CASE REPORT

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Fatal hypersensitivity pneumonitis after chemical occupational exposure

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Abstract

Hypersensitivity pneumonitis (HP; extrinsic allergic alveolitis) is a rare non-immunoglobulin E (IgE)-mediated inflammatory lung disease caused by inhalation exposure (occupational, recreational or ordinary home exposure). A 36-year-old female patient, without significant medical history, is referred to an outpatient pulmonology clinic for dry cough, shortness of breath, fever, fatigue and weight loss. Chest high-resolution computed tomography (HRCT) was performed, and significant lung fibrosis (especially centrilobular and interlobular in bilateral "thick lines"), traction bronchiectasis and alveolitis in both superior lobes are described. Lung function tests showed severe restrictive dysfunction. Transfer factor of the lung for carbon monoxide (TLCO) being very low, the flexible bronchoscopy was contraindicated. Surgical lung biopsy was performed. Histopathological examination showed characteristic lesions of chronic bilateral hypersensitivity pneumonitis. The patient died four days after the surgical intervention due to post-operative complications. Exposure to various chemical substances can form bonds with human proteins molecules and induce an exaggerated immune response in susceptible individuals. A high index of suspicion of occupational exposure can determine an early diagnosis with a better outcome.

Keywords: hypersensitivity pneumonitis, lung fibrosis, occupational exposure, plastic.

Introduction

Hypersensitivity pneumonitis (HP; extrinsic allergic alveolitis) is a non-immunoglobulin E (IgE)-mediated inflammatory lung disease caused by repeated inhalation and sensitization to a wide variety of organic aerosols and low-molecular-weight chemical antigens [1, 2]. The exposure can be occupational, recreational or ordinary home exposure [1]. Occupational HP and occupational asthma are the two immune-mediated occupational lung diseases [3]. High-risk fields for occupational lung diseases include farmers, printers, woodworkers, painters, plastic workers, cleaners, spray painters, electrical workers, and health care workers [3].

We describe a fatal case of HP in a young female worker secondary to exposure to heated plastic.

Case presentation

A 36-year-old (C.C.A, Chart No. 7839) female patient, ex-smoker, was referred to the outpatient respiratory clinic ("Leon Daniello" Pneumophtisiology Hospital, Cluj-Napoca, Romania) in August 18, 2016, for dry cough, exertional dyspnea, fever (up to 39^0C), fatigue, and weight loss (10 kg). The onset of symptoms was six months before the consultation with worsening in the last two months. She had a known chronic exposure to hot processed plastics at work for six months, which started four months before the onset of symptoms (*i.e.*, a two months exposure after the onset of the symptoms). The physical examination showed an underweight patient, fever 38^0C, pallor with cyanosis at minimal exercise, fine crackles, oxygen saturation (SaO_2) of 85% on room air, and tachycardia (110 beats/min). The chest X-ray showed linear and reticular opacities in the peripheral lung area. Chest high-resolution computed tomography (HRCT) revealed an extensive pulmonary fibrosis "in thick lines", peri-bronchial thickening with centrilobular, interlobular and subpleural localization in both lungs, bilateral ground-glass opacities, and traction bronchiectasis in the right upper lobe and left lung (Figure 1). Inflammatory markers were increased: erythrocyte sedimentation rate (ESR) 28 mm/h, C-reactive protein (CRP) 7.7 mg/dL. Lung function tests showed a severe restrictive pattern with forced vital capacity (FVC) of 30.6% (0.96 L) and forced expiratory volume in one second (FEV1) of 33.6% (0.91 L); Tiffeneau–Pinelli index (FEV1/FVC) of 95%, diffusing capacity of the lungs for carbon monoxide (DLCO) was markedly reduced (16% predicted), with decreased transfer constant. During the six-minute walk test (6MWT), the SaO_2 dropped to 71%, and the walked distance was 161 m, representing 24% of the predicted distance. The patient tested negative for the following antibodies: cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA), anti-nuclear antibodies (ANA), anti-dsDNA antibodies, and anti-topoisomerase I (anti-Scl-70) antibodies. Flexible bronchoscopy with bronchoalveolar lavage (BAL) could not be performed. Cardiology consult, with transthoracic echocardiography, was without significant findings. A

surgical lung biopsy was performed in the Department of Thoracic Surgery (Chart No. 8678, September 19, 2016). After the surgical biopsy, the patient developed a pneumothorax with atelectasis. The general condition of the patient deteriorated, with severe hypoxemia and hemodynamic instability. Despite mechanical ventilation, the lung collapse was irreversible and the patient days three days after surgery.

