

CASE REPORT

A rare association of cutaneous leukocytoclastic angiitis (hypersensitivity vasculitis) and hypersensitivity pneumonia (extrinsic allergic alveolitis) in a pigeon breeder – case report and literature review

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Abstract

Extrinsic allergic alveolitis is an occupational condition intensively studied and published about, unlike cutaneous leukocytoclastic angiitis. The coexistence of these two diseases is even more rare in the same patient with exposure to occupational pollutants of animal origin. We present the case of a 44-year-old man, a pigeon breeder admitted to hospital with a pruritic purpuric eruption and lower limb paresthesia, dyspnea on exertion, polymyalgia rheumatica, mixed polyarthralgias. Based on the clinical, paraclinical and laboratory investigations (electroneuromyography, plethysmography, computed tomography scan, musculoskeletal biopsy, current laboratory tests and immunoassays), the main diagnoses of extrinsic allergic alveolitis and leukocytoclastic vasculitis were determined. The patient underwent treatment with corticosteroids with a favorable outcome, but which becomes aggravated by the occurrence of necrotic skin lesions at the cessation of corticosteroid therapy on the patient's own initiative. After the resumption of the corticosteroid therapy, the lesions and symptoms improve. To our knowledge, this case report is the first one that describes an association of two major conditions, extrinsic allergic alveolitis and cutaneous leukocytoclastic angiitis, in the same clinical context of an occupational exposure to specific pollutants. Long-term corticosteroid therapy has proved to be useful in preventing relapses and improving the patient's clinical status with the association of cutaneous leukocytoclastic angiitis and extrinsic allergic alveolitis. Considering our findings in this case report, we may suggest the inclusion of systemic vasculitis on the list of recognized professional diseases.

Keywords: leukocytoclastic angiitis, hypersensitivity vasculitis, pneumonitis, allergic alveolitis, pigeon.

Introduction

Extrinsic allergic alveolitis (hypersensitivity pneumonitis – HP) is an occupational disease with high prevalence among farmers, the disease occurring due to the hypersensitivity reactions caused by the repeated inhalation of various antigens like bacteria, fungi or various avian proteins [1].

Clinically, it is characterized by inspiratory crackles on auscultation and centrilobular nodules, ground-glass opacification and mosaicism due to air trapping at high-resolution computed tomography (HRCT). Bronchoalveolar lavage fluid (BALF) analysis reveals usually >25% lymphocytosis, a cluster of differentiation (CD)4/CD8 ratio of <1% and >1% mast cells in the acute phase [2].

Although the first case of extrinsic allergic alveolitis was described by Bernadino Ramazzini [3] in the 1700s, today we are still far from a fair, multidisciplinary approach

of this pathology. The estimated prevalence rates of the occupational HP ranged from 1.3% to 12.9% among farmers and from 8% to 10.4% among pigeon breeders [4], but the real incidence and prevalence is basically difficult to evaluate [1].

Incidence may vary according to various reasons, such as definitions, intensity of exposure to inciting antigens, season, geographical conditions, local practices and customs, proximity to certain industries, and host risk factors, which can lead to diagnostic errors, according to King [5].

The incidence of occupational extrinsic allergic alveolitis in Romania is clearly undervalued, whereas official data shows that of 2015 there was not a single case registered in the national register of occupational diseases.

In the case of a long-term occupational contact, alveolitis may become chronic [2].

Hypersensitivity vasculitis (leukocytoclastic angiitis) affects the small vessels (arterioles, capillaries, venules) and occurs as part of type III immune reactions, induced by the presence of immune complexes at tissue level [6]. Histologically, leukocytoclastic vasculitis (angiitis) involves necrosis and inflammatory infiltrates with polymorphonuclear leukocytes which can be observed at the level of the blood vessels, both in the perivascular space and in the vascular wall, with nuclear debris that have the appearance of “a powdered lesion”. In most cases, immunoglobulins (Igs) and complements are also present and a mononuclear inflammatory infiltrate may occur in chronic phases, as well [7].

