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Case Report

Peribronchiolar metaplasia interstitial pneumonia in cleaning workers

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Abstract: A possible relationship between exposure to cleaning products and chronic interstitial lung disease is not currently recognized. This is a retrospective study of patients with a surgical lung biopsy-proven diagnosis of interstitial lung disease, treated at a university hospital pneumology department between 1994 and 2010, whose only related activity had been cleaning. Patients with acute presentation following accidents involving massive inhalation or inhalation of high concentrations of different products, and those in whom biopsy findings suggested a specific entity were explicitly excluded. Patients underwent a detailed inquiry and answered a questionnaire on exposure to cleaning products by direct interview and/or telephone contact. All patients had undergone respiratory function study, high-resolution computed tomography (HRCT), and surgical lung biopsy. Mean age was 64 (53-74) years, and 3 of the 4 patients were women. None had a history of smoking. All patients were cleaning workers who had been exposed to various products, including hydrochloric acid solution and bleach. None of the patients used appropriate airway protection. Two cases showed a certain relationship in time between exposure and manifestations of the disease. All patients presented dyspnea and disease progression to respiratory failure, and all had a restrictive respiratory disorder. In addition to alveolar-interstitial abnormalities, HRCT showed signs of airway involvement. Bronchoalveolar lavage cytology findings were non-specific. Surgical biopsy revealed mainly peribronchiolar metaplasia and a varying degree of airway-centered interstitial fibrosis. In conclusion, exposure to cleaning products might be a cause of airway-centered diffuse interstitial lung disease with peribronchiolar metaplasia.

Keywords: Cleaning workers, interstitial pneumonia, peribronchiolar metaplasia

Introduction

Cleaning work is carried out worldwide in different settings by both professional and domestic workers. Cleaning workers comprise a considerable percentage of the total working population with rates of 3% in the USA, 4% in Finland and 10% of the female working population in Spain [1]. Cleaning activity entails the use of several products, many of which are irritants, others may induce sensitisation, and some have the potential to act via both mechanisms [1]. Reported cases of interstitial lung disease (ILD) related to exposure to cleaning products are mainly due to accidents involving massive inhalation or inhalation of products at high concentrations, which produces acute respiratory symptoms such as acute respiratory distress [2] or organising pneumonia [3]. In addition, hypersensitivity pneumonitis (HP) secondary to proteolytic enzymes following manipulation of detergents [4], and silicosis due to abrasive scouring products [5], have been described. Apart from these cases, only one case of chron-

ic ILD in relation to possible inhalation of cleaning products has been reported [6]. In that case, the main pathological lesion was airway-centred fibrosis, an entity described previously by Churg et al. [7] though not in the specific context of inhalation exposure to cleaning products. The aim of this study was to describe the characteristics and evolution of a series of patients with chronic airway-centred ILD with peribronchiolar metaplasia, whose single common occupational risk factor was having worked as cleaners.

Material and methods

This is a retrospective study of 4 patients with a surgical biopsy-proven diagnosis of ILD of unknown cause, whose only work occupation had been industrial or domestic cleaning. These patients were diagnosed in 1994, 2003, 2005 and 2008 at a university hospital pneumology department. Acute cases caused by inhalation of any toxic substance, and those diagnosed of any specific entity such as HP, were excluded.

Data compiled included the patients' clinical history, with particular focus on exposure to animals or other known aetiological factors related to ILD, and results of the physical examination, laboratory analyses, respiratory function tests (RFTs), arterial blood gas study, chest radiography, chest X-rays, chest-high resolution computed tomography (HRCT), bronchoalveolar lavage (BAL) and surgical lung biopsy (SLB). Work exposure to cleaning products was assessed by a detailed inquiry supported by a specific questionnaire [8] via direct interview or telephone contact.

In addition to the results of routine biochemical analyses, data were compiled on antinuclear antibodies and specific IgG (ELISA) against avian proteins in cases where there was occupational or domestic exposure to these antigens. Spirometry was performed on a MasterLab system (MasterLab, Jaeger, Germany) following the recommendations of the European Respiratory Society (ERS) [9]. Static lung volume was determined by plethysmography [10], and the diffusing capacity of the lung for carbon monoxide (DLCO) was assessed using the single breath-hold method [11]. The theoretical values applied were those described for the Mediterranean population [12] for spirometry and those proposed by the ERS [13] for static lung volume and DLCO.