The macroscopic pathological examination revealed adhesions between the lobes of the right lung, left fibrinous pleurisy, inhomogeneous, condensed lungs with areas of high consistency. The pathological examination revealed distorted lung architecture, with extensive areas of fibrosis and hyalinization (Figure 2, a and b), zones with interrupted alveoli septa, significant stasis, hemorrhages (Figure 3, a and b). Alveoli were with edema and aggregated of red blood cells or macrophages; alternating areas with alveolar, bronchiolar or bronchial with fibrin and leukocyte exudates are found. In the interstitium, there were multinucleated giant cells (Figure 4a) and granulomas with imprecise delineation and without central necrosis. In the giant cells, there are translucent, oval and lenticular spherical structures. Also, there were diffuse, and peribronchial inflammatory infiltrates with lymphocytes (Figure 4b), plasma cells, and numerous eosinophils. Vascular structures have intimate hyperplasia, media hypertrophy and wall hyalinization.

For the evaluation of the cells involved in the inflammatory reaction and the intensity of lung lesions, we proposed the completion of the histopathological study with an immunohistochemical study. For this, of the biopsy material harvested and included in paraffin, there were performed 4-µm thick serial sections in the rotary microtone Microm HM350, equipped with a bath water section transfer system (STS, microM), placed on poly-L-lysine covered slides. The processing of the biological material consisted in the deparaffinization and hydration of the sections, antigen demasking by boiling the slides in a sodium citrate solution, pH 6 or ethylenediaminetetraacetic acid (EDTA), for 21 minutes (seven cycles of 3 minutes) in a microwave oven. After the slides cooling off, they were washed in tap water and then washed with distilled water for 15 minutes. The endogenous peroxidase blocking was performed by placing the slides in 3% oxygenated water for 30 minutes, at room temperature, following the blocking of non-specific sites, using 2% skimmed milk for 30 minutes. Subsequently, the sections were incubated with primary antibodies for 18 hours (overnight), in a fridge, at 4^0C, and the next day there was applied the biotinylated secondary antibody for 30 minutes, at room temperature, followed by the washing in 1% phosphate-buffered saline (PBS – three baths of 5 minutes), after that there was applied Streptavidin–HRP (horseradish peroxidase) for 30 minutes, at room temperature, followed by slides washing in 1% PBS for 5 minutes. The immunohistochemical signal was detected using 3.3'-Diaminobenzidine (DAB) (Dako) and the reaction was stopped by passing the slides in 1% PBS. The contrasting was performed with Mayer's Hematoxylin staining. There followed the dehydration in ethylic alcohol in ascending concentrations, xylene clarification and slides fixing using a DPX environment (Fluka). In our study, we used the following markers (Table 1):

Table 1 – ***Antibodies used for the immunohistochemical study***

Antibody	Code	Clone	Antigen retrieval	Specificity	Dilution	Source
Anti-CD68	M0814	KP1	Sodium citrate	Macrophages	1/100	Dako
Anti-CD3	M7254	F7.2.38	EDTA	T-lymphocytes	1/50	Dako
Anti-CD20	M0755	L26	Sodium citrate	B-lymphocytes	1/50	Dako
Anti-CD79 alpha	M7050	JCB117	EDTA	Plasmocytes	1/50	Dako
Anti-tryptase	M7052	AA1	Sodium citrate	Mastocytes	1/500	Dako
Anti-CD34	M7165	QBEnd 10	Sodium citrate	Endothelial cells	1/50	Dako
Anti-*α*-SMA	M0851	1A4	Sodium citrate	Myofibroblasts	1/100	Dako

α-SMA: Alpha-smooth muscle actin; EDTA: Ethylenediaminetetraacetic acid.

Most inflammatory cells present in the lung parenchyma were represented by macrophages (Figure 5a). They were identified by using the immunohistochemical marking with the anti-CD68 antibody in the tissue necrosis areas, where they had variable shapes and sizes (Figure 5b), in the septa of remaining lung alveoli, where they presented small sizes and even in the alveoli lumenus, where they had large sizes and spongy aspect (Figure 5c). Frequently, the immunohistochemical reaction highlighted the multinucleate giant cells (Figure 5d). All the cells of the macrophage system presented an intense immunohistochemical reaction, showing a high phagocyte activity, with an increase of lysosome quantity in every cell.

Regarding the lymphocyte distribution in the inflammatory infiltrate of the lung parenchyma, there was observed that the most numerous were T-lymphocytes (Figure 6a), having a diffuse and relatively homogenous distribution, while B-lymphocytes were less numerous, with a tendency of nodular distribution (Figure 6b).

