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Occupational Interstitial Lung Diseases (Part II)

Enfermedades del intersticio pulmonar de causa laboral. (Parte II)

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OCCUP DILD SIMILAR TO CHRONIC ORGANIZING PNEUMONIA (COP)

COP is defined by a histological pattern, and the corresponding clinical, radiological, and pathological diagnosis is cryptogenic organizing pneumonia when there isn't a clear cause.

Due to the fact that there may be outbreaks in the distal bronchioles, the disease was previously called "bronchitis obliterans with organizing pneumonia" (BOOP); that was the typical, predominant pathological pattern. At present, it is internationally recognized as COP.[1]

After assessing the clinical, tomographic, and histopathological features that lead to the COP diagnosis, other disorders have to be considered, such as tumors, infectious processes or inflammatory coditions of the lung. Although the histological pattern of COP is non-specific, it can be related to other diseases, thus it has a relative value when it is found in a sample of such size. The first step for a presumptive diagnosis can be the chest CT (computed tomography). When COP shows unique or multiple areas of parenchymal consolidation, the differential diagnosis includes lepidic carcinoma, pulmonary eosinophilia, Churg-Strauss syndrome, rheumatoid arthritis, polymyositis, radiation therapy or the consequence of the use of drugs or monoclonal antibodies.

In relation to the Covid 19 pandemic, there are COP publications as a result of the subacute evolution of this new viral disease.[2-10]

Zhang et al reviewed 1,346 cases of COP from the Shanghai Pulmonary Hospital in the period between January 2000 and December 2000. The cause was diagnosed in 1,170 patients (86.9%), whereas in 176 cases (13.1%) the origin was unknown. Only in 13 cases, the disease was related to the individual's work, including 2 welders, 3 assembly line workers and 3 textile machine operators. 4 foundry workers and 1 case with prolonged exposure to glass dust.[11]

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GIANT CELL INTERSTITIAL PNEUMONIA (GIP)

GIP is a serious and rare occupational lung disease that occurs as a consequence of exposure and aspiration of hard metals with abrasive properties (tungsten carbide and cobalt). Most of the time, exposure occurs in the industry of cemented tungsten carbide, mining processes, manufacturing of alloys, and polishing and grinding of tools with the grinding wheels of hard metals. People with chronic exposure can develop interstitial lung disease and show worsening of dyspnea, nonproductive and persistent cough and exercise intolerance.

In the initial classification of Liebow and Carrington it appeared as a disease of the interstitium, but then, once its relationship with hard metals had been proven, it was reclassified as pneumoconiosis, also after it was widely recognized that GIP is characterized by a histologic pathognomonic pattern of multinucleated cells.[12, 13]

Cobalt has several industrial uses but not all of them cause OCCUP DILDs (occupational diffuse interstitial lung diseases). It occurs when workers are exposed to cobalt through the manufacture or use of tools created for the process of powder metallurgy. This is a procedure for the manufacture of metal objects. It starts from fine dusts that are then compacted and are finally given a certain shape by heating them at a determined temperature to obtain a tool. When tungsten and cobalt are heated, they combine to form a tight metal matrix.

The worker who is specialized in powder metallurgy is an expert in such techniques. The manufactured pieces show special characteristics, such as lubrication or anti-friction. In the industry of diamond tools, cobalt dust is used as a matrix for diamonds.[14] One patient revealed he had worked as a plumber in the oil industry, from 1982 to 1991. During that period, he frequently assembled pipes using sanders and grinders with hard metal discs, which he grinded every time they went blunt. When he did that, he only wore a visor. When the symptoms began, an X-ray was performed, showing a lung infiltrate.[15]

On other occasions, as in the description of Carmo-Moreira, the symptoms began with a spontaneous pneumothorax in a worker whose job was to sharpen saws and knives, and he had done that job for 8 years without protection.[16]

The consulted literature includes some observations; some of them draw our attention due to the number of cases being described. Between 1985 and 2016, Chiarchiaro et al identified 23 patients with a pathological pattern, 93% of which showed "ground glass", and 85% of those showed GIP in the biopsy that was performed. Thanks to corticosteroid treatment, these cases had a better evolution.[17]

