Case reports

Occupational Extrinsic Allergic Alveolitis in a poultry farmer

Smărăndescu Raluca Andreea¹,
Mircea-Constantin Diaconu¹, Claudia-
Mariana Handra^{1,2}, Agripina Rașcu^{1,2}

¹ Department of Occupational Medicine, Colentina Clinical Hospital, Bucharest, Romania

² Occupational Medicine Department, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Corresponding author
Claudia-Mariana Handra
claudia.handra@gmail.com

Abstract

Hypersensitivity pneumonitis is a group of inflammatory interstitial lung diseases caused by hypersensitivity immune reactions to the inhalation of various antigens: fungal, bacterial, animal protein, or chemical sources, finely dispersed, with aerodynamic diameter $<5\mu$, representing the respirable fraction. The national register for interstitial lung diseases records very few cases of hypersensitivity pneumonitis (extrinsic allergic alveolitis), a well defined occupational disease. Although not an eminently of occupational origin, the extrinsic allergic alveolitis can occur secondary to occupational exposure to organic substances (animal or insect proteins, bacteria, fungi) or inorganic (low molecular weight chemical compounds) and the occupational doctor is a key actor in the diagnosis. The disease has chronic evolution and exposure avoidance, as early as possible, has major prognostic influence. The occupational anamnesis remains the most important step and the occupational physician is the one in charge for monitoring and detection of the presence of respiratory symptoms in all employees with risk exposure. Next, we present the case of a farmer, without other comorbidities, who develops various respiratory and systemic diseases and manifestations due to repeated exposure to animal proteins and molds, in order to review the risk factors and the consequences of exposure in poultry farms.

Keywords: *extrinsic allergic alveolitis, occupational exposure, diagnosis*

Introduction

Extrinsic allergic alveolitis (EAA) is a type of diffuse interstitial pneumonia characterized by alteration of the lung parenchyma, epithelial, and capillary slopes of the alveoli or even all structures of the alveolar wall [1,2] with occupational and non-occupational etiology [3]. In 1713, Ramazzini makes the first mention of EAA, which he discovers in workers

exposed to grain dust. Later, in 1932, Chambell first described the etiological context of the disease. Over time, this epidemiological context has been updated continuously [4]. Clinical data show that extrinsic allergic alveolitis can develop acutely or chronically, depending on the duration and frequency of antigen exposure. The intensity of the immune response, the concentration of dust in the inhaled air, and the length of exposure have implications for the severity of the clinical picture, respectively, mild, moderate, or

severe symptoms [3].

A 48-year-old non-smoking patient from a rural area with a total professional experience of 18 years, of which the last nine months at a poultry farm, first presented in our clinic in May 2019, with general impairment and noisy respiratory symptoms.

From the anamnesis, we note insignificant family medical history and pathological antecedents. He has been working on a poultry farm for nine months, which consists of 10 halls. The farms' activity is carried out in a continuous flow and consists of the intensive growth of meat birds using the technology of growing on the ground, on bedding from vegetable waste (straw). About 20,000 birds are raised in each hall.

The worker is involved in the following activities:

- sanitizing the halls
- unloading the crates and populating the rooms with the newcomer birds
- depopulating the halls at the end of the breeding process and eliminating the bedding, fodder, and manure.

The straws used to make the vegetable bedding come from warehouses, where they are stored after harvest. The sanitation of the halls consists of collecting the dead animals during the growing process (about a month), managing the straw bedding containing molds and manure, which is done by workers with a bucket cleaning machine, and in hard to reach places, manually. After gathering the litter, wash, and clean the halls with water and calcium oxide (quicklime). To populate the halls with birds is achieved by unloading the crates with newborn chicks (aged 1-2 days), which after 30 days of intensive growth, reach from a few hundred grams to 3-4 kg. At the end of the breeding period, the workers collect the birds, depopulating the halls, and resetting the process.

According to the occupational risk factor identification sheet, the patient had exposure to organic dust (feathers, down, manure, cereals, hormones, enzymes), airborne microorganisms (fungi, molds), amoebae, bacteria, viruses, prolonged orthostatism, manual handling of masses and unfavorable microclimate. The personal protective equipment consisting of clogs, overalls, and a surgical mask, is used only on the first day of the trial when handling newborn chicks. Although the patient comes from a rural area, he states that he does not raise poultry or pigeons at home.

The patient's symptoms began five months after employment on the poultry farm, with fever, chills, profuse night sweats, insomnia, fatigue, bouts of irritating dry cough, dyspnea at moderate exertion.

Before the presentation in our clinic, the patient repeatedly addressed the family doctor, who recommended antibiotic and anti-inflammatory treatment for seven days; the evolution was towards the progressive aggravation of dyspnea, from moderate exertion to resting dyspnea, which was associated with loss of appetite and weight loss. Even in these conditions, the patient continued his activity.