Similarly to B-lymphocytes, the plasma cells, the main antibody producing cells, were less represented in the lung parenchyma, having a heterogeneous distribution, with a tendency of forming perivascular cellular groups (Figure 7a). Mastocytes, the cells involved in the immunoallergic reaction and in stimulating angiogenesis, were distributed relatively even in the remodeled lung parenchyma (Figure 7b). Most mastocytes presented faded margins, due to the processes of massive degranulation, denoting the involvement of these cells in the tissue remodeling processes.

Starting from the fact that in the inflammatory and tissue remodeling processes there intervene fibroblasts, myofibroblasts and endothelial cells, we wanted to highlight the changes in lung microcirculation and myofibroblast distribution. The lung microvessels, specifically highlighted by marking the endothelial cells with the anti-CD34 antibody, were present in a relatively high number in the remaining alveolar septa, where they had a

homogenous and relatively ordered distribution (Figure 8a) and a disordered and heterogeneous distribution in the remodeled lung tissue. However, we observed the presence of a high number of myofibroblasts present in the remodeled lung tissue (Figure 8b).

The clinical presentation, history of antigen exposure, HRCT images and characteristic histopathological findings (diffuse chronic interstitial inflammation, poorly formed interstitial granulomas and interstitial pneumonia), were highly suggestive for HP with pulmonary fibrosis.

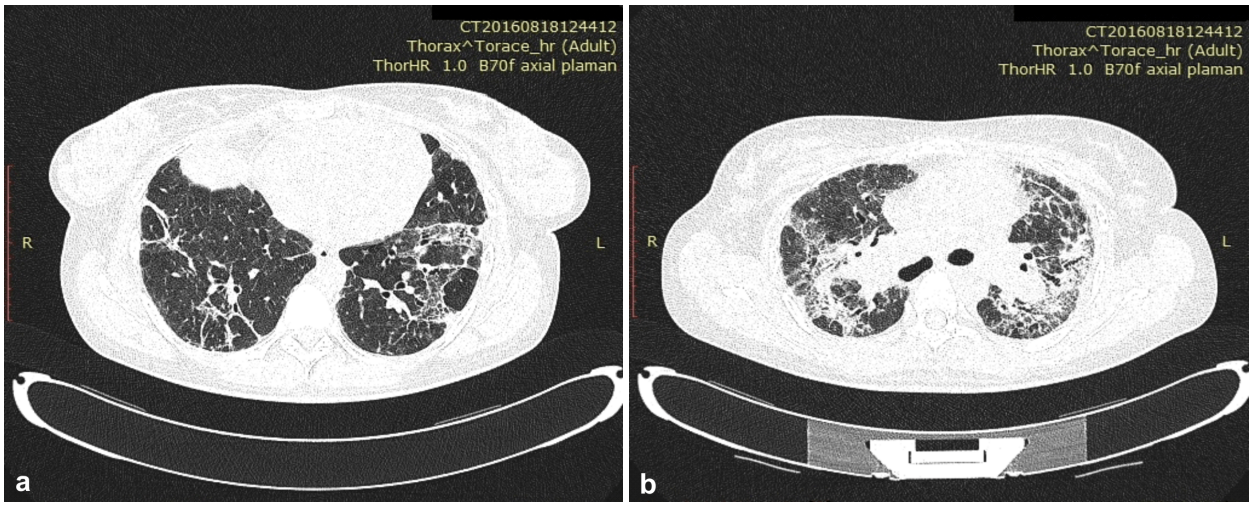

Figure 1 – *(a) Chest HRCT showing significant pulmonary fibrosis "in thick lines" with centrilobular, interlobular and subpleural localization in both lungs; (b) Traction bronchiectasis in the right upper lobe and left lung and ground-glass opacities in upper lobes.*

