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RESEARCH ARTICLE

Occupational Hypersensitivity Pneumonitis: Occupational, Clinical and Radiological Profiles. About 14 Patients from North Tunisia

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Abstract

Objectives: occupational hypersensitivity pneumonitis (OHP) is a group of occupational lung diseases with alarming and internationally ever-increasing incidence, prevalance, socio-economic cost and mortality rates. Its diagnosis remains difficult. The aim of the study was to describe epidemiological, clinical and occupational characteristics of OHP among Tunisian patients.

Material and Methods: a cross sectional study was carried out from July 2015 to the 31st of December 2021. It included confirmed OHP patients registered in occupational medicine clinics in a university hospital in the north Tunisia specialized in thoracic diseases. Results: fourteen patients were included. Sex ratio 1. Average age of 47 ±13 years. Four out of fourteen patients were smokers. Clinical syndrome consisted of cough, dyspnea, flu-like symptoms and weight loss. The respiratory functional exploration uncovered a restrictive ventilatory defect and a decrease of the CO diffusion. The bronchoalveolar lavage showed signs of active inflammation with a lymphocyte predominated cellularity. Radiological signs were ground glass preferentially in the inferior regions, expiratory air trapping and fibrosis including pleural thickening, traction bronchiectasis, diffuse fissure distortion, head cheese sign pattern and mediastinal adenopathy. Patients worked in the prosthodontics sector (06/14), chemical industries (02/14) and other industries automotive, construction and public works, agricuture, textiles, carpentry, and metal fabrication. Organic antigens were resins in 9/14 and metals in 2/14.

Conclusions: OHP are a group of underdiagnosed diseases that must be immediately evoked subsequently to clinico-radiological and histologic picture, after which the worker is referred to an occupational medicine service in order to reduce the socio-economic burden of these diseases.

Introduction

Hypersensitivity pneumonitis (HSP) is an immune system disorder that can result from either brief or prolonged repetitive exposure to an allergen among genetically predisposed individuals. One of the main causes of this disease is workplace exposure, which was in fact the first context in which HSP was described in the literature by Bernardino Ramazzini in the eighteenth century in his book «Diseases of Workers » [1,2]. Occupational hypersensitivity pneumonitis (OHP) is the manifestation of an inflammatory response in the lung parenchyma and bronchi caused by an allergic reaction following exposure to organic dust, animal, vegetal or chemical antigens [3].

The incidence and prevalence of OHP vary vastly from one country to another. From 0.3 to 0.9/100 000 workers in developed countries to 47% of all reported cases of pulmonary fibrosis in India [1,4]. This variation could be the consequence of differences in genotypes between populations, climates between countries, the use of protective measures or the lack thereof, the diagnostic criteria adopted by different countries, the predominant antigens and time of exposure, the major industries in each country…

The diagnostic technique for OHP usually adopted nowadays is high-resolution computed tomography (HRCT). The information provided by this technique along with the patient's work history and clinical data are sufficient to retain the diagnosis [5]. The aim of the study was to describe epidemiological, clinical and occupational characteristics of OHP among Tunisian patients.

Material and Methods

Study organization

We have conducted a descriptive cross-sectional study, carried out by physicians competent in occupational medicine clinics in a university hospital in the north Tunisia specialized in thoracic diseases. It has been conducted over a period of 6 years starting from July 2015 to the 31st of December 2021.

Participants

The study population was composed of confirmed OHP patients. Data was collected from medical records labeled « HP » archived within the occupational medicine clinics. It specified socio-medical, occupational and radiological data. Each curriculum laboris encompasses the patient's past and current occupations, performed tasks, involved chemicals and protective measures etc.

According to the Tunisian law, there is a number of conditions to be met before bringing up an OHP diagnosis. These criteria are specified in a joint order between the ministries of public health and social affairs dating back to 10 January 1995 and that is regularly updated with the last version issued on 20 November 2020. The mentioned order states in tables 53-54-55-56-57 and 58 that to consider an OHP diagnosis, the criteria to be fulfilled are 1) the existence of the notion of exposure to the suspected antigen, 2) the existence of clinical signs that are suggestive of an interstitial lung affection, 3) respecting the legal support limit, 4) the worker in question practices in one of the fields specified in the respective tables, 5) sometimes, the existence of anatomopathological and radiological evidence that is conducive to HSP.