The *Chapel Hill Consensus Conference* recommended changing the name of hypersensitivity vasculitis to cutaneous leukocytoclastic angiitis, due to the cutaneous manifestations that dominate the clinical picture, in which neutrophils have a special involvement [8, 9].

In 1990, the *American College of Rheumatology* (ACR) introduced the characteristic features of each form of vasculitis used as differentiation principles and proposed the classification criteria for hypersensitivity vasculitis: over 16 years of age, the use of possible allergy medication in relation to symptoms, palpable purpura, maculopapular rash and skin biopsy that highlight the neutrophils with periarteriolar and perivenular infiltrates [10, 11].

The clinical picture is dominated by skin lesions at the level of the lower limbs [12], but other organ or systems like musculoskeletal, gastrointestinal, pulmonary, otorhinolaryngological and neurological could also be involved [13].

In the early stages, the lesions are flat, erythematous, last about one week, occur in successive waves, sometimes itchy and hyperpigmented scars or edema could also be present. In severe forms, cutaneous manifestations may occur in the form of nodules, blisters, bubbles with bloody fluid or necrotic lesions [14].

The aim of this paper is to describe, for the first time in the literature to our knowledge, an association of two pathological entities – cutaneous leukocytoclastic angiitis (hypersensitivity vasculitis) and hypersensitivity pneumonia (extrinsic allergic alveolitis) – in a pigeon breeder, detailing the clinical findings and microscopic examination. In the same time, a review of the literature was performed for an appropriate inventory of similar or different findings.

☐ Case presentation

We present the case of a 44-year-old man, a pigeon breeder in a small family business, who was involved in all stages of this occupation, from feeding, treating, cleaning pigeons' cages on a daily basis, training them to participate in specific competitions as well as in competitions across Europe.

The patient was admitted to the Clinic of Rheumatology, Mureș Emergency County Hospital, Târgu Mureș, Romania, in November 2014, with pruritic purpuric eruption and lower limb paresthesia, dyspnea on exertion, polymyalgia, mixed polyarthralgias at the level of the tibiotarsal and bilateral radiocarpal joints.

From the patient's past medical history, we have found that he has been smoking for about 26 years, two packs

of cigarettes/day, being diagnosed with chronic obstructive pulmonary disease (COPD) eight years ago. He has also chronic venous insufficiency of the lower limbs, and one year ago was bitten by a tick and underwent neither a prophylactic antibiotic therapy, nor other laboratory investigations. There is no family history of lung diseases or vasculitis and the patient also has a good psychosocial status. The written consent of the patient was obtained and the approval from the Hospital Ethics Committee, as well.

Clinical findings

On admission, the anamnesis and clinical examination reveal a pruritic purpuric eruption at lower limb (Figure 1), paresthesia that appeared a year and a half ago, extended later at the level of the forearms and subumbilically, dyspnea on exertion, polymyalgia rheumatica (disease of the pelvic girdle), mixed polyarthralgias at the level of the tibiotarsal and bilateral radiocarpal joints.



Figure 1 – Appearance of the skin of the lower limbs on physical examination.

Diagnostic assessment

We used a wide spectrum of diagnostic methods to assess this interesting case.