A radiologist (E.P.) with extensive experience in lung disease interpreted the HRCT images. Abnormal findings related to lung parenchyma were graded according to the criteria of Warrick et al. [14]. A value was assigned to each parenchymal abnormality described: ground glass opacities (1 point), irregular margins (2 points), subpleural septa/lines (3 points), honeycombing (4 points), and subpleural cysts (5 points). Disease severity was defined in a range from 0 (normal) to 15 (presence of all abnormalities). The number of affected lung segments determined disease extension: 1 to 3 segments (1 point), 4 to 9 segments (2 points), and more than 9 affected segments (3 points). This process was repeated for each of the parenchymal abnormalities detected, with possible disease extension ranging from 0 (normal) to 15 (>9 affected segments showing the 5 possible abnormalities). Disease severity and extension were jointly defined in a range of 0 to 30. Airway abnormalities studied included centrilobular involvement, mosaic pattern, and bronchial thickening and/or non-traction-related bronchiectasis, according to the radiological criteria proposed by Hansell et al. [15]. Similarly to the assessment of parenchymal involvement, a value was assigned to each of the airway abnormalities detected: centrilobular involvement (1 point), mosaic pattern (2 points), and bronchial thickening and/or non-traction-related bronchiectasis (3 points). The severity and extension of airway disease was established according to the same criteria as those used for lung parenchyma.

BAL was performed according to ERS guidelines [16]. Cell count reference values for BAL were those established for the healthy, non-smoking population [17]. SLB specimens were examined by a pathologist (M.A.M.) experienced in lung disease. The explanted lung of a patient who underwent lung transplantation was also reviewed.

Patients were followed up to 2010, to the time of transplantation or until the death of the patient.

Patient data were kept anonymous to meet the ethical requirement for confidentiality and to comply with personal data protection legisla-

Table 1. Patient characteristics at diagnosis of diffuse airway-centered interstitial lung disease with peribronchiolar metaplasia

Case characteristics	1	2	3	4
Sex/age	♀/74 years	♀/65 years	♀/64 years	♂/53 years
Cleaning products	Soaps, ammonia, bleach, *hydrochloric acid solution, *multipurpose products, scented products	Soaps, ammonia, bleach, *hydrochloric acid solution, *multipurpose products, scented products and degreasing products	Ariel®, **ammonia, hydrochloric acid solution, *bleach, *, degreasing products, multipurpose products, scented products	Bleach, *hydrochloric acid solution, *soaps, various degreasing products
Other exposures	Birds	No	Birds	No
RFT	FVC: 1.5 (54%); FEV1: 1.63 (69%); FEV1%: 93; VR: 75%; TLC: 72%; DLCO: 74%; KCO: 98%	FVC: 1.56 (59%); FEV1: 1.46 (77%); FEV1%: 93; VR: 56%; TLC: 61%; DLCO: 43%; KCO: 76%	FVC: 2.31 (80%); FEV1: 2.01 (96%); FEV1%: 87; VR: 60%; TLC: 77%; DLCO: 69%; KCO: 85%	FVC: 2.49 (55%); FEV1: 2.07 (60%); FEV1%: 83; VR: 56%; TLC: 58%; DLCO: 41%; KCO: 65%
BAL	14×10^6 cel/100 mL. Formula: M: 76%, L: 6%, PMN: 16%, T4/T8 index: 5.7 (1.7 in blood)	Formula: M: 59%, L: 11%, PMN 30%. T4/T8 index: 1.3 (1.46 in blood)	33×10^6 cel/100 mL. Formula: M 84%, L: 9%, PMN: 6%, E: 1%.	Formula: M 90%, L 10%.
SLB	Peribronchiolar metaplasia Interstitial lymphocytic inflammatory infiltrate Airway-centered fibrosis Cellular bronchiolitis Anthracotic macules	Peribronchiolar metaplasia Interstitial lymphocytic inflammatory infiltrate Airway-centered fibrosis with obliteration of bronchioles	Peribronchiolar metaplasia Interstitial lymphocytic inflammatory infiltrate Airway-centered and subpleural fibrosis Bronchioloectasis	Peribronchiolar metaplasia Interstitial lymphocytic inflammatory infiltrate Airway-centered fibrosis Anthracotic macules

*Cleaning products most often used; **Ariel®: water, ethoxylate alkyl sulphate and scent; BAL: bronchoalveolar lavage; M: macrophages; L: lymphocytes; PMN: polymorphonuclear leucocytes; RFT: respiratory function testing; SLB: surgical lung biopsy.