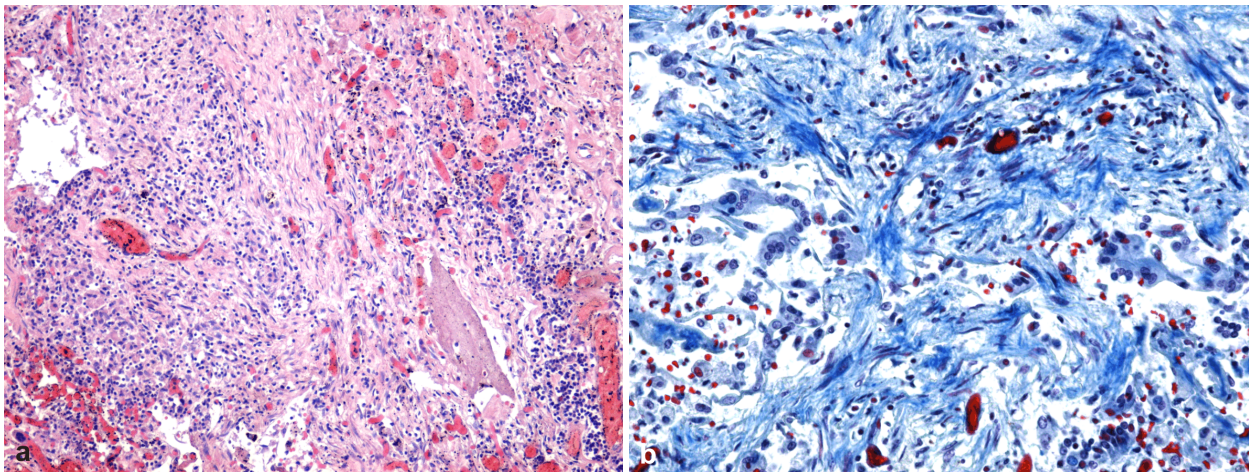

Figure 2 – *(a) Distorted lung parenchyma with collagen fibrosis and inflammatory infiltrate [Hematoxylin–Eosin (HE) staining, ×100]; (b) Image of lung parenchyma with a deeply altered structure, by the development of an intense collagen fibrosis [Goldner–Szekely (GS) trichrome staining, ×200].*

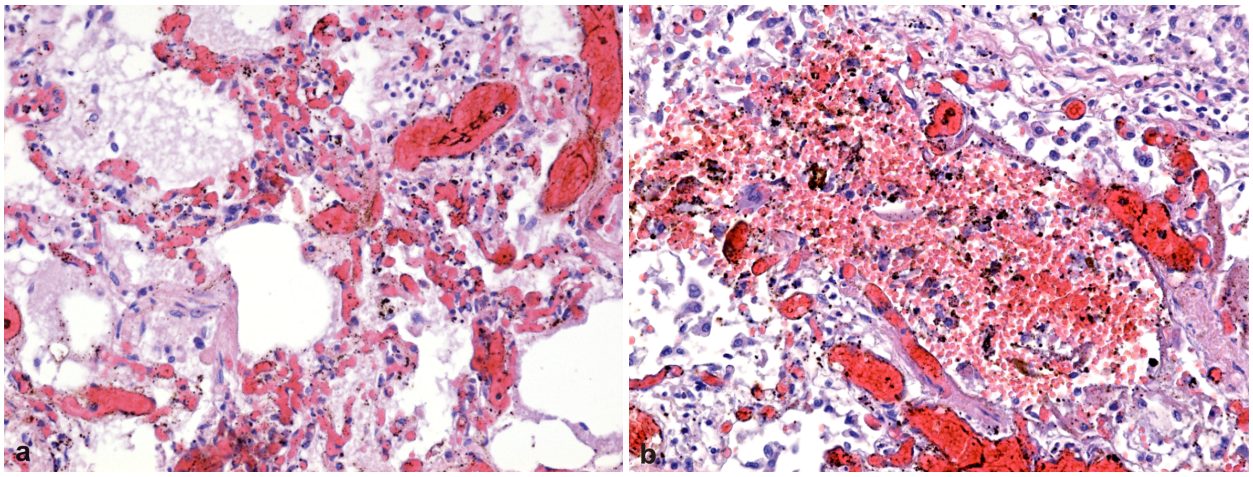

Figure 3 – *(a) Alveolar exudate, thickened, deformed, interrupted interalveolar septae with vascular congestion; (b) Lung parenchyma with extended hemorrhage areas. HE staining, ×200.*