Naqvi et al reviewed 100 cases of these pneumoconiosis that had been studied for 50 years. GIP was histologically proven in 59 cases, and in the remaining 41 it was confirmed through scanning electronic microscopy and x ray spectroscopy. The cases of GIP in the industry of cemented tungsten carbide revealed high concentrations of tungsten, though cobalt was only detected in 6% of the cases.[18]

To conclude, as a non-work-related etiology, there are publications that relate GIP with the prolonged use of nitrofurantoin.[19, 20]

HYPERSENSITIVITY PNEUMONITIS (HP), AN OCCUP DILD:

HP is produced immunologically by the repeated inhalation of a great variety of chemical substances or environmental organic antigens to which a genetically susceptible individual has been previously sensitized.

Alternative definitions for HP have been proposed, but experts disagree on how to describe the disease in detail and use their diagnostic orientation and criteria.

Maybe one of the most complete definitions is the one of Cormier, who defines HP as "*An inadequate immune response to inhaled antigens that causes difficulty to breathe, a restrictive pulmonary defect, and interstitial infiltrates observed in lung images (chest X-ray and high resolution tomography) caused by the accumulation of a high number of T lymphocytes activated in the lungs. On some occasions, the disease is also characterized by fever episodes a few hours after the exposure*".[21, 22]

According to Hirscmann et al, from the tomographic viewpoint, HP can be classified as ACUTE, when it shows "ground glass", centrinodular pattern and air trapping, and CHRONIC, when there is reticulation, "honeycombing", peribronchovascular thickening and lung architectural dislocation.[23]

Therefore, the possibilities of suffering HP, whether it is occupational or non-work related, are unlimited, and there may exist as many observations and/or publications as potential offensive antigens. One proof of that is found in the Consensus published in 2020 by the American Thoracic Society, the Japanese Respiratory Society and the Latin American Thoracic Association.

Table 1 shown in the article includes sources of known antigens that cause HP, for example: organic particles, yeast, environmental fungi, protozoa, bacteria, enzymes, animal and plant proteins, inorganic substances, pharmacological agents, and metals.[24]

Yoshida et al conducted a national investigation to look into the epidemiological and clinical characteristics of HP in Japan. 185 doctors completed a questionnaire, and 835 cases were classified as HP, with occupational HP in 115 of those cases (13.8%), and predominance of "farmer's lung disease" (59%). 19 of the workers manipulated isocyanates and 10 office clerks had suffered microbiological contamination through the air conditioner. The investigation concludes with the recommendation of a thorough environmental assessment and a panel of antigens adapted to exposure variations, as diagnostic orientation.[25]

Moon Bang et al reported that there are few studies in the United States population that investigate HP. National data of the NIOSH (National Institute of Occupational Safety and Health) can contribute to understand the epidemiology of this disease. They analyzed the identification of causes of death for the 1980-2002 period. Mortality rates according to the type of industry and occupation were adjusted per age, sex and race in 26 states that provided industry and occupation information between 1985 and 1999. This mortality rate for HP was significantly high for the agricultural and livestock production, also for farmers. They conclude their investigation by saying that agricultural industries are closely associated with HP mortality, thus it is extremely important to evaluate preventive strategies to protect the workers of these industries.[26]

The literature review allows us to appreciate that there is an overlapping of publications about occupational asthma (OA) and the OCCUP DILD HP. When evaluating both, it is estimated that in sensitized individuals, progression from one disease to the other would depend both on the concentration of the offensive agent and the prolonged period of exposure with inadequate protection or without any protection at all.

