Atopy and sarcoidosis – What is the relationship between these conditions?

Atopia e sarcoidose – Que relação entre as duas entidades?

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ABSTRACT

Background: The relationship between diseases associated with Th1 and Th2 type immune responses remains unclear, namely the influence of Th2 responses on the evolution of diseases characterised by Th1 deviation. **Case report:** Thirty year-old female with allergic rhinoconjunctivitis to grass pollen; no previous respiratory symptoms; past episode of erythema nodosum. After four years of specific immunotherapy she started wheezing and dyspnoea. Lung function tests showed a restrictive syndrome; chest CT revealed mediastinal lymphadenopathies and small parenchymal nodules, and bronchoalveolar lavage showed lymphocytic alveolitis with a predominance of $CD4^+$ cells. These findings were suggestive of sarcoidosis. **Discussion:** Previous studies suggest a lower prevalence of atopy in patients with sarcoidosis, despite a better sarcoidosis prognosis in patients with atopy. However, the current understanding of the pathogenesis of sarcoidosis questions these data, making prospective studies needed to better clarify these issues.

Keywords: Atopy, diagnosis, sarcoidosis.

RESUMO

Introdução: *A relação entre patologias associadas a respostas imunológicas de tipo Th1 e Th2 permanece por esclarecer, nomeadamente a influência de respostas Th2 na evolução de patologias caracterizadas por desvios Th1.* ***Caso clínico:*** *Mulher de 30 anos com rinoconjuntivite alérgica a pólenes; sem queixas respiratórias e sem antecedentes relevantes, além de episódio prévio de eritema nodoso. Após 4 anos de imunoterapia específica, iniciou pieira e dispneia, a avaliação funcional respiratória revelou síndrome restritiva, a tomografia computorizada do tórax adenomegalias hilomediastínicas e nódulos pulmonares infracentimétricos e o lavado broncoalveolar alveolite linfocítica com predomínio de células CD4+, achados sugestivos do diagnóstico de sarcoidose.* ***Discussão:*** *Estudos prévios sugerem menor prevalência de atopia em doentes com sarcoidose, apesar de um prognóstico mais favorável da sarcoidose em doentes atópicos. No entanto, o actual conhecimento da fisiopatogenia da sarcoidose questiona estes dados, sendo necessários estudos prospectivos para melhor esclarecimento dos mesmos.*

Palavras-chave: *Atopia, diagnóstico, sarcoidose.*

INTRODUCTION

Epidemiological studies have shown that atopy, a T helper (Th) 2 lymphocyte-mediated response, impacts on the course and prognosis of several Th1--mediated diseases via counter-regulatory immune mechanisms[1]. The role of atopy in sarcoidosis, a Th1-mediated disease, remains to be elucidated: there is insufficient clinical evidence on the type of relationship the two conditions share.

CASE REPORT

We describe a female patient, aged thirty, Caucasian, nonsmoker, referred to an allergology and clinical immunology appointment at the Hospital de São João in 2005 for a five-year history of nasal symptoms (runny nose, sneezing, blocked and itchy nose), ocular symptoms (itching and tearing) and ear and throat symptoms (oropharyngeal and ear itch), mainly in Spring/Summer. She had no prior respiratory symptoms, namely dyspnoea, cough or chest pain.

Patient had a family history of asthma and relevant past episode of skin lesions, suggesting erythema nodosum, in 2002 for which she took oral corticosteroids (dose and treatment length unknown). She currently works in a bakery and had previously worked in a dressmaker's. The nasal and ocular symptoms are not connected to the patient's current and previous places of employment and were worse in Spring/Summer. Initial examination, particularly anterior rhinoscopy, revealed lower turbinate hypertrophy and deviation of the nasal septum convexity to the right.

Diagnostic work-up revealed sensitisation to grass and tree pollen in skin tests using aeroallergen extracts and serum dosing of specific IgE to grass pollen (12.50), *Betula verrucosa* (0.47) and *Olea europeae* (0.53) (negative<0.35kU/L). Basal spirometry suggested restrictive syndrome, and bronchial challenge test was negative. Fractional exhaled nitric oxide was 6.5 ppb. Plethysmography revealed slight restrictive ventilatory syndrome, and the remaining parameters were within normal ranges.