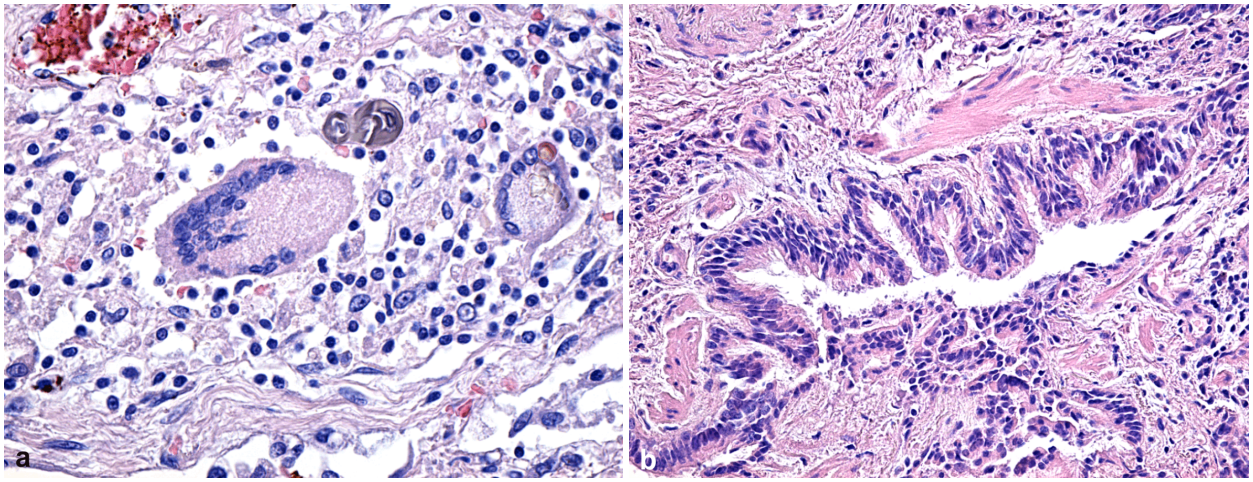

Figure 4 – ***(a) Multi-nucleate giant cells; (b) Collagen fibrosis altering the bronchiolar wall, associated with an inflammatory infiltrate mainly formed of lymphocytes. HE staining, ×200.***