Subsequently, he addressed the territorial pulmonology service. The pulmonologist recorded altered general condition, significant weight loss (7-8 kg in 3 weeks), oxygen saturation in the peripheral blood (SaO₂) 86%, and basal crackling rales in both lung fields. Koch's Bacilli sputum sampling and Koch Bacilli cultures were performed, which were negative. Chest computer tomography (CT) examination revealed interstitial infiltrates in the matte glass and bilateral pulmonary alveolar infiltrates. Antibiotic therapy and systemic corticosteroids were administered, with the improvement of the general condition. Due to the suspicion of EAA recommendations were the following: continuation of anti-inflammatory treatment at home for another seven days, medical leave, and hospitalization in a specialized service for further investigations.

After returning to work, the symptoms reappeared and worsened progressively, requiring emergency admission in the clinic for Occupational Diseases.

Clinical examination at hospitalization revealed the following pathological elements: "full moon" facies (under corticosteroid therapy), convex thorax, bilateral "crackles" at the bases, and on the middle axillary lines. The clinical exam and the following supplemental series of clinical and diagnostic investigations support the diagnosis of extrinsic allergic alveolitis:

1) Pulmonary radiography revealed opacities with a matte glass appearance in the lower half of both lung fields (Figure 1); the CT scan showed centrilobular nodules with a matte glass appearance - air sequestrations and mosaic-like infiltrations (Figure 2)

2) Biologically, a nonspecific inflammatory syndrome was observed;

3) Spirometry revealed the presence of restrictive ventilatory dysfunction (Table 1);

4) The positive 6-minute walking test showed significant desaturation from 93% initially, to 81% in the first 4 minutes;

5) Severely altered alveolar-capillary diffusion with 48% DLCO;

6) Bronchoalveolar lavage: 81% lymphocytes, with subunitary CD4 + / CD8 + lymphocyte ratio (0.91), suggestive for subacute extrinsic allergic alveolitis.

Figure 1. Postero-anterior radiography, May 2019, D.A., 48 years

Figure 2. Chest CT, 2019, D.A., 48 years. There are centrilobular nodules with a matte glass appearance - air sequestrations and mosaic-like infiltrations

Table 1. Spirographic values, May 2019

Test	Actual values	Predicted values	%
FVC(L)	0.95	3.19	29.8
FEV1 (L)	0.49	2.57	19
FEV1/FVC (%)	52	83	

To establish the occupational etiology of this pathology is essential to recognize and determine the presence of occupational risk factors. Thus, we were able to support the diagnosis of occupational extrinsic allergic alveolitis based on the following arguments:

- occupational history: the patient has worked for the last nine months at a poultry farm, where he had exposure to organic dust (feathers, down, manure, cereals, hormones, enzymes), airborne microorganisms (fungi, molds), amoebae, bacteria, viruses, and unfavorable microclimate;
- suggestive symptomatic picture: the symptoms began five months after the date of employment at the poultry farm, with repeated episodes of fever, chills, irritating dry cough, dyspnea at moderate exertion and then resting dyspnea, profuse sweating, fatigue, symptoms under systemic treatment corticosteroid and after discontinuation of exposure, improved;
- imaging table of "frosted glass" on standard chest x-ray and pulmonary computer tomography (CT) (Figure 2);

-respiratory functional tests: the spirometry performed revealed the presence of restrictive ventilatory dysfunction and severely low alveolar-capillary diffusion with DLCO 34%;

-nonspecific inflammatory syndrome;

-positive 6-minute walking test;

-broncho-alveolar lavage provides a definite diagnosis being characteristic of the subacute form of extrinsic allergic alveolitis.

The discharge recommendations were:

-prophylactic: stopping exposure to organic dust (feathers, down), mold, considering a job change;

-emphasis on respiratory monitoring, the continuation of corticosteroid treatment, and re-evaluation at 3 and 6 months.

Upon re-evaluation in our clinic, under the recommended treatment and change of job, the patient's evolution was favorable, with decreased respiratory symptoms and improved clinical and paraclinical lung function.

Discussion

Allergic alveolitis is considered a rare disease, and the exact prevalence remains unknown. Studies have shown a prevalence in the UK of 1/100,000 individuals [4,6]. Another epidemiological study estimated the incidence of interstitial lung disease at 7.6 cases / 100,000 individuals/year, and hypersensitivity pneumonitis accounted for 6.6% of these cases [7]. In the To Regis, only 15 cases diagnosed with EAA in Romania without significant differences depending on gender or background are recorded [8].