Statistics

For the qualitative variables we calculated both simple and relative frequencies. As to quantitative variables, the average, standard deviation and range (extreme values: minimum and maximum) were calculated when the distribution of the variable was normal. The median and the 25th and 75th percentiles were calculated for not normal distribution of the variables. The comparison of qualitative values was performed using Pearson's chi-square test; whenever the conditions of the test weren't met, we have proceeded to a Fisher exact test. The statistical significance threshold was fixed at 0.05.

Results

The study population was composed of 14 patients : 07 men and 07 women, meaning a 1 sex ratio. The average age was 47 ± 13 years with extremes ranging from 27 to 65 years. Among the 14 OHP patients, 10/14 were non-smokers. The smoking median was measured at 59 PY with a 25th percentile of 35 PY and a 75th percentile of 57 PY. Also among the 14 patients, 06/14 had a primary educational level and 08/14 had a tertiary educational level.

Patients were split according to their occupational fields into three groups 06/14 in the prosthodontics sector, 02/14 chemical industry and other industries automotive, construction and public works, agricuture, textiles, carpentry, and metal fabrication. Organic antigens were resins in 9/14, acrylates and isocyanates, and metals in 2/14. Wood was incriminated in one case and hay in one case. Detection of specific precipitins for all these organic antigens was not possible (no appropriate reagent available).

The median age of exposure to the incriminated chemicals in the workplace was 25 years with a 25th percentile of 13 years and a 75th percentile of 28 years. The average delay between the first occupational exposure and the first medical visit for respiratory or general symptoms was 19 ± 15.5 years[1-50]. The median delay between the ending of the occupational exposure to the harmful substance and the diagnosis was 12 months with a 25th percentile of 11 months and a 75th percentile of 27 months. The median age of diagnosis was 49 years [30-55].

Symptoms encountered in this series for which the patients consulted a doctor, are distributed as follows : dyspnea 13/14, weight loss 12/14, flu-like syndrome 07/14, dry cough 09/14, productive cough 03/14, hemoptysis 02/14, fever 02/14 and deterioration of general condition 03/14. Pulmonary auscultation revealed the following particularities : crackles 05/14, wheeze 01/14 and no particularities 8/14. During the first doctor's visit, at rest, 10/14 patients were eupneic and 04/14 patients were polypneic. Six out of fourteen patients had peripheral cyanosis, a symptom that was absent in 08/14 patients. The average arterial oxygen saturation measured via blood gas was around 94 ± 3.5% [89- 98]. Cardiac auscultation was normal in all cases. Tachycardia was observed at rest in 04/14 patients during the first consultation. Clinical severity was medium to high in 07/14 patients.

The average lung capacity was 3.5 ± 0.9 L with a maximum of 6 L and a minimum of 2 L. The median VEMS/CVF was 86 ± 11% with a 25th percentile of 78% and a 75th percentile of 90%. The CO diffusing capacity showed that all patients had a decrease in their baseline levels, and was pathologic in all cases. Twelve out of fourteen patients had a restrictive lung disorder, 2/14 had a mixed one.

The cytology of the bronchial fibroscopy showed inflammatory changes in all cases with signs of active inflammation in 100% of them. The bronchoalveolar lavage (BAL) showed lymphocyte predominance in 11/14 patients (lymphocytes≥35%) and a neutrophil predominance in 3/14 of them. Asbestos fibres were not detected in any of the patients, and so for birefringent materials. The anti-dsDNA antibody test, anti-Sm and anti-Scl was negative. The rheumatoid factor test was also negative. Tuberculosis tests in the sputum and bronchi were negative in all cases as well.

Analysis of the statistical results gathered from the HRCT of the 14 OHP patients established the presence of radiological lesions in all of them (Table I).

Table 1: Radiologic lesions described in patients with OHP

Radiologic description	OHP n=14
Reticular opacities	1
Miliary opacities	13
Nodular opacities	11
Ground glass	13
Condensation of the parenchyma	0
Traction bronchiectasis	8
Fissural distortion	7
Honeycomb	7
Fibrosis	8
Cysts	3
Excavations	0
Emphysema	1
Expiratory air trapping	13
Pleural thickening	3
Pleural plaques	0
pleura effusion	0
Pleural effusion	0
Head cheese sign	12
Lymphatic lesion distribution	14
Bilaterality of the affections	14
Symmetry of the lesions	10
Sup paratracheal adenopathy	3
Inf paratracheal adenopathy	3
Latero-tracheal adenopathy	12
Retrotracheal adenopathy	11
Subcarinal adenopathy	3
Hilar adenopathy	9
Aggravation of existing lesions	12
Amelioration of existing lesions	3
Emergence of new lesions	6

