

DESQUAMATIVE INTERSTITIAL PNEUMONIA INDUCED BY METAL EXPOSURE. A CASE REPORT AND LITERATURE REVIEW

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ABSTRACT. *Background:* Forms of interstitial pneumonia secondary to exposure to an air-contaminant are varied and so far, insufficiently described. *Objectives/Methods:* We report here a case of a 57-year-old patient managed in our department for the exploration of MRC grade 2 dyspnoea and interstitial pneumonia. He mentioned multiple occupational and domestic exposures such as hens' excrements, asbestos and metal particles; he also had a previous history of smoking. *Results:* High-resolution computed tomography showed ground glass opacities predominating in posterior territories and surrounding cystic lesions or emphysematous destruction. The entire etiological assessment revealed only macrophagic alveolitis with giant multinucleated cells on the bronchoalveolar lavage. A surgical lung biopsy allowed us to refine the diagnosis with evidence of desquamative interstitial pneumonia and pulmonary granulomatosis. Finally, the analysis of the mineral particles in the biopsy revealed abnormally high rates of Zirconium and Aluminium. We were therefore able to conclude to a desquamative interstitial pneumonia associated with pulmonary granulomatosis linked to metal exposure (Aluminium and Zirconium). The clinical, functional and radiological evolution was favorable after a systemic corticosteroid treatment with progressive decay over one year. *Conclusion:* This presentation reports the first case to our knowledge of desquamative interstitial pneumonitis related to exposure to Zirconium and the third one in the context of Aluminium exposure. The detailed analysis of the mineral particles present on the surgical lung biopsy allows for the identification of the relevant particle to refine the etiological diagnosis, to guide the therapeutic management and to give access to recognition as an occupational disease.

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KEY WORDS: Interstitial lung disease, desquamative interstitial pneumonia, Aluminium lung, Metal analysis, Zirconium lung

I. INTRODUCTION

Forms of interstitial pneumonias secondary to exposure to an air-contaminant are varied and so far,

insufficiently described. Based on the 2012 ATS/ERS classification of Interstitial Lung Disease (ILD), we can find these forms of pneumonia in each category of ILD (1). There is no separate class of ILD due to an air-contaminant. The identification of the causal agent remains difficult in a large amount of cases of ILD even if current recommendations insist on systematic investigation on possible exposure including medications, inhalation of organic antibodies or mineral particles... (2). Surgical lung biopsy is an

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important diagnostic tool and can be used to refine the diagnosis, but its use may be risky – 30-day and 90-day mortality up to 2.4% and 3.9% respectively in some series (3) – and should be indicated after a Multidisciplinary Discussion.

II. CASE REPORT

A 57-year-old man was hospitalized in our service in 2017 to explore a mMRC grade 2 dyspnoea in the context of interstitial pneumonia on his chest X-ray.

His main medical history was emphysema of upper lobes diagnosed 5 years earlier, his follow-up consisted of a medical consultation with CT scan and pulmonary function test every 6 months (his last spirometry found a FEV1/VC ratio of 73% and a DLCO of 71%); he also presented a ventricular tachycardia which required the installation of a cardiac defibrillator. We did not find any significant family medical history.

This patient was living in a healthy house, but, reported multiple exposures. In his past work as a

plumber, he was exposed to asbestos then he worked in a foundry with possible exposition to alloys of copper, bronze, iron, aluminium and zirconium compounds. He also described domestic exposures (hens of which he cleaned the excrement for 5 years) and during his current hobbies (welding, grinding); finally, he had a smoking history of 30 pack-years, stopping 10 years ago. His daily medications were amiodarone, bisoprolol and esomeprazole.

On examination, we found finger clubbing and dry crackles at the lung bases at auscultation; the remainder of the clinical examination was without particularity, we did not find in particular any extra thoracic sign or symptom such as arthralgia, myalgia or a dry eye or dry mouth syndrome.

High-resolution computed tomography (HRCT) showed ground glass opacities surrounding cystic lesions or emphysematous destruction; these anomalies predominated in posterior territories (Fig. 1a, 1b, 1c).