Due to the lack of respiratory symptoms (dyspnoea, wheeze, cough, exercise intolerance), no other exams to assess restrictive syndrome were performed. A diagnosis

Table I. Lung function course

	Units	Reference	2006		2010	
			Absolute	% prev	Absolute	% prev
FVC	Litres	3,55	2,55	72	2,27	66
FEV_1	Litres	3,10	2,31	75	1,98	66
TI	%	84	91		87	
FEF 25-75%	Litres/s	4,07	3,89	95	3,20	81
TLC	Litres	4,77	3,44	72	3,08	65
RV	Litres	1,30	0,88	68	0,80	59
DLCO	mL/mmHg/min	27,3	17,10	63	7,00	79
DLCO/AV	mL/mmHg/min/L	5,72	6,47	113	2,53	135

FVC, forced vital capacity; FEV1, forced expiratory volume in one second; TI, Tiffeneau index; FEF, forced expiratory flow; TLC, total lung capacity; RV, residual volume; DLCO, carbon monoxide diffusing capacity; DLCO/AV, carbon monoxide diffusing capacity corrected for alveolar volume

of moderate-severe persistent allergic rhinoconjunctivitis was made and treatment prescribed. This consisted of avoiding the trigger allergens, pharmacological treatment with topical nasal corticosteroids, ocular and oral anti-histamines and later subcutaneous specific immunotherapy (SIT) using polymerized 100% grass pollen extract. This latter was continued for four years and there no adverse reactions were seen.

Although most symptoms had a favourable clinical course, the patient maintained persistent and incapacitating nasal obstruction which led to septoplasty and turbinectomy, performed in April 2009. There was clinical (fatigue, wheeze and dyspnoea) and functional (Table I) worsening in June 2010. Teleradiography abnormalities led to computerised tomography being performed and this revealed multiple mediastinal lymphadenopathies and small parenchymal nodules (Figure 1). Analysis showed peripheral eosinophilia (640 mm^3) and elevated *angiotensin-converting-enzyme* (72, normal<52). Viral biochemical markers (BHV, CHV, HIV) and protein electrophoresis had no changes. Bronchoalveolar lavage (BAL) and endobronchial ultrasound with real-time guided transbronchial needle aspiration (EBUS-TBNA) were also performed. Microbiological analyses (bacteriological, mycological, direct and cultural mycobacteriological) and BAL cytology and biopsy were negative. Total BAL cell count was normal, and the differential showed intense lymphocytosis (cell count $0.8x10^5$/mL; macrophages 50.4%; lymphocytes 42.6%; neutrophils 4.6%; eosinophils 0.0%; mast cells 0.2%), with predominance of T $CD4^+$ lymphocytes associated to a high CD4/CD8 ratio (3,8).

The clinical picture and imaging described, associated to changes in the differential BAL count (lymphocytosis with CD4/CD8 > 3.5) fitted with a diagnosis of sarcoidosis. The patient was referred to a diffuse lung disease appointment and is currently under three-monthly clinical, functional and imaging follow-up. There has been no indication as of yet to begin treatment directed at sarcoidotic pathology.

DISCUSSION

Sarcoidosis is a multisystemic disease of unknown cause and characterised pathologically by the existence of noncaseous granulomas in the affected organs[2]. Sarcoido-

