10]. Other data has shown that a small proportion of hard metal pneumoconiosis demonstrates a pattern of usual interstitial fibrosis. A bronchioleentric injury pattern suggests aerosol exposure of hard metal dusts. We also commonly observed eosinophils, which, we speculate, may indicate an IgE component to the pathophysiology that could respond to immunosuppression. Although we found that radiographic honeycombing is common, histologic honeycombing was rare. This is probably because lung biopsy sampling is usually not from the area of radiographic honeycombing but rather on the margin of injury.

Anecdotally, our experience suggests that patients' lung disease worsens without therapy, including both systemic corticosteroids and steroid-sparing immunosuppression. With the side effects of corticosteroids, treatment of this disease with steroid-sparing agents may be associated with less long term toxicity, especially as some of these patients do eventually go on to lung transplant. The cumulative experience at the University of Pittsburgh and the Dorothy P. and Richard P. Simmons Center for Interstitial Lung Disease suggests that patients with

this disease benefit from steroid-sparing immunosuppression compared with those who receive only steroid or no treatment. Basic studies to elucidate the pathogenesis of hard metal pneumoconiosis and the effect of immunomodulatory therapy on the natural history of disease are lacking. In addition to immunologic mechanisms, one consideration is the observation that, *in vitro*, cobalt carbides produce toxic reactive oxygen species which leads to the speculation that individuals with lower antioxidant defense are more susceptible—a possible explanation for why not all exposed workers develop the disease [11].

Our radiographic and histopathologic findings may help to identify patients who may respond to immunosuppression in the following ways. First, in a small cohort of patients with chronic diffuse infiltrative lung disease without honeycombing, areas of ground glass attenuation on CT have been shown to correspond to inflammation over half the time [12]. Since the predominant radiographic finding in this cohort was ground glass opacities, it may be reasonable to attempt immunosuppressive therapy. Second, we commonly observed lymphoid aggregates and eosinophils on histopathology-findings that are associated with responses to immunosuppression in other diseases such as asthma and inflammatory bowel disease [13].

Our study has several limitations. First, this is a retrospective, observational study that is prone to bias. For example, patients with more severe impairment in FVC may be more likely to be treated with steroid and steroid-sparing immunosuppression which may result in larger changes in FVC, while treatment for milder cases may only consists of steroid alone or no treatment. Second, this is a report of our experience at a single, large academic medical center. Our experience with this disease and with immunosuppression in this disease may not be generalizable. Finally, we looked only at the effect of immunosuppression at the time of diagnosis. We do not know how starting immunosuppression later in the disease course or how stopping immunosuppression would affect the trajectory of the disease.

In conclusion, we found that hard metal pneumoconiosis presents a variety of radiographic and histopathologic findings with the most common being ground glass opacities and giant cell interstitial

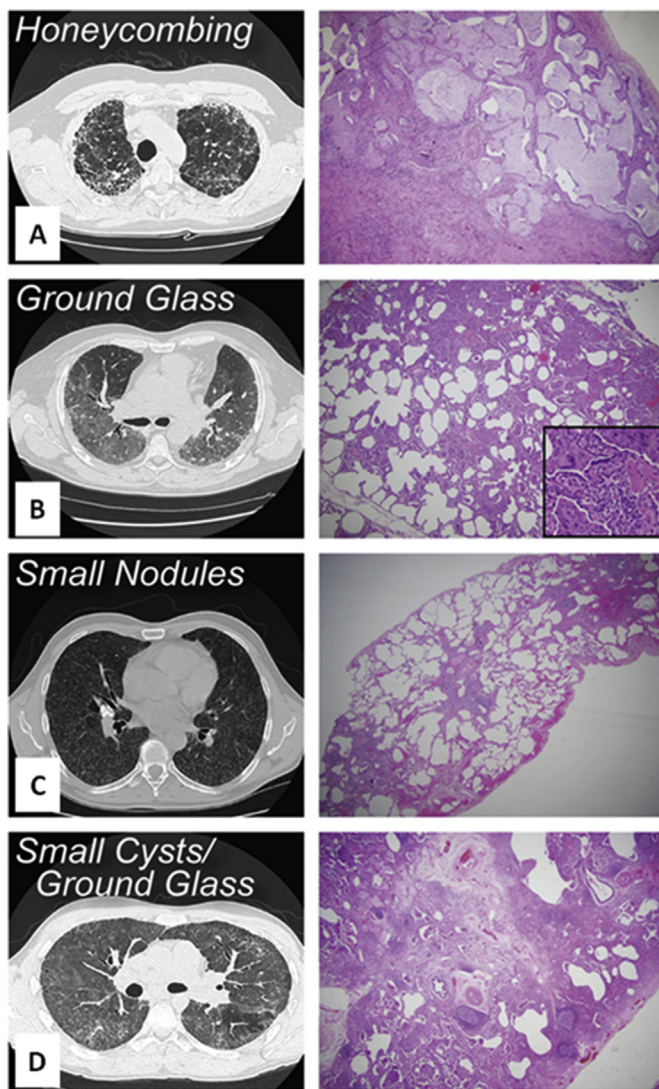


Fig. 2. Radiographic and pathologic manifestations of hard metal pneumoconiosis. Representative computed tomographic (CT) scanning and histopathologic patterns: (A) Radiographic honeycombing with pathologic honeycomb change manifested by remodeled lung with cysts of varying sizes filled with mucous plugs. (B) Radiographic ground glass opacities with pathologic ground glass change formed by patchy airspace filling by cannibalistic giant cells (see insert for high power view). (C) Radiographic small nodules with pathology showing peribronchiolar scars with peribronchiolar airspaces filled with histiocytes and giant cells separated by intervening normal lung. (D) Radiographic small cysts and ground glass opacities with pathology showing small cysts distorting the parenchyma in the upper right corner and in the lower left corner airspaces filled with giant cells merged with microscopic emphysematous type cysts.

pneumonia. Clinicians experienced with immunomodulatory medication may consider a trial of steroid-sparing immunosuppression early in the disease to try and salvage pulmonary function and spare patients the side-effects of long-term systemic corticosteroids.

Author contributions

JC, LT, SS, MN, DJK, and KFG contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript and approved the final version.

KL, JS, KOL, LOA, FCS, RK, SAY, and CRF contributed substantially to data analysis and interpretation, and the writing of the manuscript and approved the final version.

Conflicts of interest

The authors have no relevant conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.rmcr.2018.08.006>.

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