The antinuclear antibodies (ANA) were at 1/200, speckled type and nonspecific; the rest of the autoimmune evaluation was without particularity. The search for bird fancier's precipitin was negative

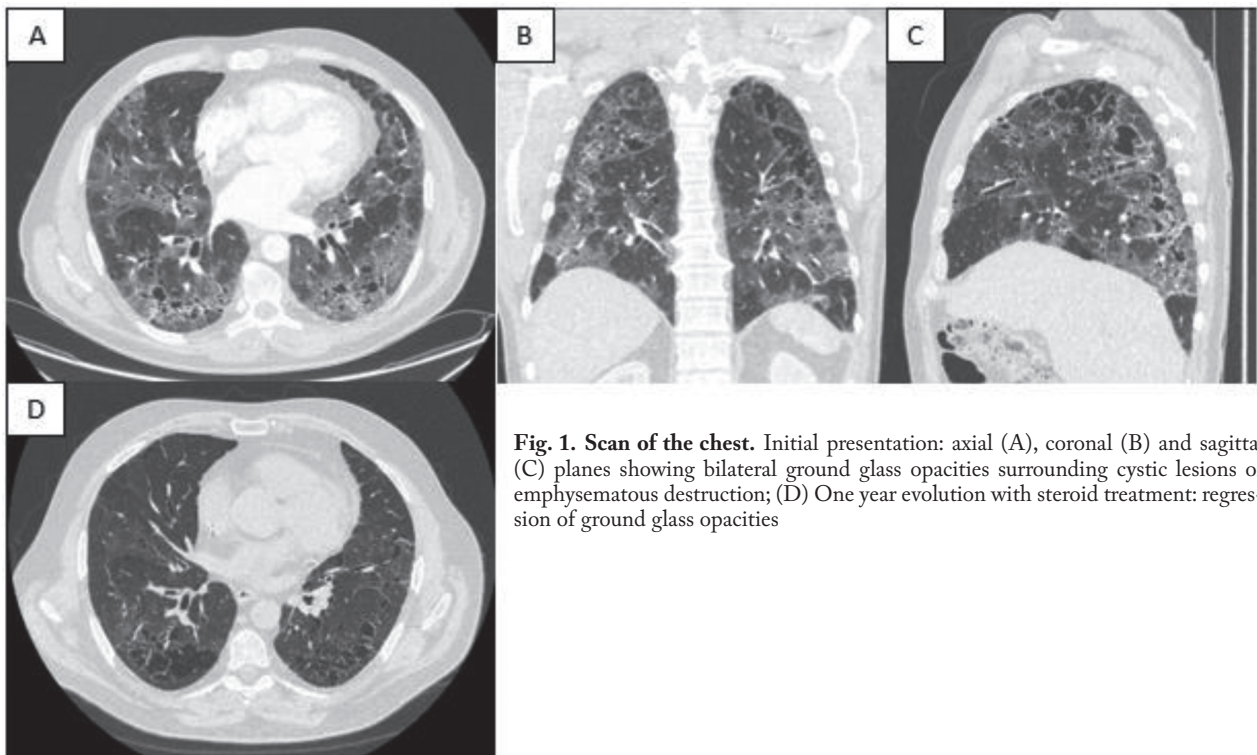


Fig. 1. Scan of the chest. Initial presentation: axial (A), coronal (B) and sagittal (C) planes showing bilateral ground glass opacities surrounding cystic lesions or emphysematous destruction; (D) One year evolution with steroid treatment: regression of ground glass opacities

especially for hens' excrements. Bronchoalveolar lavage (BAL) found a macrophagic alveolitis (presence of 180 elements/mm³ including 80% macrophages, 5% lymphocytes, 10% neutrophils and 4.5% polynuclear cells eosinophils) with multinucleated giant cells. The bacteriological and mycobacteriological cultures were sterile. An accessory salivary gland biopsy showed no arguments for Sjögren's syndrome and the Schirmer's test was negative.