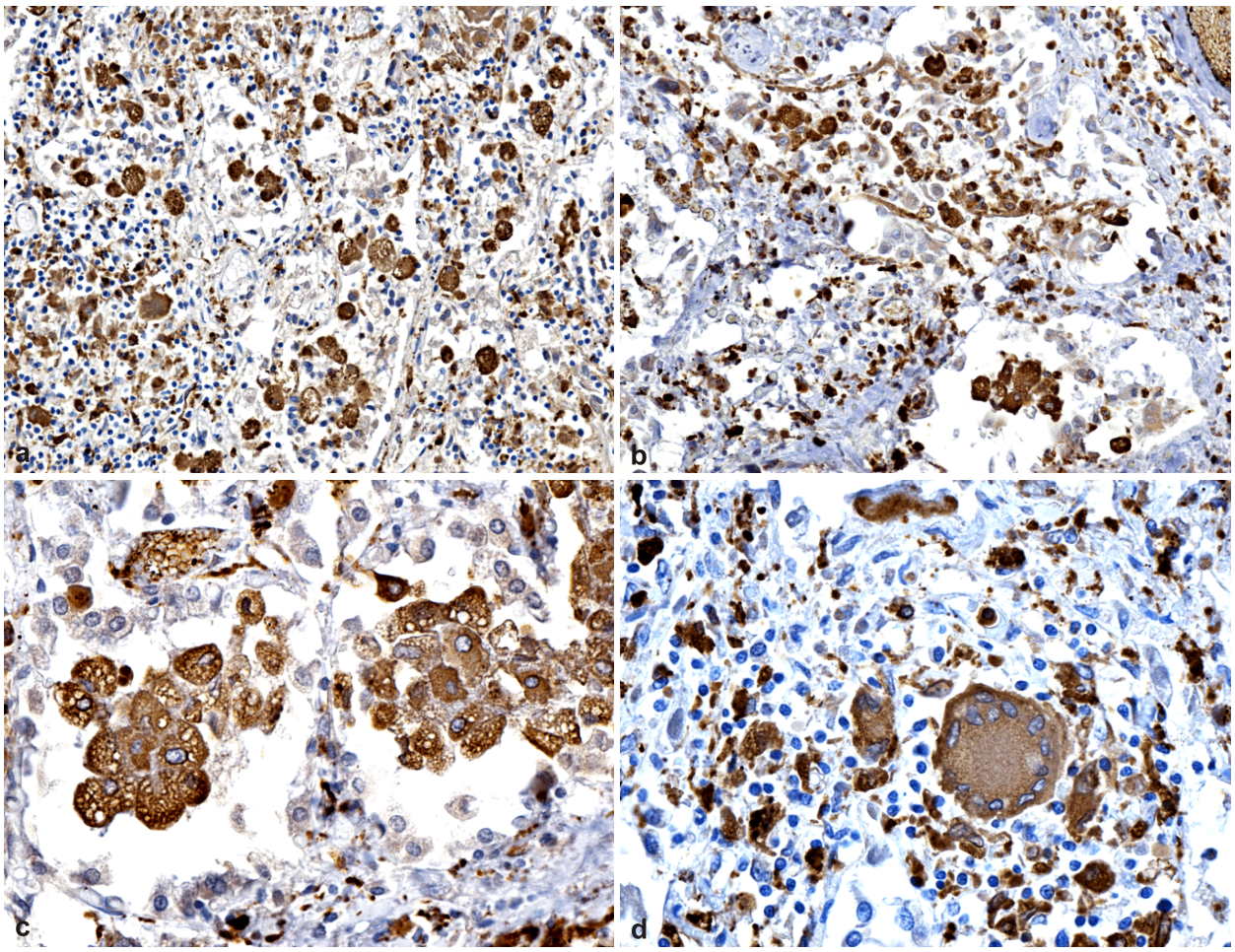

Figure 5 – ***(a) Intensely remodeled lung parenchyma, with a high quantity of macrophages; (b) Lung macrophages with heterogeneous distribution in the tissue necrosis foci; (c) Cluster alveolar macrophages, of large sizes, with a spongy aspect; (d) Macrophages and multi-nucleate giant cells present in the remodeled lung stroma. Anti-CD68 antibody immunomarking: ×100 (a and b); ×400 (c and d).***

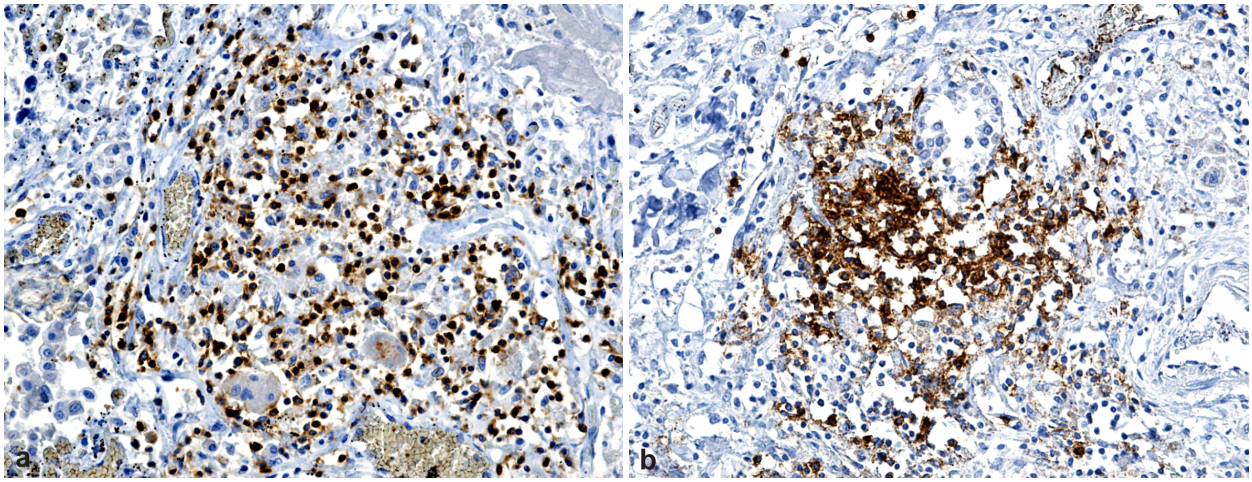

Figure 6 – *(a) Lung parenchyma with a high number of T-lymphocytes, diffusely distributed (Anti-CD3 antibody immunomarking, ×200); (b) B-lymphocytes with a nodular distribution tendency (Anti-CD20 antibody immunomarking, ×200).*