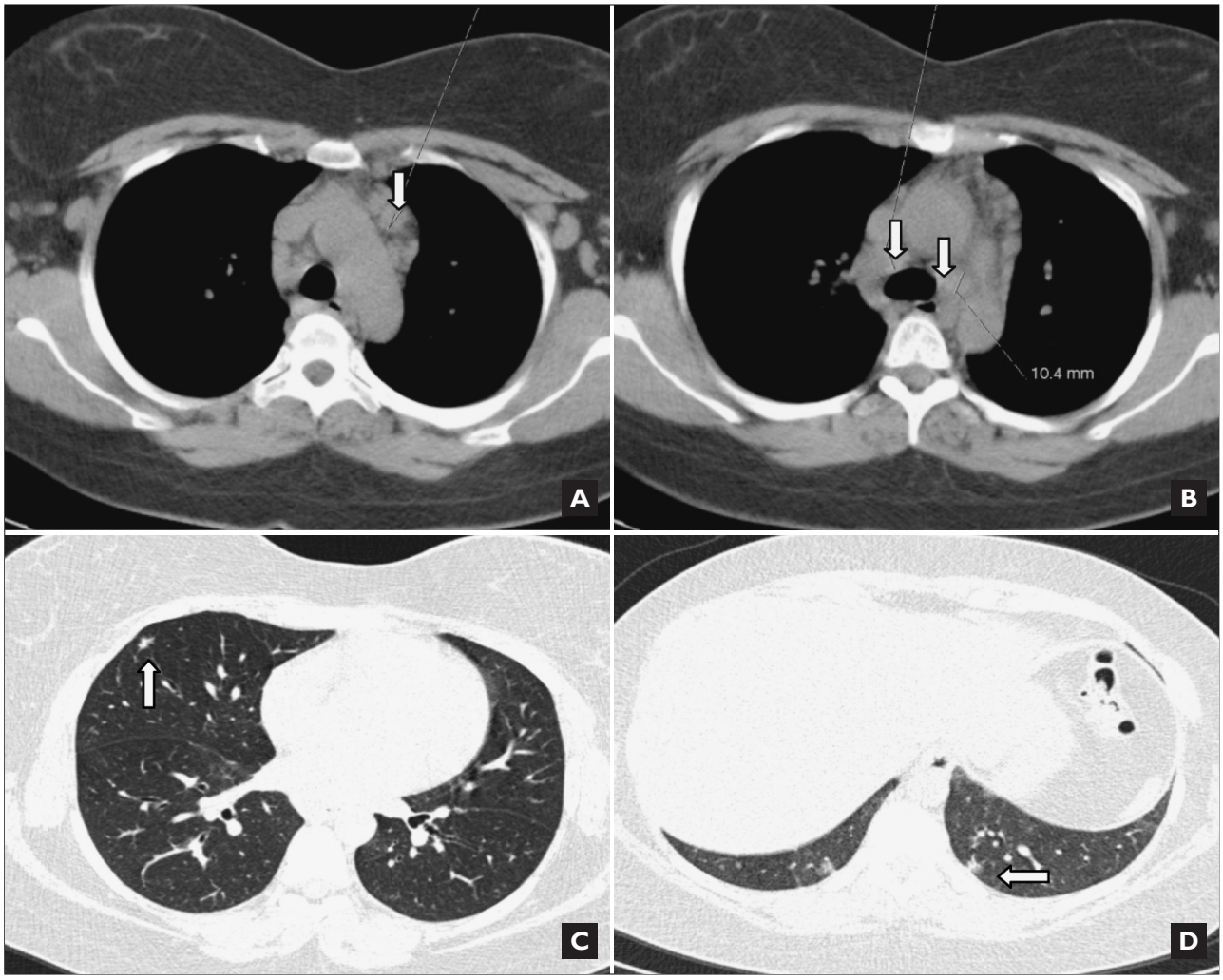

Figure 1. High resolution chest CT: multiple mediastinic adenomegalies (a, b), the largest with 13 mm short axle in pre-aortic topography (a); some random-distribution small peripheral nodules, some with ground-glass halo and poorly defined limits (c, d).

sis has an incidence ranging from 1-40/100000 cases and frequently affects young adults (peak incidence 20-29 years), mainly females[2]. Its aetiology is still unknown, with the most likely hypothesis that it is the result of susceptible individuals being exposed to an environmental agent or agents[3]. Factors such as family aggregation, prevalence, clinical and severity varying according to race and region, and association to determined genetic polymorphisms suggestgenetic predisposition.[2,4]. In terms of environmental factors, questions have been raised over the role of microorganisms (virus, bacteria such as *Propionibacterium acnes* and *Mycobacterium tuberculosis*), inorganic (aluminium, talcum) and organic particles (pollens)[2]. We highlight the history of allergic rhinitis with sensitisation to pollen in this case.

Studies into the rate of atopy in sarcoidosis patients and atopy's potential effects on sarcoidosis's clinical spectrum and course have been published[5-7]. Kokturk *et al.*

showed that the rate of respiratory allergy in a Turkish population of 41 sarcoidosis patients was lower than in the general population (5% *versus* 25%)[5]. Sarcoidosis is pathogenically characterised by a Th1 lymphocyte--mediated immune cellular response and atopy by a Th2 and specific-IgE humoral response[2,8], mechanisms which could explain this epidemiological difference. However, a recent report cast doubt on this dichotomy: Wilsher *et al.* determined a rate of atopy of 34% in 123 sarcoidosis patients, similar to that previously reported for the general population[7].