Ground glass (13/14) dominated the inferior region always occupying more than 60% of the lung surface with a symmetrical and bilateral distribution in both the craniocaudal and anteroposterior plans. Expiratory air trapping included images of the air trapped during exhalation were present in 13/14 patients in association with the unaffected segments of the parenchyma gave a mosaic attenuation pattern. Signs of fibrosis with all its manifestations were observed in 8/14 patients. It preferentially touched the inferior lobes with an anarchic distribution, traction bronchiectasis (8/14), scissure distortion (7/14), honeycomb (7/14) and head cheese (12/14).

Micronodules were present in 13/14 patients with a diffuse distribution in 12 patients and predominantly in the inferior regions in one patient. These lesions were always distributed bilaterally in a centrilobular and symmetrical manner. Nodules were present and diffusely distributed in 11/14 patients. These lesions were always bilaterally distributed in a centrilobular and symmetrical manner. An affection of the mediastinal lymph nodes was present in eleven patients with a proclivity for latero--tracheal, subcarinal and hilar chains. The results also showed the absence of certain radiological lesions such as: cysts, emphysema, pleural plaques and condensation of the parenchyma.

Discussion

The results of this work are consistent with those of an indian series of 103 patients suffering from OHP that revealed an average age of 47 ±1.2 years [1]. The sex ratio is explained by the occupational diversity among the patients : the proesthetics, sanitation and hygiene, agriculture, and textiles sectors are generally known to be dominated by the female sex, whereas the automotive, construction and public works, carpentry, and metal fabrication sectors are dominated by the male sex, which generates a 1:1 sex ratio.

Smoking among workers suffering from OHP was close to the 30% national rate which adds up to 4.2 patients, a number that agrees with the real composition of our series being 4 smokers out of 14 [6]. As to the educational level, the primary level predominance is also explained by the nature of the job sectors : workers performing tasks that only require on-the-job training and no higher education.

Clinical description was in accordance with chronic form of HSP. Thaon et al. in a general review entitled «hypersensitivity respiratory diseases in the workplace», concluded that for OHP there were two clinical pictures : an acute one characterized by a flu-like syndrome and a chronic form involving cough, dyspnea, expectoration, chest pain and deterioration of general condition. Respiratory functional explorations were marked by a restrictive ventilatory defect with reduced TLC, vital capacity, pulmonary compliance and decrease of CO diffusion capacity, and a residual volume that is either normal or increased. The reduced DLCO is the most sensitive functional disorder, it helps predict the degree of oxygen desaturation during exercise and it lasts one year on average [7].

According to the bronchoalveolar lavage, according to the same review, it provides an essential element to the diagnosis : the inflammatory aspect with an increase in cellularity reaching up to 500 elements/mm^3 with a lymphocyte predominance averaging between 30% and 60%. This excess of lymphocytes consists of T-cells with a low CD4:CD8 ratio. Additionally, this lymphocytic alveolitis persists a long time. It can last even years in case of no evacuation, which makes it a very important retrospective diagnosis element [7]. The negative bacteriological, immunological and anatomopathological tests presented one more argument in favor of an occupational origin of the HSP.

Radiological abnormalities were similar to those described in «Adult chest imaging» in the occupational inhalational lung diseases chapter [8]. The combination of normal lung regions, ground glass and trapped air produces a headcheese pattern which, when present, evokes OHP with over 90% certainty. Fibrosis is anarchically distributed with no clear topographic predominance. The presence of ground glass, which usually covers over 70% of lung surface, along with : lymphocytic alveolitis, expiratory air trapping, centrilobular micronodules, headcheese sign and fibrosis, are in favour of OHP and exclude most other diagnoses.

The same results were described in « Clinical Decision-Making in Hypersensitivity Pneumonitis: Diagnosis and Management » written by Fernández Pérez ER et al. Combination of centrilobular micronodules, extensive ground glass, along with images of trapped air, anarchic fibrosis or the presence of a few cysts and an important lymphocytic alveolitis, was typical of OHP and gives a very high diagnostic certainty [9].