Thus, the laboratory investigations revealed a biological inflammatory syndrome and leukocytosis, the immunogram (IgA, IgG, IgM) is in the normal range, positive antinuclear antibody (ANA). Antibodies (Ab) anti-double stranded deoxyribonucleic acid (dsDNA), anti-cardiolipin, antineutrophil cytoplasmic antibodies (ANCA), ANA profile [Ab anti-nuclear ribonucleoprotein (nRNP)/anti-Smith (Sm), anti-Sm, anti-Sjögren's syndrome-related antigen A (SS-A), anti-SS-B, anti-Ro-52, anti-topoisomerase I (SCL-70), anti-polymyositis–systemic sclerosis (PM-Scl), anti-antihistidyl transfer ribonucleic acid RNA {tRNA} synthetase (Jo-1), anti-centromere protein B (CENP-B), anti-proliferating cell nuclear antigen (PCNA), anti-dsDNA, anti-nucleosome, anti-histone, anti-ribosomal P protein, anti-mitochondrial M2 (AMA-M2)], Ab anti-*Borrelia* IgG, IgM, cryoglobulins, rheumatoid factor, liver, kidney samples, blood sugar, lipidogram, angiotensin converting enzyme, hepatic markers, ionogram, lupus anticoagulant – all within normal limits, electrocardiogram (ECG) – normal appearance.

In addition, a musculocutaneous biopsy was performed of left pretibial region. Microscopic examination on Hematoxylin–Eosin (HE)-stained serial sections emphasized diffuse thrombotic vasculopathy small vessel damage caused by angiocentric segmental inflammation: blood vessel with thickened walls and fibrinoid necrosis with

abundant perivascular inflammatory infiltrates in the superficial and deep dermis (Figure 2a). Striated muscle with bundles, in which the inequality in shape and size can be observed, angulated muscle fibers sometimes fragmented and with rare focal inflammatory cells substituting the fiber; body fat replacement between the muscle fibers; endomysial and perivascular fibrosis cell. Angiocentric inflammatory infiltrates largely composed of neutrophils, lymphocytes and macrophages/siderophages (Figure 2b). Extravasation of red blood cells and numerous neutrophils [visualized by anti-CD15 antibody and 3,3'-Diaminobenzidine (DAB) chromogen] are also found in the stroma (Figure 2c). The immunophenotype of inflammatory cells was evaluated using neutrophil, macrophage and T-lymphocyte markers (CD15, CD4

and CD68) in combination with EnVision™ FLEX/ Horseradish peroxidase (HRP) (Dako) secondary antibody and a DAB solution for the visualization of the above-mentioned antigens. The lymphocytes show predominantly CD4 phenotype (Figure 2d).

Some of the red blood cells are phagocytized by macrophages that turn into siderophages (Figure 2e). Hematoxylin/Periodic Acid-Schiff (H-PAS) staining reveals stratified epidermis with micro-erosion in the *stratum corneum*. Under basal membrane, thick collagen strips and collagen degeneration is observed; in the superficial dermis plexiform vessels, collagen degeneration of the wall and fibrinoid necrosis of the vascular wall and the presence of cellular debris and dermal fibrosis in thick collagen bands (Figure 2f).