The lack of data on the disease's presence is primarily due to the difficulty of establishing the diagnosis, caused by the lack of clinical and functional pathognomonic criteria and the multitude of incriminated etiological factors [5]. A rigorous history of highlighting the correlation between the time of exposure to antigens and the onset of symptoms and the follow-up of the evolution can help develop a diagnosis.

The antigens involved in the production of extrinsic allergic alveolitis are numerous, so a first step is their recognition and identification [4]. The causal agents referenced might be of:

- high molecular weight proteins (HMW) - fungal, bacterial, animal, protozoan proteins, etc or
- (2) low molecular weight chemical compounds [6, 9].

Poultry farmer's lung disease is one of the main etiological types of EAA that can progress to pulmonary fibrosis, with an unfavorable prognosis. In fibrotic forms, the chance of survival is lower compared to the Farmer's Lung disease [10, 11]. The antigens involved can be bacteria, fungi (*Aspergillus*, *Candida albicans*, *Penicillium*, etc.), intestinal mucins, avian proteins, or undetermined avian substances, contained in feathers, flakes, down, manure, fodder, straw [4,12]. These organic particles mobilized during the rooms' cleaning enter the respiratory tract as airborne particles [13]. The wide range of these substances resulting from various activities on a poultry farm, together with an unfavorable microclimate and inadequate protective equipment, can contribute to the onset of the disease.

Although the mechanisms of pathogenesis so far are not fully elucidated, EAA is considered an inflammatory disease with an immune mechanism, involving hypersensitivity reactions III (mediated by the production of specific antibodies) and IV (cell-mediated) [14].

Numerous cell types participate in the characteristic inflammatory process of EAA. The serial head is

the Th1 lymphocyte that, once activated, secretes inflammatory cytokines (IFN γ , IL-2, IL-12, TNF β). IL-2 activates B lymphocytes, stimulating their secretion of IgG antibodies. The soluble antigen binds to IgG, causing complement cascade activation. The C5 fraction of complement will cause the activation of alveolar macrophages, which will subsequently lead to the release of cytokines: IL-1, IL-8, IL-12, IL-6, TNF (tumor necrosis factor), RANTES/CCL5 (Regulated on Activation, Normal T cell Expressed and Secreted chemokine), MCP-1 and CCL18, the latter having a strong chemoattractive role for lymphocytes. Activated alveolar macrophages cause an unusual response of antigen-presenting cells, which will activate and stimulate lymphocyte production. Other cells involved in the inflammatory process are dendritic cells (antigen-presenting cells) and neutrophils. The latter, by degranulation, will release elastase, an enzyme involved in the hydrolysis of elastic fibers in the lung parenchyma, which in some chronic forms of EAA leads to pulmonary emphysema. Macrophages, together with neutrophils, release oxygen free radicals with a critical role in maintaining the inflammatory process, while fibrocytes secrete IL-17, both involved in fibrogenesis. Smoking would have a protective role in the case of EAA by decreasing the expression of cytokines produced by macrophages (IL-1, TNF) or by inhibitory action on lymphocyte proliferation [15].

From a clinical perspective, the disease can evolve as a form: acute, subacute, and chronic [3].

Clinical symptomatology: dry cough alternating with productive cough, exertional dyspnea, weight loss, phenomena of acute respiratory failure, respiratory function (alteration of alveolar-capillary diffusion) and imaging (nodular opacity "in frosted glass"), in our case is characteristic for the subacute form of the disease [3,4].

In chronic forms, respiratory functional changes can be restrictive, with reduced compliance and lung volumes, secondary to fibrosis. In most cases, the 6-minute walking test is positive, and the measurement of blood gas shows hypoxemia (exercise or rest) [4].

Pulmonary radiography can guide the diagnosis, the presence of nodular opacities with the "ground glass" aspect being characteristic for the acute and subacute cases. The images with "honeycomb" appearance are specific for chronic cases associated with fibrosis. [3,4].

Bronchoalveolar lavage (LAB) is a more sensitive test than identifying IgG antibodies in patients' serum [16]. Based on the disease stage, LAB cytology

is different, with the predominance of neutrophils in the acute forms, while in subacute and chronic forms, with lymphocyte predominance [4]. In our presented case, in LAB, we observed the lymphocyte dominance (> 50% of the cell population present in lavage), with the subunitary ratio of (0.91) for CD4+/CD8+ lymphocytes, characteristic of the subacute form [16].

Regarding management in the case of patients with EAA, the essential measure is removing the environment with exposure. Studies have shown this measure alone to lead to a favorable evolution of the disease. The development depends on the incriminated antigen, so in the chronic phases, the farmer's lung is frequently associated with emphysema and obstructive syndrome. Conversely, in the case of poultry farmer's lung disease, the progress is often to pulmonary fibrosis. Mortality is related to the presence of pulmonary fibrosis, which varies depending on the clinical form.