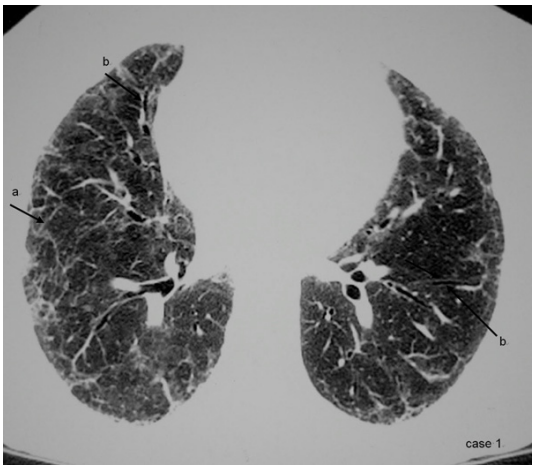

Figure 1. HRCT (case 1) shows areas of ground glass opacities with reticular lines and septa (arrow a). Bronchiectasis (arrow b) is also seen.

tion. The study was undertaken in accordance with the Principles of the Declaration of Helsinki and was approved by the Ethical Committee of our center (Comité Ètic d'Investigació Clínica "CEIC", number 216). At this was a retrospective study, patients were not asked to give their informed consent.

Results

The study included 3 women and 1 man, aged from 53 to 74 years at the time of diagnosis. All patients were non-smokers and none had a history of smoking. Two of our patients (Cases 1 and 2) were sisters, and a brother of Case 3 worked as a plasterer and had been diagnosed of usual interstitial pneumonia by SLB. In addition, Case 2 had a history of allergic asthma. Patient demographics and disease-related characteristics are shown in **Table 1**.

The latency period between the time of work-related exposure to cleaning products and onset of symptoms ranged from 5 to 33 years, with a mean of 22.7 years. The main symptom at the time of diagnosis was dyspnoea in Cases 2 and 4. Case 1 debuted with cough and expectoration, whereas Case 3 was asymptomatic, with ILD being diagnosed on routine chest X-ray. All patients presented dyspnoea at some time after diagnosis. In Case 2, the specific interview revealed that symptom onset occurred 30 days after exposure to fumes from hydrochloric acid which she said was being used more frequently than usual. Years later, following a lengthy stable period in which she avoided cleaning products, the patient again experienced clinical, functional and radiological worsening of her condition after she returned to her former activity. Case 1 showed clinical and functional deterioration during follow-up after again using several cleaning products (bleach and hydrochloric acid solution, among others) following a period of stability. On physical examination, all 4 patients presented dry crackles in lung bases. No signs of nail clubbing or evidence of systemic or other diseases were observed in any case that would indicate a specific cause of ILD. Analytical data, including specific IgG (ELISA) against avian proteins in cases of avian exposure (Cases 1 and 3) were negative or normal.

Respiratory function tests revealed a restrictive disorder in all 4 patients. DLCO showed a variable decrease in all cases, which corrected in 2 patients after adjusting for alveolar volume. On chest X-ray, a bilateral diffuse interstitial pattern with basal predominance was seen in all 4 patients, and all showed a pattern of diffuse interstitial disease on HRCT. Areas of ground glass opacities with irregular margins and an increase in subpleural lines and septa were seen in all cases. A honeycomb pattern was observed in 1 patient and subpleural cysts in 2. Mosaic pattern on expiratory slices, and bronchial thickening and/or non-traction-related bronchiectasis were seen in all cases (**Figure 1**). Small centrilobular nodules were observed in 2 patients. Grading for disease extension and severity according to HRCT abnormalities is reported in **Table 2**.