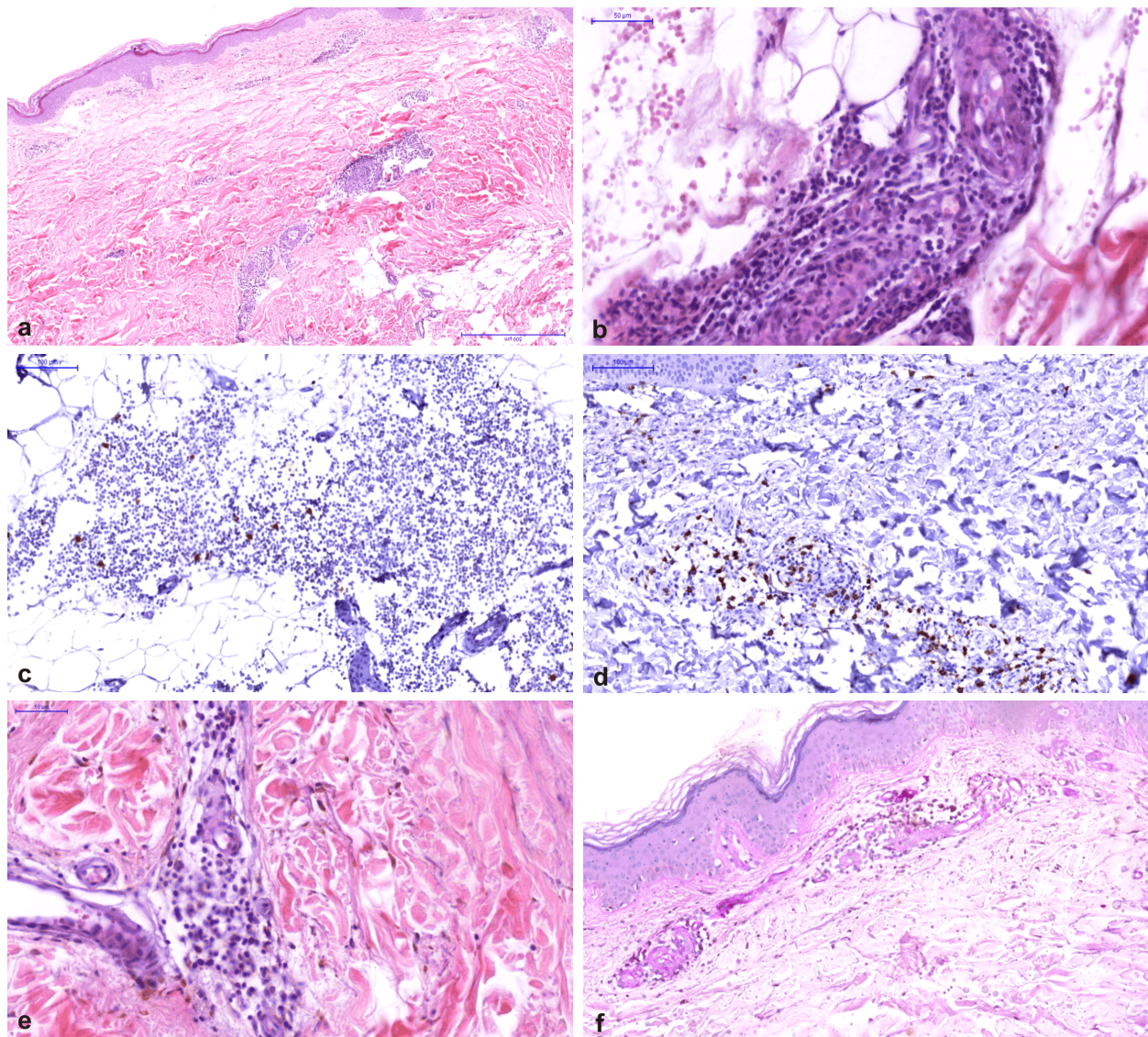


Figure 2 – (a) In the superficial and deep dermis, it can be noted fibrinoid necrosis and small vessel thrombotic vasculopathy (HE staining, $\times 40$); (b) Angiocentric mixed inflammatory cell infiltrate consisting of neutrophils, lymphocytes and macrophages/siderophages (HE staining, $\times 100$); (c) Extravasation of red blood cells and neutrophils – visualized by anti-CD15 antibody and DAB chromogen, are also present in the stroma (Anti-CD15 antibody immunomarking, $\times 50$); (d) CD4+ T-helper cells have been involved in the acute inflammatory process (Anti-CD4 antibody immunomarking, $\times 50$); (e) Some of the red blood cells are phagocytized by macrophages that turn into siderophages (HE staining, $\times 200$); (f) Stratified epidermis with micro-erosion in the *stratum corneum* – under the basal membrane is observed collagen degeneration, plexiform vessels, blood vessel with thickened walls and fibrinoid necrosis and dermal fibrosis in thick collagen bands (H-PAS staining, $\times 60$). HE: Hematoxylin–Eosin; CD: Cluster of differentiation; DAB: 3,3'-Diaminobenzidine; PAS: Periodic Acid–Schiff.

The morphological aspect of the diffuse lesions and the immunophenotype of the inflammatory cells confirm the histopathological diagnosis of leukocytoclastic angiitis.

