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CASE STUDY

Eosinophilic lung disease associated with *Candida albicans* allergy

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Eosinophilic lung disease associated with Candida albicans *allergy. A. Pacheco, M. Cuevas, B. Carbelo, L. Máiz, M.J. Pavón, I. Pérez, S. Quirce. ©ERS Journals Ltd 1998.*
ABSTRACT: A significant number of cases of chronic eosinophilic pneumonia remain idiopathic in spite of a comprehensive search of associated causes. This study reports a patient with a classical clinical presentation of chronic eosinophilic pneumonia and peripheral blood eosinophilia in whom selective sensitization to *Candida albicans* was demonstrated. This yeast was present in the bronchoalveolar lavage culture and specific serum immunoglobulin (Ig)E and IgG against *C. albicans* were found in the patient's serum. Levels of these specific immunoglobulins diminished with corticosteroid treatment and increased coinciding with a new outbreak of symptoms after lowering the dosage of corticosteroids. To the author's knowledge, this is the first case described of chronic eosinophilic pneumonia associated with sensitization to *C. albicans*. Evaluation of allergy to *C. albicans* should be performed in chronic eosinophilic pneumonia before labelling cases as idiopathic.
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There are few references in the literature about the role of *Candida albicans* (CA) in eosinophilic lung disease. Asthma related to immunoglobulin (Ig)E-mediated allergy to CA [1] as well as allergic bronchopulmonary candidiasis has been described [2], but the implication of CA in chronic eosinophilic pneumonia has not been previously reported. In this paper we report on a patient in whom chronic eosinophilic pneumonia developed and levels of specific anti-CA IgE in the serum paralleled the clinical course of the disease.

Case report

A 43 yr old female was admitted to the hospital reporting symptoms of an intermittent fever of 38°C, nocturnal sweat, chills, dyspnoea, dry cough and malaise, with a weight loss of 4–5 kg during the last 45 days. No improvement was observed despite several courses of amoxicillin and cephalosporin being given. These symptoms were reported by the family because she had had severe mental deficiency since 11 months of age, as a result of severe traumatic head injury. The physical examination revealed a respiratory frequency of 32 breaths·min^{-1} and crackles in both pulmonary bases. The blood count detected 2,400 eosinophils·mm^{-3}. The chest radiograph showed a patchy, nonsegmental infiltrate of peripheral distribution in the upper right lobe. This radiological pattern changed its localization at 48 h, inside the same lobe (fig. 1). There was no previous history of asthma, ingestion of drugs or inhalation of fumes. Although bronchoscopy was indicated, transbronchial biopsy was not possible owing to a lack of collaboration. Bronchoalveolar lavage (BAL) showed a predominant fraction of 40% eosinophils in cytological analysis, with 57% macrophages and 3% lymphocytes. CA was the only fungus isolated from the BAL culture.

The serum rheumatoid factor, anti-nuclear antibody, c-anti-neutrophil cytoplasmic antibody (ANCA) and p-ANCA were all negative. Negative skin-prick test responses were obtained to grass, weed and tree pollens, house dust mite and dog and cat dander. Four examinations of stools for ova of parasites at different times were negative. Total serum IgE and antifungus specific IgE were determined by a fluoroenzyme immunoassay (CAP System; Pharmacia Diagnostics, Uppsala, Sweden) and the results expressed in kU·L^{-1}. Specific anti-fungus IgG was assessed by an enzyme-linked immunosorbent assay (ELISA) method as described previously [3] and the results were expressed in optical densities (OD). A value at least twice over the negative control (0.6 OD) was considered positive. Serum immunological assays were carried out for seven fungi: *Mucor* spp., *Penicillium* spp., *Alternaria alternata*, *Aspergillus fumigatus*, *Cladosporium herbarum*, *Trichophyton* and CA, and also for *Echinococcus granulosus* and *Toxocara canis*. A positive result was only detected for anti-CA IgE: 32.7 kU·L^{-1} (normal <0.35 kU·L^{-1}). The ELISA deter-mination of anti-CA IgG showed a titre of 2.3 OD. Total serum IgE was 1,430 kU·L^{-1}. Leukocyte histamine release test using peripheral blood was performed as described previously [4] and a strongly positive response to CA was observed with maximum histamine release up to 39% (normal value <10%).