Fibrobronchoscopy showed no malignant cells, and microbiological examination yielded normal findings in all patients. Cytological study of BAL specimens demonstrated increased cellularity in two patients (Cases 1 and 3), with absolute cell counts of 14×10^6 and 33×10^6 cells/100 mL, respectively. In all cases, cellularity was mainly composed of macrophages, with values ranging from 59% to 90% (mean: 77.2%). Lymphocytes were mildly increased (10%, 10% and 11%) in 3 patients and polymorphonuclear leucocytes in 2 cases (16% and 30%).

SLB showed mainly a pattern of chronic bronchiolitis with interstitial peribronchiolar meta-

Table 2. Severity and extension of parenchymal[2] and airway abnormalities[3] on high-resolution computed tomography study at the time of diagnosis

Patient	Parenchymal abnormalities								Airway abnormalities				
	Grading	Ground-glass	Irregular margins	Subpleural septae/lines	Honeycomb	Subpleural cysts	Total		Centrilobular	Mosaic	Bronchial thickening or ectasia	Total	
1	Severity	1	2	3	0	0	6	13	0	2	3	5	8
	Extension (NS[1])	2 (9)	2 (8)	3 (13)			7		0	2 (5)	1 (3)	3	
2	Severity	1	2	3	4	5	15	26	0	2	3	5	10
	Extension (NS[1])	3 (16)	3 (12)	3 (16)	1 (2)	1 (3)	11		0	2 (7)	3 (12)	5	
3	Severity	1	2	3	0	0	6	12	1	2	3	6	12
4	Extension (NS[1])	2 (9)	2 (4)	2 (7)			6		(1) 2	2 (4)	3 (10)	6	
	Severity	1	2	3	0	5	11	19	1	0	3	4	9
	Extension (NS[1])	2 (8)	2 (9)	3 (15)		1 (2)	8		(2) 8	0	3 (10)	5	

[1]NS: number of affected lung segments; [2]Criteria of Warrick et al. [16]; [3]Modified criteria of Fleishman et al. [17].

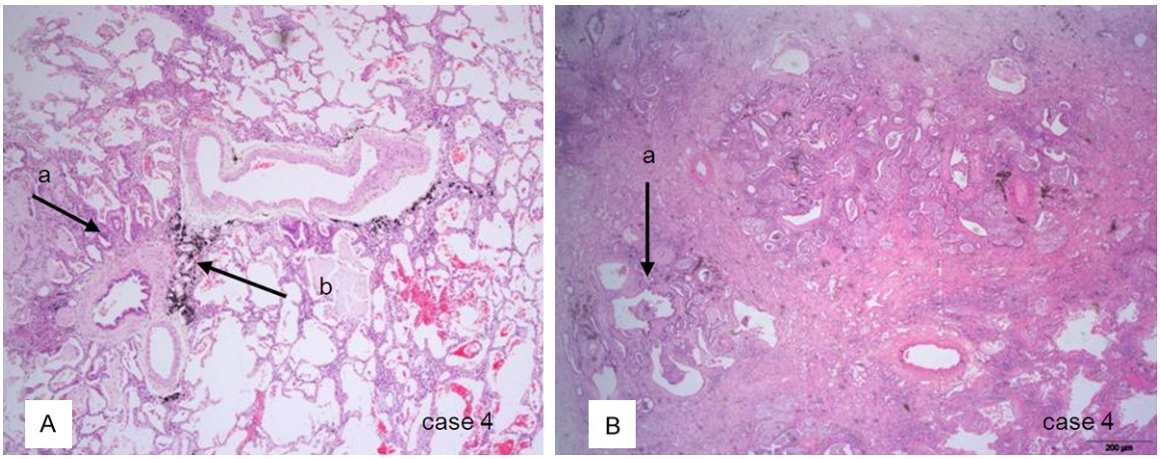

Figure 2. A. Pre-transplantation surgical lung biopsy (case 4) shows peribronchiolar metaplasia (arrow a), patchy areas of increased interstitial chronic inflammation and black dust pigmentation (arrow b). B. Recipient lung with extensive areas of honeycomb pattern (arrow), mainly in the lower lobe.