Thoracic CT scan shows areas of ground glass opacity and fibrotic bands, consistent with HP.

Full body-plethysmography, including diffusing capacity of the lung for carbon monoxide (DLCO) showed a mixed ventilatory dysfunction with mild obstruction of the small airways and an increased raw, with a normal DLCO. Electroneuromyography was also carried out, showing a normal appearance.

The patient was also referred to a multidisciplinary team, for differential diagnosis, considering the patient's complaints and initial clinical evaluation. Thus, the dermatologist diagnosed the patient with vascular purpura (edematous purpuric vasculitis). The cardiologic examination (specialized clinical examinations, ECG, echocardiography) reveals no pathological evidence, thus excluding a heart-related cause of dyspnea. The specialized angiology investigation (including a venous Doppler ultrasound) highlights the following aspects: primary varicosity of the great saphenous vein and bilateral tributary branches without any thrombotic changes or post-thrombotic syndrome (suspected as a possible cause of leg ulcers) as well as chronic venous insufficiency – stage C4 and vasculitic purpura. Lung examination confirmed COPD, reticular interstitial fibrosis and extrinsic allergic alveolitis.

During admission, therapeutic interventions consisted in corticosteroids (Prednisone 15 mg per day) with a considerable clinical improvement after a week. On discharge from the Hospital, the patient was advised to avoid further exposure to allergens (activities related to pigeon breeding and smoking cessation). Five months later, the patient stops using corticosteroids and two more months later he returns to the Hospital with an exacerbation of the paresthesia and pain in the lower limbs as well as perimalleolar necrotic lesions (Figure 3).



Figure 3 – Necrotic perimalleolar lesion (left leg) after discontinuation of cortisone treatment.

The patient was readmitted to Hospital and he was given minipulses of corticosteroids (Methylprednisolone 125 mg for five days). He was discharged on chronic treatment with corticosteroids and Colchicine (2×0.5 mg daily), being advised again to avoid further exposure to avian debris and physical therapy program, with favorable evolution on the follow up visits.

The final follow-up visit took place in February 2017 (28 months later), with a significant improvement of the

respiratory complaints and the appearance of the preceding skin lesions (only a mild hyperpigmentation, without open lesions or local pain). During this time, the patient has drastically reduced contact with the pigeons, being involved only in their training and participation in competitions, not taking care of their feeding, treatment and cage and annexes cleaning, following both a respiratory recovery therapy and medical treatment as prescribed.

Based on the clinical picture and the laboratory findings (confirmed by the pathological examination), we could established the association of two pathological entities, namely hypersensitivity (leukocytoclastic) vasculitis (clinically sustained by the pruritic purpuric eruption at the level of the lower limbs, continuous exposure to allergens, skin examination and confirmed by the musculo-cutaneous biopsy) and extrinsic allergic alveolitis (based on the occupational exposure, respiratory symptoms and the CT findings).

✚ Discussions

According to our knowledge, this is the first case reported in literature that clearly describes and proves through pathological examination, the co-existence of hypersensitivity (leukocytoclastic) vasculitis with extrinsic allergic alveolitis caused by occupational exposure in a pigeon breeder.

There are many case reports in the specific literature describing isolated hypersensitivity pneumonia in bird fanciers, as well as many case reports describing hypersensitivity vasculitis, especially after different drug administration, but only a few depicting the association of these two pathological conditions. One of these case reports in an interesting hypersensitivity syndrome associating cutaneous and systemic manifestations following Azathioprine therapy [15].

The diagnosis of allergic alveolitis is always a challenge because it can arise in the context of other lung diseases as well as other clinical symptoms occurring as a result of exposure to organic substances [16]. The first pulmonary manifestations of hypersensitivity were described in farmers as a result of exposure to microbial antigens (actinomycetes) present in moldy hay [17].