Pulmonary function tests were the following: FVC 2.72L or 73% of the predict values, FEV1/VC ratio of 77%, DLCO at 27% of predict values. During a 6-minute walk test, the patient travelled a distance of 434m with an 83% O₂ desaturation.

After a Multidisciplinary Discussion, it was decided to perform a surgical lung biopsy using video-assisted thoracoscopic surgery.

The left lower lobe biopsy led us to find outbreaks of desquamative interstitial pneumonitis with "plump" macrophages associated with emphysema lesions and with numerous giant-epithelioid granulomas without necrosis, sites of dusting. We did not find foamy macrophage that could evoke an amiodarone impregnation (Fig. 2).

Therefore, our conclusion was a Desquamative Interstitial Pneumonia associated with pulmonary granulomatosis.

We studied the mineral particles on the lung biopsy with the following method: the anatomopathological slides were analysed with an electronic scanning microscope (JEOL JSM-6010LV) coupled to a spectrometer EDX (EDS detector Oxford Aztec-DDI X MAXN 50), each mineral particle has a specific spectre. This analysis revealed abnormally high rates of zirconium compounds (5.2% versus 0.0%), aluminium compounds (4.4% versus 0.05%), aluminium oxide (2.0% versus 0.2%) and steel (14.0% versus 0.6%) in our patient compared to a reference population from the Forensic Institute of Lyon (Fig. 3).

The diagnosis then retained in our patient is a Desquamative Interstitial Pneumonia associated with granulomas secondary to an exposure to metals: Aluminium, Zirconium compound and Steel.

Systemic corticosteroid therapy at a dose of 0.75 mg/kg was introduced for 3 months followed by a progressive decrease over 1 year.

The one-year evaluation showed (i) a clinical improvement: a reduction in dyspnoea to MRC grade 1

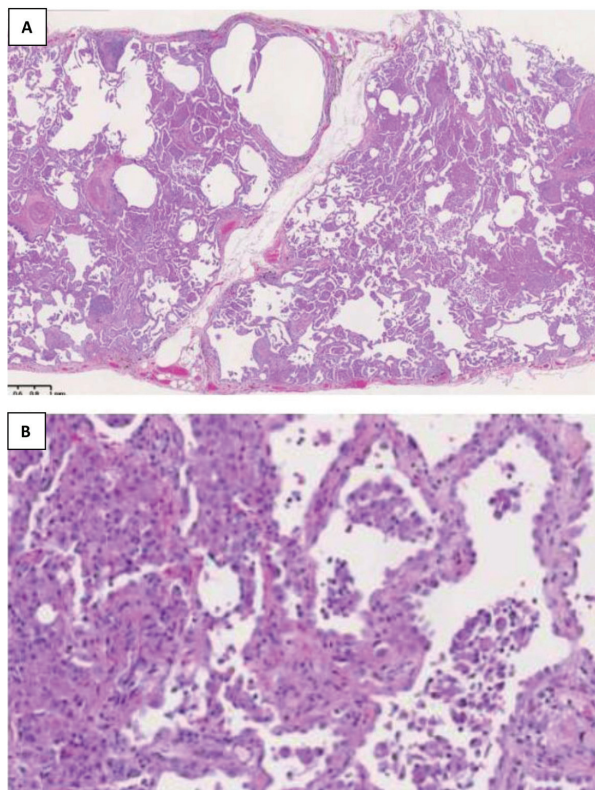


Fig. 2. Histological analysis of the lung biopsy.

(A) Left lower lobe biopsy (HPS coloration, x4): Emphysema and desquamative interstitial pneumonia patterns, "plump" macrophages. Numerous giant-epithelioid granulomas without necrosis, granulomas with micro calcifications and Schaumann bodies. (B) Left lower lobe biopsy (HPS coloration, x20): Pneumocytes hyperplasia, "plump" macrophages within alveolar spaces

and an improvement of 80 meters over the distance covered in the 6-minute walk test; (ii) a functional improvement: the FVC was about 4.15L, i.e. 107% of predict values (gain of 34%) and the DLCO was 44% (gain of 17%); and (iii) a radiological improvement: the HRCT showed a marked improvement with the disappearance of the areas of ground glass opacities, however, there remained emphysematous zones that may correspond to its emphysematous medical history (fig. 1d).