A good clinical and radiological response was obtained after therapy with 0.5 mg·kg body weight·day^{-1} of methylprednisolone for 1 month. The titre of anti-CA IgE diminished up to 11.2 kU·L^{-1} at the end of this period. The dose of corticosteroids was then tapered from 2.5 mg·day^{-1} per week to 10 mg·day^{-1} as a maintenance dose. After 2 months of therapy with methylprednisolone, 10 mg·day^{-1}, symptoms of cough, malaise and nocturnal sweat reappeared but without infiltrates on the chest radiograph. This recidive

was associated with a rise in titre of anti-CA IgE to 47.6 kU·L^{-1}. The dose of corticosteroids was increased to 0.5 mg·kg body weight·day^{-1}, with clinical improvement within a few days, together with a decrease in levels of anti-CA IgE to 10.2 kU·L^{-1}. Time courses of specific anti-CA IgE and total serum IgE levels are shown in figure 2.

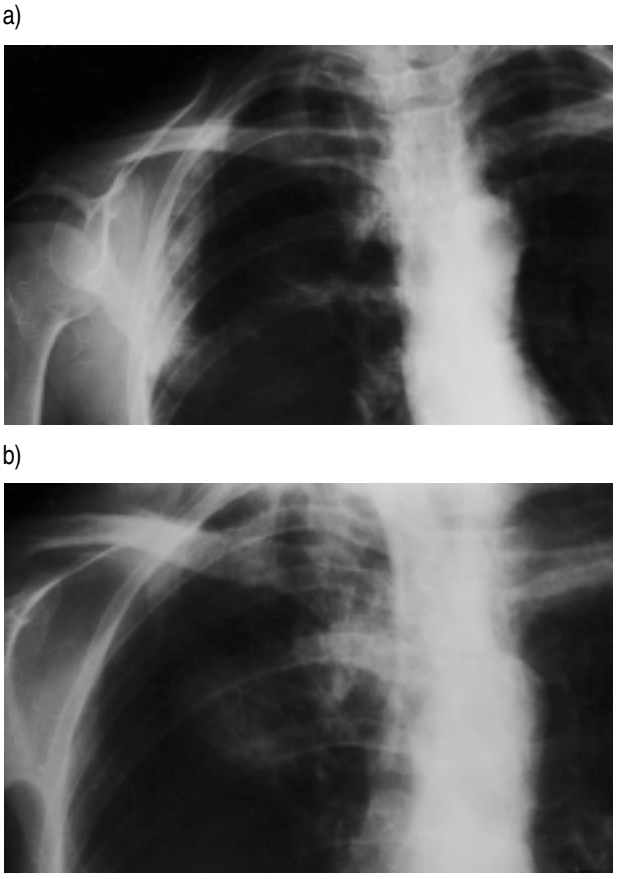

Fig. 1. – Chest radiograph showing a peripheral infiltrate in the upper right lobe (a), which migrated 48 h later (b).