In our case, the diagnosis of extrinsic allergic alveolitis was based on the respiratory symptoms and radiological evidence of diffuse lung disease, considering specific occupational exposure, as per a diagnosis protocol used at Mayo Clinic in a series of 85 cases [18]. The peculiarity of our case is represented by the association of alveolitis with COPD, the patient being a former smoker (two packs of cigarettes a day for 26 years until the first hospitalization). A limitation of this study is represented by the lack of the BALF analysis used to identify cellularity, but this criterion is not standardized, the BALF analysis being a pleomorphic one in different studies and the patient has a certain occupational exposure and reacted very well to the corticosteroid therapy.

Cutaneous leukocytoclastic vasculitis is characterized by inflammation of small superficial dermal vessel walls but it may also involve larger and deeper vessel. The cornerstone in establishing the diagnosis of hypersensitivity (leukocytoclastic) vasculitis was represented by the histo-

pathological examination. In our case, all of histological criteria were present: fibrin deposition, fibrinoid necrosis, neutrophil infiltration of the vessel walls, fragmented neutrophil nuclei and extravasated erythrocytes. To characterize the inflammatory infiltration, we examined the immunophenotype of inflammatory cells, and found that CD15+ leukocytes and CD4+ T-lymphocytes constituted most of the cellular elements that infiltrated the damaged vessels in the early stage of disease, these findings suggest, that not just granulocytes but CD4 positive T-helper cells have been involved in the acute inflammatory process, expressing pro-inflammatory cytokines. In this context, they might represent a potential therapeutic target in leukocytoclastic vasculitis. These findings are also partly similar with those of Kawakami [19]. Moreover, just as in Wall *et al.* description [20], we described and highlighted rash as the main symptom in diagnosing vasculitis, which should be considered for future cases assessments.

Our microscopic findings are also similar with those presented by Roberts & Chévez-Barrios in a case of cutaneous vasculitis associated with Levamisole-adulterated cocaine [21].

Although in our patient's case pulmonary symptoms appeared several years before skin lesions showed up, it is possible that the initial pulmonary suffering was due to COPD (heavy smoker patient), being overlapped by extrinsic allergic alveolitis as a result of specific occupational exposure (avian proteins).

According to the literature, it is known that pulmonary manifestations are sometimes involved in vasculitis, presenting aspects of extrinsic allergic alveolitis [22]. It is also well known that in extrinsic allergic alveolitis there is associated necrotizing small vessel vasculitis [23]. It is therefore interesting that in this patient's case impaired multiorgan and multisystem type vasculitis is confirmed which can also be associated with other disorders as hepatitis C, cancer or other systemic autoimmune diseases [24] that imply a very closed and particular medical follow-up of this patient.

The association between the clinically revealed lung disease and the specific manifestations of an autoimmune rheumatic disease made it possible to diagnose the patient, which emphasizes the role of the multidisciplinary teams, especially the collaboration between a specialist in respiratory diseases and rheumatologist, as also analyzed by Ferri *et al.* [25].

Considering isolated and mild vasculitis, the patient could have a good prognosis, with self-limitation of the lesions [9], but our case is a complicated one, therefore corticosteroid treatment had a key role, which has been demonstrated by the patient's relapse after ending the treatment on his own initiative. The positive response when resuming the corticosteroid therapy reiterates once again this fact.

Similar evolution was found by Mohamed, who describe a case report of hypersensitivity vasculitis in a young adult, complicated with avascular necrosis of both hip joints, mentioning that patients was advised to stop the corticosteroid treatment too early [26].

The patient's outcome might be influenced by smoking, both in terms of COPD worsening as well as the effects

of smoking on blood vessels, the role of smoking in the development and aggravation of extrinsic allergic alveolitis being also evoked in Patel *et al.* researches [27].

There are also studies which demonstrate that smoking may decrease serum antibody response to inhaled antigen [2], this could count for a „protective” role in our patient. Anyway, our patient underwent an intensive respiratory recovery treatment, which contributed to his functional and clinical improvement. Among the effective and useful kinetotherapeutic means used in respiratory therapy, we highlight relaxing postures, which facilitate breathing in sitting and standing positions [28].