Like the expert Salvaggio said in an editorial 50 years ago, HPs (occupational or non-occupational) are a kind of "Pandora's box", and research could provide the suitable answers for each particular case.[27]

The HPs more frequently cited in the literature are: "farmer's lung disease", "baker's lung

TABLE 1

Occupational disease	Antigen of causative organism
Cheese washer's lung	Penicillium casei / roqueforti
Bagazosis	Thermoactinomyces sacchari
Farmer's lung	Thermoactinomyces/Thermo polispora
Air conditioner lung	Saccaromyces rectivirgula / Termoactinomyces vulgaris/ Aspergillus
Bird fancier's lung	Feathers/ feces of birds
Isocyanate manipulation lung	Trimellitic anhydride
Metalworking fluid lung	Various microorganisms, mainly Mycobacterium immunogenum
Malt worker's lung	Aspergillus clavatus

disease", the ones caused by MWF (metalworking fluids) and isocyanates and those caused by waterproofing substances.

"Farmer's lung disease"

An eventually serious disease that results from the manipulation of moldy and dusty organic materials. Exposure to such materials induces the disease in certain people, whereas other people are not affected. The lung biopsy reveals granulomatous interstitial pneumonitis. Individual hypersensitivity to fungi or fungal products seems to be a crucial factor in getting this disease. The treatment is to avoid exposure of sensitized workers. The thermophilic actinomycetes, Saccaromyces rectivirgula, Termopolyspora polyspora or Micropolyspora faenii are considered particularly important antigens responsible for most reported cases of HP. Campbell was the first to consider causality, even though he didn't call it that way, and Fawcitt thought it was related to aged, moldy cereal. [28, 29]

An epidemiological survey conducted among farmers in China showed 6% of producers diagnosed with HP: 19% of them had occupational asthma, and 17% had COPD (chronic obstructive pulmonary disease). Influencing factors were high humidity and the high capacity and short height of warehouses.[30] Factors contributing to agricultural HP in France were high humidity and tight hay packing, correlated with a higher concentration of HP-promoting microorganisms. As a prevention measure, respiratory protection shall be used when packing down the hay and manipulating potentially moldy hay and during forage drying.[31]

Over the decades, numerous studies have been reported on this condition and its relationship with rural tasks, with Peppys' work being essential for its research and serological confirmation after studying 327 agricultural workers with different antigens, where 89% showed positive reactions; and 87% of 205 farmers were due to hay contaminated with Termopolyspora polyspora.

The higher the serological titers, the more reactions there were to other antigens, and the more severe and frequent the episodes, with a male predominance. Only 18% of 122 non-exposed farmers who didn't have the disease showed reactivity. Peppy concludes by emphasizing that the "farmer's lung" disease was insidious in 49%, sub-clinical in 9% and with typical symptoms in 32%.[32-34]

This occupational disease is not usually seen in our environment because the cattle are fed on pastures rather than stored hay or cereal that favor fungal contamination.

Cuthbert and Gordon conducted a 10-year follow-up study of 29 cases of this disease. The results revealed that respiratory protection and the replacement of hay with pasture stored in silos favored prevention. To be safe, respirators should be used in situations where there is agricultural dust, especially in enclosed environments.[35]

In recent decades, the frequency with which chronic bronchitis, non-smoking-related emphysema, and tomographic signs of HP appear in this disease has been reported. Depierre et al investigated 1,763 rural workers in France with serology and questionnaires, obtaining a response in 69%, out of which 270 were suspected of having the disease. They found a relationship between chronic bronchitis and this condition, and suggested that fungal dust was responsible (50.6% in those affected versus 8.6% in controls with a $p < 001$). They concluded that chronic bronchitis in farmer's lung was independent of smoking and age. There were 9.2% radiological abnormalities of the lung interstitium and were less common in plains or mountains, probably due to cold environmental conditions.[36] As a rare case, Soumgane et al describe a woman with "farmer's lung" who showed PEEP (positive end-expiratory pressure). She had excellent evolution with corticosteroids and 1-year follow-up.[37]

Lung interstitium disease due to metalworking fluids (MWF)

The MWFs are essentially oil-in-water emulsions with additives (corrosion inhibitors, emulsifiers, anti-foaming agents, and biocides). Their microbial contamination is almost systematic, as their components serve as nutrients for contaminating microorganisms. Biocides for MWFs are protective products used to counteract microbial contamination and growth. (The appropriate criteria for a biocide for MWFs are: 1. Broad-spectrum activity. 2. Suitable for low concentrations. 3.