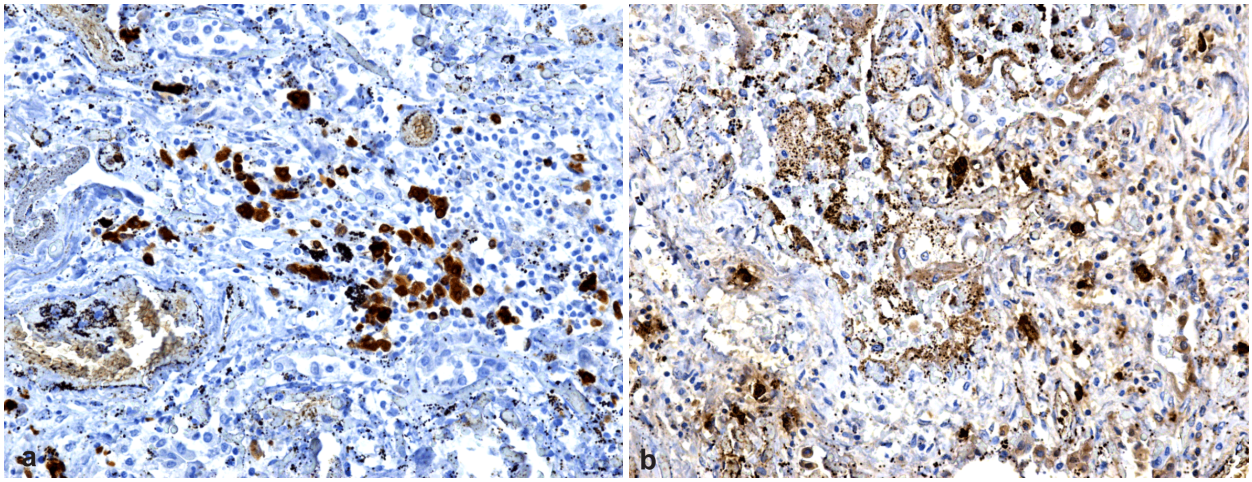

Figure 7 – *(a) Plasma cells unevenly distributed in the lung parenchyma, arranged perivascularly (Anti-CD79 alpha immunomarking, ×200); (b) Mastocytes with massive degranulation with a relatively uniform distribution in the lung parenchyma (Anti-tryptase antibody immunomarking, ×200).*

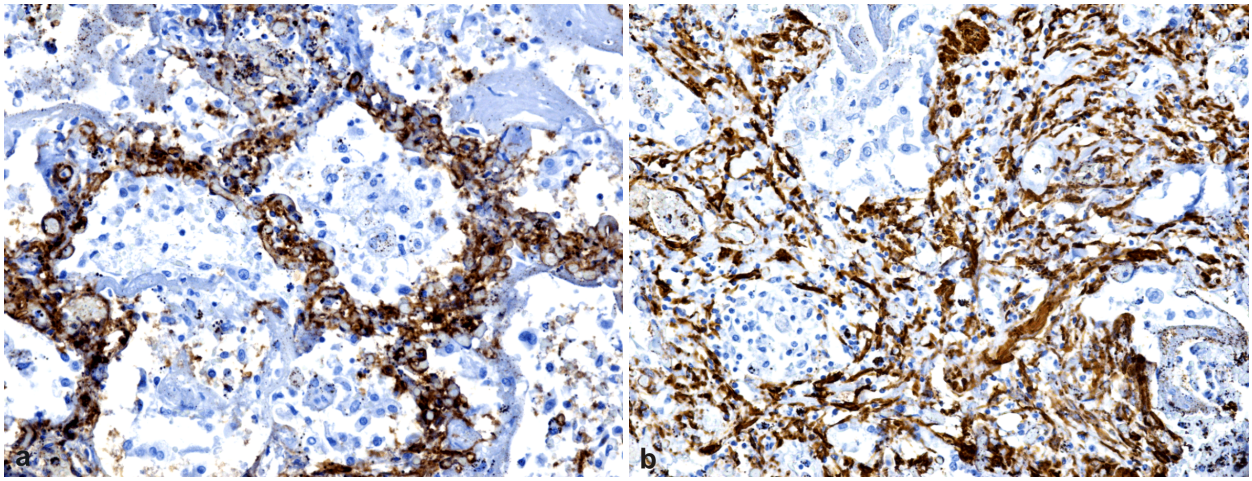

Figure 8 – *(a) Well-represented network of blood capillaries in the remaining interalveolar septa (Anti-CD34 antibody immunostaining, ×200); (b) Dense network of myofibroblasts present in the remodeled lung tissue (Anti-α-SMA antibody immunostaining, ×100).*

Discussion

HP is a rare disease. In a large general population-based study, in UK, HP prevalence was 1/100 000 individuals [4]. The prevalence of isocyanate-induced HP, one of the plastic manufacturing process related HP, was 1.3% out of all chronic HP in Japan; there were only three cases described in a ten years interval [5].

More than 200 antigens have been recognized as causal agents: high molecular weight (HMW) proteins (fungal, bacterial, protozoan, animal proteins) and low-molecular-weight chemical compounds [3, 4]. A characteristic feature of the disease is that only 5–15% of subjects exposed to a provoking antigen develop HP [6, 7]. Synthetic low-molecular-weight compounds can form bonds with human protein molecules and induce dysregulations and dysfunction of the immune system in susceptible patients [8, 9]. Antigens related to plastic manufacturing process HP are acid anhydrides (chemical worker's lung, plastic worker's lung, epoxy worker's lung) or isocyanates (paint refinisher's lung) [10–12]. Isocyanates are used for the production of polyurethane polymers for flexible and rigid foams, as elastomers, adhesives, and surface coatings, and in two-part paints [13, 14]. Acid anhydrides are used in plastics, paints, and epoxy resins [15]. The plastic injection process facilitates exposure of workers to various products generated by the pyrolysis of resins melting at high temperature [16]. Although the causative substance was unknown, our patient appears to have died because HP that occurred as a consequence of exposure to various elements generated by the plastic injection process.