Multi-organ impairment also affects the patients' quality of life, which should be taken into consideration [29] in the clinical management of the patient.

Given the multi-organ impairment, a comprehensive and multidisciplinary approach of a patient with systemic vasculitis should always be required, due to the possibility of a poor prognosis [30].

The best outcome is offered by early recognition and consistent prevention of further exposures (what we consider to be a must) along with corticosteroid therapy [31], which was decisive for our patient's evolution.

While pulmonary manifestations, such as extrinsic allergic alveolitis as an occupational disease is commonly reported in the specialty literature, there are few descriptions of systemic vasculitis in such exposures. In this regard, Mulloy [32] described manifestations of systemic vasculitis in a worker's case occupationally exposed to free crystalline silica. Lane *et al.* [33] also highlights that systemic vasculitis has been associated with exposure to particulate silica (*e.g.*, quartz, granite, sandstone) and grain dust. Lane also stated that an exposure to metal and welding fumes has been reported to increase the risk of pulmonary vasculitis. The same author also considered that there has been conflicting evidence regarding a link between occupational exposure to hydrocarbons (*e.g.*, paints, glues) and Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA).

Hypersensitivity (leukocytoclastic) vasculitis can be idiopathic in most cases, but it may also occur be triggered by an infection, medication, connective tissue disease or a paraneoplastic context [34]. Half of the cases are idiopathic ones [12, 35], while 10% of cases of leukocytoclastic vasculitis become chronic or recurrent [36].

In our case, hypersensitivity (leukocytoclastic) vasculitis occurred after an occupational exposure and the diagnosis was decided based on the musculocutaneous biopsy.

As secondary prevention, it is always important to ban further exposure to allergens (microbial, viral and proteic substances) in such cases. Persistent symptomatology and its exacerbation the occurrence of perimaleolar necrotic skin lesions, arisen as a result of chronic venous insufficiency were due to the fact that exposure to allergens was not interrupted and corticosteroid therapy was stopped in our case.

Due to the necessity of a histopathological examination, the diagnosis of hypersensitivity (leukocytoclastic) vasculitis is difficult to be determined. This obstacle leads implicitly to underdiagnose this condition. For avoiding this, we suggest that leukocytoclastic vasculitis (angiitis) should always be taken into consideration as a differential

diagnosis in all cases of suspicious skin lesions, especially in those with palpable purpura associated with respiratory symptoms and specific occupational exposure.

Apart of the occupational exposure of our case, it is important to emphasize the importance of drugs frequently associated with vasculitis, such as Propylthiouracil, Hydralazine, colony-stimulating factors, Allopurinol, Cefaclor, Minocycline, D-Penicillamine, Phenytoin, Isotretinoin, Methotrexate, with an important percentage of fatalities (10% of all published cases), mainly due to multiple organ and systems failure [37].

Thus, clinicians need to be aware of both, occupational and drug-induced systemic hypersensitivity to enable prompt diagnosis and treatment.

✉ Conclusions

Extrinsic allergic alveolitis may be associated with cutaneous leukocytoclastic angiitis within the same clinical context of exposure to specific occupational agents. Long-term corticosteroid therapy has been proved to be useful in preventing relapses and in improving the patient's clinical status in associating cutaneous leukocytoclastic angiitis with extrinsic allergic alveolitis. Considering the findings of our case report and literature review, we may suggest the inclusion of systemic vasculitis on the list of recognized occupational diseases. Biopsy and immunohistochemistry methods could be proposed as a valuable diagnostic tool in associating cutaneous leukocytoclastic angiitis with extrinsic allergic alveolitis, if suggestive occupational exposure exists.

Conflict of interests

The authors declare no conflict of interests and they would like to express special consideration to the patient for his attitude, promptitude and for the informed consent. All the authors have read and approved this manuscript.

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