Compatible with the formula and physicochemical properties of the MWF and stable over time. 4. Effective in the presence of dirt. 5. Non-corrosive to metals. 6. Safe for people and the environment. 7. Economical.

The future lies in developing new molecules with biocidal activity that correspond to: A.-Optimizing the performance of current molecules. B.-Establishing different strategies to enhance biocidal activity. With over 1.2 million workers in the US involved in the manufacturing of machinery, machine tools, and automobiles, exposure to MWFs is common.[8, 39]

Epidemiological surveillance methods are useful for revealing causality by demonstrating that the MWFs are the most common factors in occupational asthma, along with isocyanates. In Bakerly's publication, they accounted for 11%, and the latter for 21%, while in the publication of Rosenman et al, MWFs accounted for 11% and isocyanates, 14%.[40, 41]

There are periodical publications of cases or series of cases of occupational asthma caused by MWFs, whereas those of HP caused by the same products are less frequent.[42-45]

In 1995, Bernstein et al published the first 6 cases of HP caused by MWF, and episodes of this occupational disease appear relatively frequently. [46-49]

Systematic studies show that both HP and occupational asthma are caused by fluids, but also by microorganisms or fungi that grow in them, mainly Mycobacterium immunogenum, which is responsible for contamination and causing hypersensitivity in experimental animals.[50-52]

"Baker's lung" disease

Baker's asthma is one of the most common causes of occupational asthma, and its incidence is estimated to be between 1-10/1,000 bakery workers. A bakery establishment is a complex habitat with an unlimited number of potential sensitizers. Employees in this industry, including millers, bakers, and food processors who are exposed to bakery allergens, may develop this disease. The main allergens are the flour (wheat, rye, and barley), the enzymes added to the dough (such as α-amylase), and the parasites and fungi that can contaminate the flour. This type of occupational asthma is IgE-mediated (mediated by immunoglobulin E); and titration of IgE is essential for the diagnosis of the condition.[53, 54]

A study published by Simonis et al studied in 433 bakers the IgE and IgE levels specific to baking enzymes investigated in the Asthma Prevention Program at the German Social Accident Insurance Institution for the Woodworking and Metalworking Industries, calculating personnel exposure to environmental dust, including the concentration of the α-amylase level in the work area.

They reached the following results and conclusions:

a. Significant decrease (from 26% to 13%) in sensitization to α-amylase.
b. Sensitization to glucoamylase was much higher than to cellulase.
c. Sensitization to all three enzymes is common in bakers.
d. 30% of bakers are sensitized to at least one of the enzymes.
e. Exposure to α-amylase has decreased.
f. 11% fewer bakers are exposed to α-amylase, compared to 10 years ago.
g. The high sensitization to glucoamylase in affected bakers leads to investigating exposure levels in bakeries and evaluating sensitizations in the context of occupational diseases.[55]

The research of Diederichs and Lubers from 60 years ago revealed a sensitivity incidence of around 54 percent among bakers. The expected presentation of signs and symptoms was estimated at 12.7 years for occupational rhinitis and 15.3 years for occupational asthma.[56] In 1980, Thiel and Ulmer published a comprehensive study reporting that in Germany it was a recognized occupational disease. In ancient Rome, it was known that slaves who made bread had great suffering, and the first scientific reference was due to Ramazzini around 1700. However, HP caused by flour, parasites, fungi, or enzymes is exceptional. The publication by Gerfaud et al on HP in a baker showed that there was good evolution with corticosteroids and mycophenolate, but the serology was positive for corn, oats, Aspergillus fumigatus, and mites such as Glyciphagus destructor or Sitophilus granarius, thus showing the complexity of the diagnostic

studies required when testing, in this case, 26 antigens.[57, 58]