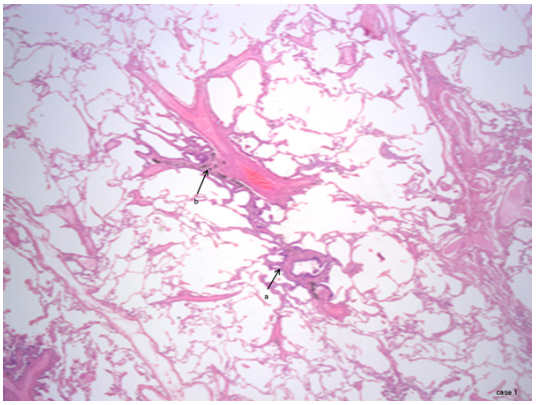

Figure 3. Peribronchiolar metaplasia (arrow a), patchy mild interstitial chronic inflammation, airway-centered fibrosis and black dust pigmentation (arrow b) (case 1).

plasia (**Figures 2A** and **3**) in all cases. Airway-centered fibrosis (**Figures 4** and **5**) spreading more or less into the alveolar walls and mild interstitial lymphocytic infiltrate was also observed. Black dust pigmentation (**Figures 2A** and **3**) but no birefringent particles under polarised light, were seen in two patients (Cases 1 and 4). Abundant intra-alveolar mucostasis related to bronchiolar obstruction was seen in one patient (Case 1). Special stains for amyloid (Congo red) were negative. Lung histology from the explanted recipient lung (Case 4), three years after the surgical lung biopsy, mainly showed extensive diffuse interstitial fibrosis with areas of centrilobular bronchiolization (**Figure 2B**).

Follow-up from the onset of symptoms ranged from 3 to 13 years, with a mean of 7.7 years. All patients received corticosteroid treatment. In addition, one was given azathioprine and another mycophenolate mofetil. Two patients (Cases 1 and 2) died of the disease at 11 and 13 years of follow-up. Consent was not given to perform autpsies. A third patient (Case 4) received a single right lung transplant 3 years after diagnosis, and the fourth patient (Case 3) progressed to chronic respiratory failure and required chronic home oxygen therapy 5 years post-diagnosis.

Discussion

In this study, we describe 4 cases of airway-centred ILD with peribronchiolar metaplasia in cleaning workers. Data in this series suggest a causal relationship between exposure by inhalation of cleaning products and the patients' respiratory disease: first, owing to the radiological and histological evidence of lesions in structures prone to inhalation injury in patients who had no other known or specific cause of ILD; second, because of the patients' prolonged, intense contact with cleaning products in the absence of other types of exposure or entities that could have caused their disease; and third, since in two cases there was a temporal relationship between worsening of the condition and the use of cleaning products.

Familial idiopathic pulmonary pneumonia is attributed to an autosomal dominant disorder

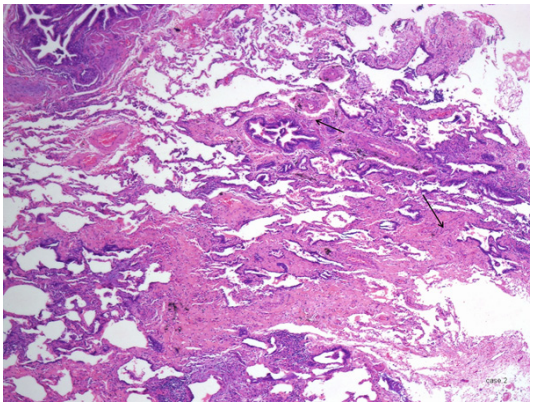

Figure 4. Airway-centered fibrosis with extense peribronchiolar compromise (arrows) (case 2).

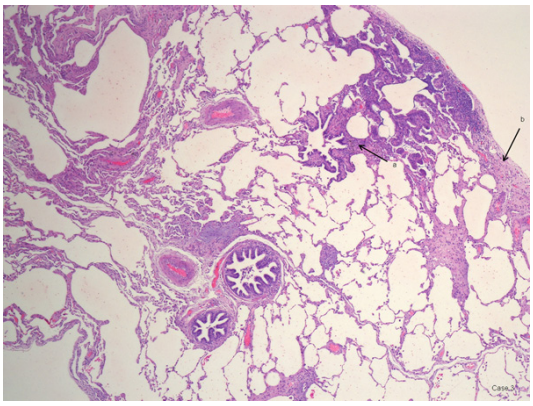

Figure 5. Peribronchiolar metaplasia, interstitial chronic inflammation, and airway-centered (arrow a) and subpleural (arrow b) fibrosis (case 3).