HP pathogenesis results from a combination of type III (immune complex-mediated) and type IV (delayed) hypersensitivity reactions after a susceptible individual is exposed to an etiological agent [17]. In acute HP or early in the chronic HP, the dominant reaction seems to be type III, whereas in subacute and chronic HP the reaction shifts to type IV [17]. It appears that the mechanisms of isocyanates- and anhydrides-induced HP is similar to HP caused by high-molecular weight organic compounds, *i.e.*, type III and type IV hypersensitivity [5, 18, 19]. In general, it is accepted that for isocyanates to induce HP, exposure should be at high levels [19].

Smoking is less prevalent in patients with HP compared with unaffected controls with similar antigenic exposure [20, 21]. Moreover, when exposed to high levels of HP antigens, smokers have lower levels of specific antibodies to the causative antigen [22, 23]. The mechanisms that account for the "protective" impact of smoking are poorly understood [24], but it has been shown that nicotine has a significant anti-inflammatory effect in experimental HP [25] through several mechanisms [26, 27]. Although more common in nonsmokers, when it occurs in smokers, HP is associated with a more chronic and severe course and higher mortality [28]. In a recent study, smoking was not a significant predictor of mortality in HP patients [29]. Our patient was an ex-smoker and is it less clear what can be the implications of this status.

Time elapsed from exposure to onset of symptoms is variable in HP. In a series of five cases of isocyanate-induced HP (plastic-related HP), time elapsed from exposure to onset of symptoms varied from one month to 27 years [19]. In the presented case, this interval was four months.

HP can present in an acute, a subacute, or a chronic form [3, 4, 30], without widely accepted criteria to differentiate these clinical types. Our patient had features of acute [fever, dry cough, restrictive pattern on pulmonary function tests (PFTs)], subacute (rales, ground glass opacities on HRCT) and chronic HP (weight loss, rales; fibrosis and traction bronchiectasis on HRCT), according to Blatman & Grammer classification criteria [10].

In a series of five cases with HP to isocyanates, lung function testing showed normal or restrictive pattern [19]. In our patient, lung function showed a restrictive pattern. DLCO was very low in our patient (16% of predicted). In one series HP of all etiologies, the lowest DLCO was encountered in isocyanate-induced HP (31.6%) [5].

In acute HP, results of biopsies show lymphocytic interstitial infiltrates and a neutrophilic and lymphocytic alveolitis [2]. Foci of eosinophilic infiltrates can also be observed, but generally, eosinophils are rare or absent, corresponding with the proposed mechanism of types III and IV hypersensitivity reactions (as opposed to a type I reaction, where eosinophils are present) [2, 17]. Granulomas are not apparent in acute HP [2]. In subacute HP, the histopathological findings include cellular bronchiolitis, interstitial mononuclear cell infiltrates and scattered, small, non-necrotizing granulomas [12, 31]. The chronic (fibrotic) form of HP is characterized by foci of peribronchiolar interstitial fibrosis and giant cells. Granulomas are much less frequently found [4, 32]. In one series of chronic HP, giant cells were present in 37.2% of patients, and granulomas in 30.2% of patients [5]. The described case showed histopathological features of acute (*i.e.*, eosinophils), subacute (*i.e.*, granulomas), and chronic (*i.e.*, fibrosis) HP.

The acute, subacute, and early chronic form of HP is characterized by a CD4+ Th1 and CD8+ lymphocyte alveolitis [3]. The prognosis for HP is variable and depends on the degree of fibrosis with mortality ranging from 0% to 29% at five years [12, 33]. In a study performed in Japan, the median survival time was approximately seven years in chronic HP of all etiologies [5]. Predictors of unfavorable outcome have been associated with older age, a history of cigarette smoking, crackles on lung examination, baseline low total lung capacity (TLC) and DLCO, absence of lymphocytosis in bronchoalveolar lavage, presence of radiological and/or histopathological signs of fibrotic changes and unidentified source of exposure [32, 34–38]. Our patient was an ex-smoker, presented fine crackles at first consultation, DLCO was very low and showed fibrosis on HRCT and histopathological examination.

One of the limits of our case presentation is that specific antibodies against isocyanates or anhydrides were not tested. On the other hand, these antibodies are a marker of exposure and not an indicator of disease [2]. Moreover, in a series of five cases with isocyanates-induced HP, only one case had specific IgG antibodies to isocyanates [19].

Conclusions

HP related to plastic manufacturing is an uncommon type of HP. Here, we presented a young female ex-smoker patient that had a fatal HP with mixed features (clinical, radiological, and histopathological) of acute, subacute and chronic HP.

Conflict of interests

The authors declare that they have no conflict of interests.

Acknowledgments

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