A case of HP caused by flour parasites has been published, but the most interesting one is that of van Heemst et al about HP induced by phytase in a worker who performed his tasks for 20 years without protection, producing food for chickens. Phytase catalyzes the hydrolysis of phytate, which is a way of storing the phosphate existing in soy and cereals. Poultry and pigs use this phosphorus partially, so in order to increase its availability, the enzyme is added to the food.[59, 60]

To conclude, Brant et al conducted a survey and performed serological tests in 239 bakers from different British supermarkets. Results showed that 15% had respiratory signs and symptoms, 11% had positive serology for flour, and 4% for α-amylase. Despite their low levels of dust exposure, this population of bakers shows significant levels of sensitization and respiratory symptoms related to their work. Changes in the workplace and modifications in the bread-making process have caused a shift in the distribution of occupational asthma and HP among bakers in the United Kingdom.[61]

"Bird fancier's lung" disease

The bird breeder is exposed to an immunological lung disease due to repeated exposure to avian antigens transmitted through the air. It is a type of HP triggered by the excretion of highly antigenic avian proteins and/or waxy proteins that cover the feathers of a variety of birds, causing a hypersensitivity reaction in a susceptible host.[62]

The disease may be more a consequence of a recreational activity than a work-related one. This condition, which in the vast majority of cases is expressed as occupational asthma, is associated with a variety of abnormal findings: skin tests, radiographic abnormalities, serology, and disturbances of the lung function. Unfortunately, none of these are diagnostic, the disease is best identified through clinical criteria.[63]

To that end, Morel et al studied 86 patients with HP between 1977 and 2003, where one-fifth of the patients had the chronic form of the disease. All of them were studied with serology, chest radiography and CT, skin tests, FBC (fibrobronchoscopy) with BAL (bronchoalveolar lavage) and/or TBB (transbronchial biopsy). 82% had cough, and 98% had dyspnea, with 25% in functional class III or IV and 18% with chest tightness. Lymphocytosis was found in 83% of BALs, and the CT showed 79% of interstitial pattern and 68% of ground glass opacity. Serology was positive in 92% of the series. [64]

Serology is of great value in collaborating with the diagnostic suspicion. The ELISA method (enzyme-linked immunosorbent assay) used proved to be useful for evaluating specific IgG responses. In a meta-analysis carried out by Shiroshita et al, ELISA showed high sensitivity, and the Ouchterlony method exhibited high specificity.[65, 66]

The study of McSharry in 50 affected individuals to validate an automated fluorometric antibody detection procedure provides a method for international standardization of HP, thus improving quality control and refining its suitability as a diagnostic complement.[67]

There are relatively few publications about HP caused by bird antigens, most related to pigeon activity, but it is worth noting the case of Chopra, with exposure to birds for 35 years, or that of Cooper, in which the person's job was cleaning in a restaurant and collecting duck and goose feathers which he then placed in a vase in his home for the last 6 months. Outside the individual's home, there were no birds. Sometimes, it is presented with unexplained dyspnea or as an expression of a COP.[62, 68, 69]

Induction by isocyanates

In many nations, isocyanates (ICN) are a very common cause of occupational asthma. Although this reference is very important and HP has been occasionally reported, it may be a more common result than originally believed as a consequence to ICN exposure.

ICNs are used in the manufacturing of a wide variety of products, especially in the production of flexible urethane foam, lacquers, varnishes, paints, and rubber modifiers. Their toxicity has been known for decades: cited by Blake et al, the first description was in 1951 by Fuchs; and Schurman and Rein reported two cases of patients who died from severe asthma in 1955.[70]

Little is known about the inevitable occupational levels related to the induction of HP by ICN.