with variable penetration which accounts for less than 2% of cases of idiopathic pulmonary pneumonia [18]. Although two of our patients were sisters and another had a brother with ILD, it is unlikely that these patients had familial idiopathic pulmonary pneumonia. The main pathological lesions found in this entity are usual interstitial pneumonia or a form of unclassifiable fibrotic lung disease [19]. In contrast, bronchiolocentric involvement with bronchiolar metaplasia, the main histopathological feature found in all our patients, is usually absent or not significant in familial idiopathic pulmonary fibrosis [19]. However, we cannot completely rule out the hypothesis that a certain genetic predisposition was responsible for more than one case of idiopathic interstitial pneumonia occurring in the same family.

With the exception of HP due to exposure to detergents [4] and silicosis due to abrasive scouring products [5], a possible relationship between chronic ILD and cleaning products is virtually unknown. The only study suggesting such a relationship was reported by Serrano et al. [6], who described airway-centered interstitial pulmonary fibrosis in a woman employed as a cleaning worker. Other authors have described similar conditions which, however, were not associated with the use of cleaning products. De Carvalho et al. [20] reported centrilobular fibrosis in 12 patients, and suggested that this histological pattern may have been related to aspiration of gastric content in some of the cases. However, the authors did not clearly specify whether the patients had gastro-esophageal reflux or whether they had been exposed to inhalation of other agents. The description of idiopathic bronchiolocentric interstitial pneumonia by Yousem and Dacic [21] was based on the study of 10 cases, mainly women (80%), whose prognosis was poor despite treatment with steroids and immunosuppressors. There was no mention of exposure to any agent, although the authors reported a certain similarity to HP, but with more extensive centrilobular fibrosis and absence of granulomae. Churg et al. [7] reported airway-centered pulmonary fibrosis in a series of 12 patients, mainly women (67%). Almost all patients had chronic respiratory failure and poor prognosis. The HRCT features and histological pattern of Churg's patients were similar to those in our series. The condition was related to inhalation of organic and inorganic agents in eight of the patients described, however, cleaning products were not involved in any case. Peribronchiolar metaplasia, described by Fukuoka et al. [22] was observed in a series of 15 patients, also mainly women (86%). Exposure to birds was documented in one case and exposure to welding fumes in another. HRCT showed a diffuse mosaic pattern during expiration and bilateral basal and subpleural ground glass attenuation. The only histological abnormality encountered was peribronchiolar metaplasia. Prognosis was considered favorable, since the disease had stabilized in 11 of the 15 patients at more than 2 years of follow-up. Recently, Kuranishi et al. [23] described 68 patients, most of them women (74%), whose prognosis was more favorable than that published for idiopathic pulmo-

nary fibrosis, but reduced in patients with cough, lower values of oxygen saturation at rest, organizing tissue in airways, fibroblastic foci and microscopic honeycombing. Exposure to birds and/or molds was present in 62% of patients, gastroesophageal reflux symptoms in 56%, connective tissue disease criteria in 18% and in only 2 patients no association or disease was found.

In conclusion, although the authors of those studies also mention that the majority of patients had aspirated [20] or inhaled [6, 7, 20-23], like the cleaners in our study, different types of agents, the precise etiology of these conditions remains uncertain. Moreover, based on the information provided, we cannot know whether the pathological involvement described above [7, 20-23] corresponds to different entities or, rather, different states of the same disease [24].

In our opinion, the most salient findings in our study were the airway involvement and airway-centered interstitial involvement, which could indicate that the interstitial process had originated in airway and peri-airway tissue as a response to cleaning product exposure. Also of note, is that the explanted lung study in one patient, performed 3 years after the diagnostic surgical biopsy, showed extensive fibrosis of the lung parenchyma, but no peribronchiolar metaplasia, which may signify that peribronchiolar metaplasia had been replaced by fibrosis during the evolution of the disease.

Although further studies are required, peribronchiolar metaplasia interstitial pneumonia may represent a particular response to inhaled cleaning products.

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Disclosure of conflict of interest

None.

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