The same conclusions were reported by Goundouin et al [10] in « The hidden causes of hypersensitivity pneumonitis ». Peri-

bronchovascular granulomas were behind the fuzzy centrilobular micronodule images. If the inflammatory granuloma was located in the alveolus or its wall, the secondary lobule will appear uniformly hyperdense, forming a diffuse ground glass pattern that was often heterogeneous and has a geographic appearance. Neverthless, due to the obstruction of the bronchioles by peribronchial granulomas, some lobules would be spared by the pathological process and give a mosaic appearance of the lung. Depending on the degree of bronchiolar obstruction, air trapping with lobular distension could appear either spontaneously or during exhalation.

Radiological abnormalities were described by authors carrying out studies among exposed workers. Ground glass, fibrosis, centrilobular and micronodules were commonly described. They were associated to restrictive lung disorder in 91 to 97 % [1,11,12]. Parenchymal and bronchial fibrotic lesions occur in chronic forms and could therefore produce a CT scan appearance similar to that encountered in idiopathic pulmonary fibrosis (IPF). The typical distribution, peripheral and in the bases, of IPF lesions and no signs of «activity» of the disease are important to attentively look for.

Diagnosis of HSP combined a puzzle of arguments. Radiological specificities combined with respiratory functional disorders and bronchoalveolar lavage hyperlymphocytosis were essential to retain HSP diagnosis [4]. Occupational etiology of the HSP was done according to anamnestic data collected by specialists in occupational medicine. Torén K has suggested that one in ten non-malignant respiratory diseases are explained by occupational exposure to fumes, gaz and chemicals. The occupational burden of idiopathic pulmonary fibrosis was 26% [13]. It was of 16% for asthma, of 14% for chronic obstructive pulmonary disease and of 10% of community-aquired pneumonia.

In our study, dental technicians represented 6/14. The suspected agent was acrylates. The most prevalent finding was interstitial opacity observed in ten dental technicians [14]. The occupational etiological agent was not described. In a case report study, HSP was described in a female dental technician. Based on clinical evolution, radiological and histologic results, diagnosis of OHP was retained [15].

Resins, as well as methyl methacrylates and isocyanates, found in our study were described as causing HSP (16–18). In fact, many occupational inhalational chemicals are more likely to induce HSP. These substances are lipophilic and protein cross-linkers. Other occupational inhaled antigens were described such as plastic and chemical industries, and metalworking [15,16,19–21].

To confirm the occupational exposure to the HSP, many investigation possibilities were described in the literature. Realistic workplace inhalation challenge, enzyme-linked immunosorbant assay to identify IgE and IgG antibodies in exposed patient serum were proposed to improve the etiologic diagnosis [21,22]. The lymphocyte proliferation tests [23] were used to identify beryllium sensitization in chronic beryllium disease. This testing could serve a valuable role in dlhiagnosing other metal sensitization.

The average age was 47 ± 13 years. This result was similar to a study including 86 patients [12]. In a study including dental laboratory technicians in north Iran, the mean age was 31 years [14]. Average exposure time was 25 years. Average delay between the first exposure and the first medical consultation for respiratory or general symptoms was 19 years. Symptoms can start in early exposure, less than 10 years [12,15].

Median delay between the ending of the occupational exposure to the harmful substance and the diagnosis, limited by the Tunisian law to one year, was respected in most cases. Nevertheless, there were cases where this delay reached 27 months. Exceeding the legal delay, the worker could no more benefit from compensation and free treatment. This result suggests the obligation of an early diagnosis of the occupational disease and early referring of the patient to an occupational medicine clinic for etiological diagnosis of the HSP. Criteria to compensate workers for OHP are based on work-relatedness without estimating an exposure level or detailed examination methods [24].

Conclusion

In this study, patients diagnosed with OHP were still working. They did not have typical nor specific clinical, radiologic or respiratory functional abnormalities. Diagnosis was retained after occupational detailed history with listing of occupational inhalational antigens. Diagnosis was made by typical work-related symptoms, work exposure to inhalational antigens and the combination of radiologic, functional and histological results. Further molecular and immunologic analysis should be developed according to occupational suspected antigens. Better substance and etiological circumstances knowledge, the adoption of new screening strategies incorporating chest CT scans, mandatory protection measures enforced by vigourously followed laws, as well as workplace safety and security law enforcement, play an important role in guaranteeing the workers' rights, which is the main pillar of occupational medicine.

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Conflicts of Interest

No

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