By performing adequate environmental monitoring and strict medical-occupational control, exposure to ICN is associated with low sensitization and minimal exposure to the causative agent. [71] Unprotected exposure can cause dermatitis, conjunctivitis, rhinitis, "industrial" bronchitis, occupational asthma (which is the most common finding in the literature) or, every now and then, HP. [72] Baur reported 14 cases of HP caused by ICNs when investigating 1,780 workers who used this material, , representing 1% of the workforce, while Vandenplas found 4.7% in his research. The difference would result from different working conditions.[73, 74]

Particular susceptibility plays an important role, as in the case of HP caused by ICNs in a company secretary who went several times a day to the premises where this causative agent was being used to dye boots.[75] Treatment with steroids can give excellent results, and in Japanese literature, there is a publication of an individual who got HP caused by ICNs while painting a car as a recreational activity.[76, 77]

Permitted environmental limits of ICN in the US have been decreasing from 0.1 ppm in 1956 to 0.005 ppm/8 hours of work or 0.02 ppm for 4 periods of 15 minutes/day in 1980.[78] Minimizing or preventing exposure is essential in occupational medicine, health and safety. It is essential to conduct educational talks; and medical supervision must be carried out by performing periodic spirometries to test the workers so as to detect functional changes. In areas with higher concentrations of ICNs, Nakashima et al recommend performing specific IgE serological controls, too, to enable early detection and take appropriate action.[79]

HP by waterproofing agents

Waterproofing agents are used to coat leather, fabric, or solid surfaces in order to ensure resistance to dirt and water. They typically consist of 3 components: an active compound (water repellent), a solvent, and a propellant (propane, butane), if they come in a can. The water repellent is a mixture of siloxanes or acrylate polymers that contain fluorocarbon or hydrofluorocarbon. Nowadays, aqueous mixtures of glycols and glycol ethers are often used as solvents.[80]

Over the past 20 years, different health effects from the use of waterproofing agents have been described in approximately 20 reports involving the exposure of more than 200 people.

Isolated cases related to waterproofing agents often appear, and in the majority of cases, volatile organic compounds (VOCs) play an important role.[81-83]

Scheepers et al published the impact on 10 workers exposed to a waterproofing agent with a low percentage of VOCs and nanoparticles. To sum up, a worker who had smoked right before entering the workplace was hospitalized with injuries in both lungs, and the other nine experienced respiratory symptoms within 24 hours of entering the work environment.

After the relevant studies had been conducted, the authors concluded that the hospitalized worker's cigarettes were contaminated with the liquid. The symptoms of the other workers were due to suspended material still present in the environment. The volatile compounds could have been at play if the building was completely enclosed.[84]

A very interesting observation is that of Tan et al, who published 11 cases, with 5 cases of respiratory distress and 1 death. The research revealed that a neighboring factory, 35 meters away from the affected workshop, had released fluorocarbon waste without spraying water on the waste, causing the inevitable accident.[85]

In Switzerland, between October 2002 and March 2003, there was an acute outbreak following exposure to waterproofing agents. 180 cases were reported (previously, less than 10 cases per year had been registered). The reported cases involved 3 brands of aerosols that had changed their formula prior to the incident. A retrospective analysis was carried out to clarify the circumstances and causes of the observed effects. The results obtained showed high variability of individual responses, suggesting that some indirect mechanism predominates in the incidence of the disease. The findings suggest that improvements in environmental exposure conditions are not sufficient to prevent future toxic outbreaks due to waterproofing spray. More effective preventive measures are suggested to be taken before marketing and distributing new waterproofing products.[86]

Repeated unprotected exposure to the causative agent for 4 years can lead to the evolution of chronic HP, as described in a publication from 2017, considered as the first known case at that time. [87]

OCCUP DILD induced by green tea

During the production of green tea, a fine powder called "tea fluff" is released into the factory's atmosphere. Inhalation of this powder can cause respiratory distress relatively quickly. Chronic cough in tea factories and tea taster's disease are two occupational diseases associated with the industry of this product.[88] The first case to be published was about occupational asthma caused by tea dust, and was confirmed by intradermal skin testing and specific bronchial challenge, although this author cites observations by Castellani in Ceylon dating back to 1919.