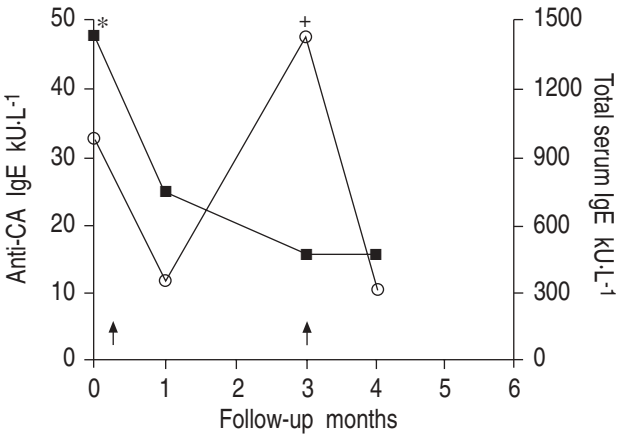

Fig. 2. – Time course of levels of specific anti-*Candida albicans* (CA) immunoglobulin (Ig)E (○) and total serum IgE (■). Clinical exacerbations of the disease coincided with a significant increase in anti-CA IgE but not in total serum IgE. ↑: Therapy with methylprednisolone 0.5 mg·kg body weight·day^{-1}. *: pulmonary infiltrate; $^{+}$: recurrence of symptoms.

Discussion

Eosinophilic lung diseases vary widely in severity, from benign asymptomatic episodes which may or may not be associated with a precipitating sensitizing agent, to persistent or recurrent pulmonary disease which is associated with high fever, dyspnoea and weakness and may prove rapidly fatal. Chronic eosinophilic pneumonia (CEP) has a more protracted clinical and radiographic course than Loeffler's syndrome. In contrast to simple and tropical eosinophilic pneumonia, CEP is likely to require lung biopsy for diagnosis [5]. However, in the appropriate clinical and radiographic setting, the diagnosis has occasionally been confirmed by needle biopsy or aspiration cytology [6]. It also appears that BAL and the presence of numerous eosinophils in the BAL fluid can establish the diagnosis, whether or not transbronchial biopsy is carried out as well [7]. Radiographically, the infiltrates may be transient and they tend to resolve and reappear in the same or a distinct location [8]. Peripheral blood eosinophilia is usually present and elevated serum IgE levels have been reported during the acute phase, which return to normal during remissions, with or without treatment, suggesting that eosinophilic pneumonia may be an IgE-mediated hypersensitivity pneumonitis [9].

A variety of agents is known to cause CEP, the main ones being drug toxicity, most notably due to bleomycin, nitrofurantoin, para-aminosalicylic, L-tryptophan and sulfonamides; fungal hypersensitivity, especially to *Aspergillus*; and parasitic infestations due to various organisms, *e.g.* filaria. Inhalation of substances such as crack or cocaine has also been implicated. In many cases, however, despite thorough evaluation, the disease remains idiopathic [10]. Recently, *Alternaria alternata* has been reported as a cause of CEP [11].

Allergic bronchopulmonary entities such as allergic bronchopulmonary aspergillosis are a well-known cause of eosinophilic lung disease. A similar immunological reaction (with specific IgE and IgG) has been reported less often to other fungi, including CA [2]. Since the present patient did not have asthma symptoms, the diagnosis of allergic bronchopulmonary candidiasis is very unlikely. Only a few studies have reported on type I allergic reactions to CA. Gumowski *et al.* [1] reported that in 86% of 53 pat-ients with asthma and a positive radioallergosorbent test (RAST) to CA, a correlation between CA IgE and the provocation test with CA was found. In the present patient, however, the absence of asthma, the protracted clinical course and the peripheral radiological infiltrates strongly suggest the diagnosis of CEP. To the author's knowledge, the association between CEP and allergy to CA has not been reported previously, probably owing to an unsuspected relationship between these entities.

Since *Candida albicans* was isolated from bronchoalveolar lavage culture and selective hypersensitivity to this fungus was demonstrated by immunological parameters, which fluctuated following the clinical course of the disease, an aetiological role for *Candida albicans* is suggested. Anti-*Candida albicans* immunoglobulins E and G may participate in the physiopathology of chronic eosinophilic pneumonia by inducing eosinophil-mediated inflammatory reaction. Therefore, the investigation of hypersensitivity to *Candida albicans*, and perhaps to other fungi, may be necessary in patients with suspected

chronic eosinophilic pneumonia before labelling this disease as idiopathic.

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