Treatment in acute and subacute forms consists of oral corticosteroid therapy. Even in the presence of complete remission, there is a risk of reactivation of the disease, with chronicity and progression to pulmonary fibrosis. For these reasons, we recommend regular medical check-ups consisting of clinical examination, respiratory function tests, and chest CT where there are risk factors.

The Poultry farmer's lung disease is one of the most publicized types of EAA. Yet, as it is understandable from our presentation, there are difficulties in establishing the diagnosis, so awareness of this type of pathology is necessary.

Conclusions

Being mostly a pathology with professional etiology and having a progressive evolution towards fibrosis, the occupational medicine doctor must recognize and identify the risks at work for the occurrence of EAA.

Prevention is central, primarily through collective action, through procedures aimed at limiting contamination, especially in the professional environment. Because of this, the occupational physician must monitor and detect the presence of respiratory symptoms or respiratory functional changes that occurred in the context of exposure to risk factors. Therefore he must diagnose the disease early, before the progression to chronic forms with

massive fibrosis, a situation in which the only therapeutic means remains a lung transplant [15].

In addition to monitoring patients, it is imperative to identify risk factors in the workplace atmosphere, reduce antigen sources, ensure appropriate respiratory protective equipment, and adequate ventilation.

References

1. Strâmbu I. Pneumonia de hipersensibilitate. In: Ghid de diagnostic și tratament al pneumopatiilor interstițiale difuze; București, 2015; p. 83-89; ISBN 978-973-0-20120-8.
2. Xaubet A, Ancochea J, Blanquer R, et al. Diagnosis and Treatment of Diffuse Interstitial Lung Diseases. *Archivos de Bronconeumologia*; vol. 39, issue 12; p. 580-600; 2003.
3. Riario Sforza GG, Marinou A. Hypersensitivity pneumonitis: a complex lung disease. *Clin Mol Allergy*; 2017;15: 6.
4. Rașcu A. Alveolitele alergice extrinseci. In: Boli profesionale ale aparatului respirator. Ghid pentru studenți și medici. Editura Universitară "Carol Davila", București, 2019; ISBN: 978-606-011-103-0.
5. Hsieh C et al. Hypersensitivity Pneumonitis. 2018. Available from: <https://emedicine.medscape.com/article/299174-overview>.
6. Selman M, Pardo A, King TE Jr. Hypersensitivity pneumonitis: insights in diagnosis and pathobiology. *Am J Respir Crit Care Med*; 2012, 186(4):314-324.
7. Xaubet A, Ancochea J, Morell F, et al. Report on the incidence of interstitial lung diseases in Spain. *Sarcoidosis Vasc Diffuse Lung Dis*; 2004 Mar. 21(1):64-70.
8. Registrul Național de Pneumopatii Interstițiale Difuze și Sarcoidoză. Available from: <http://www.regis.ro/diagnostic/vrs/diagnostic/3>.
9. Okamoto T, Miyazaki Y, Ogura T, et al. Nationwide epidemiological survey of chronic hypersensitivity pneumonitis in Japan. *Respir Investig*; 2013, 51(3):191-199.
10. Lalancette M, Carrier G, Laviolette M et al. Farmer's lung. Long-term outcome and lack of predictive value of bronchoalveolar lavage fibrosing factors. In: *Am Rev Respir Dis*; 1993; 148:216-21.
11. Sahin H, Brown KK, Curran-Everett D, et al. Chronic hypersensitivity pneumonitis: CT features comparison with pathologic evidence of fibrosis and survival. *Radiology*; 2007; 244(2):591-598.
12. Richerson HB, Leonard Bernstein IL, Fink JN et al. Guidelines for the clinical evaluation of hypersensitivity pneumonitis. Report of the Subcommittee on Hypersensitivity Pneumonitis. In: *J Allergy Clin Immunol*; 1989; 84(5 Pt 2):839-44.
13. Registrul Național de Pneumopatii Interstițiale Difuze și Sarcoidoză. Available from: <http://www.regis.ro/pneumonia-de-hipersensibilitate-ph>.
14. Cocărlă A. Alveolitele alergice extrinseci. In: *Medicină Ocupațională*, vol I. Editura Medicală Universitară "Iuliu Hațieganu", Cluj-Napoca, 2008; p. 679; ISBN 978-973-693-298-4.
15. Paris C. Pneumopathies d'hypersensibilité professionnelles. In: *Références en santé au travail*; september 2017; Available from: <http://www.inrs.fr/media.html?refINRS=TR%2062>.
16. Meyer KC, Raghu G, Baughman RP, on behalf of the American Thoracic Society Committee on BAL in interstitial lung disease, et al. An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. *Am J Respir Crit Care Med*; 2012;185(9):1004-14.