III. DISCUSSION

To our knowledge, this presentation reports the first case of desquamative interstitial pneumonitis related to exposure to Zirconium compound and the third one in a context of Aluminium exposure.

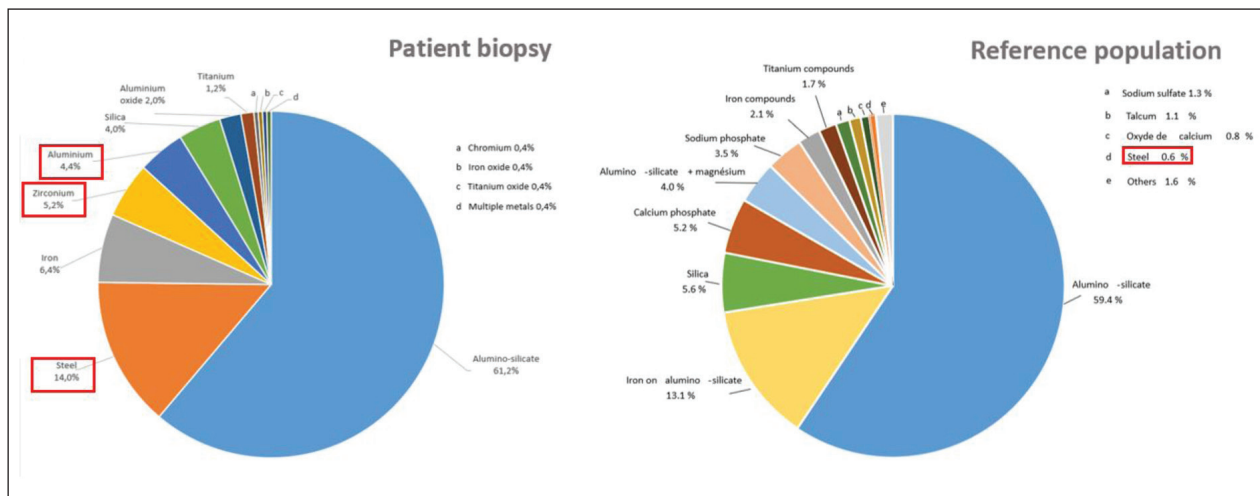


Fig. 3. Mineralogical analysis of lung biopsies. Repartition diagram of mineralogical particles observed with microscope. Comparison with a reference population (SEM-EDX in situ analysis of 53 blocks of pulmonary parenchyma from forensic institute of Lyon, 4050 particles analysed)

Metal lung disease is caused by an exposure to particles of metal alloys mostly composed of tungsten carbide and cobalt (4,5); among the first articles published that described the link between this exposure and pulmonary fibrosis, two were in Tours in 1974 and 1975 in cases of workers exposed to tungsten carbide and cobalt (6,7). A few clinical cases were described with other components such as aluminium, beryllium, copper, iron, nickel (8). The main pulmonary interstitial patterns that we can find in literature are giant cell interstitial pneumonia, usual interstitial pneumonia, hypersensitivity pneumonitis, granulomas, and bronchiolitis; histological patterns of desquamative interstitial pneumonia (DIP) are described in a very few cases.

DIP is one of the major idiopathic interstitial pneumonias, described for the first time in 1965 by Liebow (9). DIP concerns mainly men, aged between 40 and 60 years. Characteristic lesions in HRCT are bilateral ground glass opacities with a predilection for peripheral and lower lung zone; micronodular opacities can also be found with possible association with fibrosis patterns. BAL usually contains increased numbers of macrophages with an inconstant presence of giant cells. Increased numbers of neutrophils, eosinophils and lymphocytes have also been found but these findings are not very specific (10). In this context, a lung biopsy may be necessary to confirm the diagnosis. Some series of surgical biopsy showed

a morbidity up to 7% (11) but the surgical approach used was thoracotomy. The advent of mini surgery and Enhanced Recovery After Surgery (ERAS) programs seem promising given that surgical biopsy shows a better concordance with the final diagnosis of ILD than transbronchial biopsies (12).