Cartier and Malo reported on 3 similar cases studied by them, and the Japanese literature highlights publications of HP caused by green tea, with the publication of Tanaka et al being notable for the high environmental concentration of the causative agent in the factory premises.[89-93]

Green tea has 8% epigallocatechin compared to black tea, which has 1%, and is the main cause of occupational asthma and HP. Shirai et al observed a significant correlation between the maximum percentage of histamine release and epigallocatechin concentration in specific intradermal reactions, as well as positive results when doing the bronchial challenge test with green tea dust.[94, 95]

Miscellaneous

As previously explained, the inhalation of organic particles (animal proteins, fungi, or bacteria) or workplace materials can induce the appearance of HP in sensitized individuals. The literature is constantly updated with cases related to unexpected antigens and individual susceptibility, so it is impossible to dominate it in full.

Interesting observations can be gleaned from it, such as those of cork workers (Suberosis), "cheese washers" where the responsible antigen is Penicillium cassei or Roquefortii, HPs caused by air conditioning contamination, and those in mushroom processing, or an exceptional case, such as that of Marchisio et al, caused by the contamination of deli meat with Penicillium camembertii in a sausage factory. [96-108]

To conclude, we attach a concise table containing some occupational lung diseases that can lead to HP and their common causes. (TABLE)

EMERGING OCCUP DILD (NEW WORK-RELATED DISEASE?)

Cummings et al published a comprehensive study conducted in production areas of an industrial machinery factory, where five previously healthy non-smoking men who worked between 1995 and 2012 developed respiratory symptoms.

They all presented with a gradual onset of cough, sibilance, and dyspnea on exertion with an average decrease of 44% in predicted FEV1 (forced expiratory volume in the first second) and 53% in DLCO (diffusing capacity of the lungs for carbon monoxide). Chest CT showed centrilobular emphysema.

All five had chronic dyspnea, with progressive functional deterioration in three; and one underwent lung transplantation. Pulmonary histology showed bronchiolitis and alveolar ductitis with B cells, follicles lacking germ centers, and significant emphysema. This pattern was named BADE (**B**ronchiolitis **A**lveolar **D**uctitis **E**mphysema). Patients did not report any previous abnormal occupational exposure.

No cases were identified among workers from other areas or in the community. Endotoxin concentrations increased in two samples. Exposure was below occupational limits. Air was flowing from the machining process of other production areas. The MWF used developed Pseudomonas pseudoalcaligenes and lacked mycobacterial DNA, but the 16S analysis revealed more bacterial groups. There was a relationship with the workplace, since all five patients were specifically involved in production areas. Furthermore, there was an association with the job, as these previously healthy men experienced an insidious onset of respiratory symptoms during work. Four were symptomatic outside of the workplace, and explained they had exacerbation of symptoms while they were at work. One patient showed a functional

improvement during several months when he/she was outside the area, followed by functional loss upon returning to their initial tasks.

The researchers' conclusion would indicate a previously unrecognized occupational interstitial lung disease.[109]

To conclude, it is worth highlighting the work of Petnak and Moua, who conducted a careful analysis of the contributing factors of HP, commenting on how difficult it is to establish a cause-effect relationship in a problem case. To do so, they formulated a questionnaire aimed at detecting presumed exposure in individuals presenting with HP-compatible disease based on four items, namely:

1. Exposure to birds, or items containing feathers or down.
2. Expression of symptoms at home or in the workplace.
3. Use of a hot tub, jacuzzi, or sauna.
4. Medical history related to hobbies or past/current activities.

The questioning proposed by the authors would provide support when serology or other clinical and radiological elements are not irrefutable or if they are unresolved.[110]

CONCLUSIONS

1. There is an eventuality of suffering from a work-related or occupational disease in practically all tasks performed by the working population.
2. Changes in manufacturing practices and the addition of novel materials have made occupational medicine specialists continue to discover a relationship between new types of exposure and acute or chronic forms of diffuse parenchymal lung disease.
3. The etiological scope, both for medical and occupational causes of pulmonary interstitial disease is broad and permanently enriched with new bibliographic contributions.
4. The complex mechanism of lung parenchymal repair, manifests itself in the interstitium with varied responses, both to medical and non-occupational causes, and may even be different from the same etiology.
5. In order to understand the link between exposure and disease, occupational medicine specialists and professionals dedicated to safety and hygiene must observe a high index of suspicion about the potential toxicity of occupational and environmental manifestations.

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