The main histologic feature is a diffuse and uniform accumulation of macrophages within alveoli; these macrophages have eosinophilic cytoplasm and mostly contain a granular light-brown pigment when DIP is associated to tobacco exposure; alveolar architecture is generally preserved (1). DIP's main aetiology is exposure to tobacco (58 to 91% of DIP's cases); epidemiological studies suggest other rare aetiologies such as infections, medications, rheumatoid arthritis and exposure to cannabis or anorganic particles.

Our research in medical literature led us to find seven cases of DIP secondary to a metal exposure, these results are collected in Table 1. We found two cases in a context of aluminium exposure, two in a context of tungsten exposure and five with multiple metal exposure. Two of these patients had only DIP patterns on their lung biopsies but the first one was an active smoker (13) and the authors did not mention the precise pathological findings of the other one (14). Thus, histological patterns of DIP seem to always be associated with other interstitial patterns: giant cell interstitial pneumonia, bronchiolitis, non-specific interstitial pneumonia or granulomas.

Table 1. Literature review

Exposition	Case	Histology
Aluminium	<i>Iijima 2017 (19): 1 case</i>	DIP + Non Specific Interstitial Pneumonia + Granulomas
	<i>Herbert 1982 (14): 1 case</i>	DIP (<i>not detailed histology</i>)
Multiple exposures	<i>Mizutani 2016 (4): 1 case (Cobalt and Tungsten)</i>	DIP + Bronchiolitis
	<i>Ju 2017 (13): 1 case (not detailed)</i>	DIP (Active smoker)
	<i>Cai 2006 (20): 1 case (not detailed)</i>	DIP + Giant Cell Interstitial Pneumonia
	<i>Davison 1983 (21): 1 case (Tungsten, Iron, Titanium)</i>	DIP + Giant Cell Interstitial Pneumonia
Tungsten	<i>Dai 2009 (12): 1 case</i>	DIP + Giant Cell Interstitial Pneumonia

In the present case, DIP patterns were associated with granulomas. We encountered DIP lesions incriminated on Aluminium and Zirconium exposure, as previously mentioned, we found two cases of DIP in aluminium-exposed patients but none with a Zirconium exposure. The imputability of Zirconium compounds in this pneumonia is particularly suspected as cases of pulmonary granulomatosis secondary to Zirconium exposure have been described (15). Moreover, 13% of the use of Zirconium consists in protecting the interior wall of furnaces and reactors used in manufacture of foundry crucibles; this corresponds to the professional activity of our patient in the foundry. Concerning Steel particles, they seem to be involved in the granulomatous component of this interstitial pneumonia as Catinon et al. has already described this association twice (16,17).

The other particularity of our case description lies in the favourable evolution after a systemic corticosteroid treatment. Corticosteroid therapy showed its efficiency in most DIPs induced by tobacco (10) but its use seems less obvious in cases of DIPs secondary to metal exposure with bad evolution despite corticosteroids (4,18) except in the description of Iijima et al. (19).

In conclusion, our case is the first one that describes a DIP secondary to a Zirconium exposure associated with Aluminium and Steel exposure. Our report shows that finding the relevant exposure is

a challenging task that requires a complete interrogation including the patient's possible exposures. Moreover, a Multidisciplinary Discussion must be held to consider the need of a lung biopsy with the analysis of the mineral particles observed on the sampling. This analysis could be useful for epidemiological purposes, to support diagnosis or for therapeutic purposes for the eviction of the relevant particle. Patients could also benefit from this analysis for recognition as an occupational disease, and employers could guarantee protective measures to their employees.

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