The clinical presentation of sarcoidosis varies, depending on the organ(s) involved and the intensity of the granulomatous inflammation. It could be asymptomatic or course with constitutional and/or organ-specific symptoms. As the chest is affected in over 90% of cases, sarcoidosis frequently courses with dyspnoea, wheeze, cough and chest pain, and can be associated with various lung function changes (restriction, obstruction, bronchial hyperresponsiveness – 20%), and specific radiological changes (stage 0: normal; stage I: hilar adenopathies; stage II: hilar adenopathies and changes in the pulmonary parenchyma; stage III: changes in the pulmonary parenchyma, no adenopathies; stage IV: fibrosis)[2]. In this case, the age, clinical, constitutional and respiratory signs and the radiological evidence of adenopathies raised several diagnostic possibilities, such as sarcoidosis, lymphoma or infection. We stress the importance of bronchoscopy in sarcoidosis to allow BAL and transbronchial biopsies, iterative bronchial biopsies and transbronchial needle aspiration to be performed, which increase diagnostic yield and consequent diagnostic differential[2,8]. In this case, the BAL cell study showed lymphocytic alveolitis with CD4/CD8 > 3.5, reflecting the predominance of T $CD4^+$ lymphocytes, characteristic of sarcoidosis[2,8].

In line with earlier published studies, an increased CD4/CD8 ratio associated to typical clinical and imaging characteristics is highly suggestive of sarcoidosis, having specificity scores of 93-96%, obviating need for a histological confirmation in around 40-60% of cases[2]. It is crucial to rule out lymphoproliferative pathology, and we performed an EBUS-TBNA adenopathy study. This is a recent, minimally invasive and safe technique associated to increased diagnostic yield in sarcoidosis (90--96%)[9]. The diagnosis of thoracic sarcoidosis was made. There was no sign of other organs (kidney, liver, heart, uveitis) affected.

The natural course of sarcoidosis varies, and spontaneous remission is possible (stage I 55-90% and II 40-70%), as is progress to chronic stage or recurrence after treatment[2]. Since referral, the patient has been symptom free and stable radiologically (stage II) and in terms of lung function, meaning spontaneous remission could be possible; hence no treatment was started. On the other hand, patient's prior history of erythema nodosum raises the possibility of this being a case of recurrent sarcoidosis which went undiagnosed.

Hattori *et al.* describe how in a Japanese population of 134 sarcoidosis patients the atopic patients had a less frequent chest involvement and that atopy was associated to a better prognosis of sarcoidosis, independent of patient gender, age and thoracic or extra-thoracic lesions[6]. Here, atopy could be considered a factor of a good prognosis. However, in light of both conditions' pathogenesis, we question this association. Sarcoidosis has as its base a Th1--mediated immune response, and it is thought that its unfavourable course has at its root a change in this response to a Th2 response, with a different cytokine pattern (interleukins 4, 5, 6 and 10), which stimulate the proliferation of fibroblasts and production of collagen, leading to fibrosis[3]. Thus, if atopy has as its base a Th2-mediated immune response, which leads to evolution to advanced stages of sarcoidosis, how can this be associated with a better disease prognosis?

On the other hand, Jundi *et al.* questioned the role of SIT in sarcoidosis in their description of three cases of atopic patients who underwent SIT to pollen and house dust mites with a later diagnosis of sarcoidosis 22, 1 and 4 years after ending SIT[10]. These authors speculate as to

whether SIT could have uncovered undiagnosed subclinical forms of sarcoidosis and thus SIT's possible role as a causal agent of sarcoidosis, or whether this was a mere temporal coincidence[10].

CONCLUSION

In describing this case, the authors seek to pose questions on the possible link between atopy and sarcoidosis. The answers remain to be elucidated in the face of the scientific literature data here detailed. The majority is descriptive studies of small populations and limited geographical areas, which in itself could impact on the prevalence of both conditions. Further, their distinct pathology throws doubt on the prognostic role of atopy in sarcoidosis. Descriptions of more clinical cases and case series or running prospective studies with populations from several geographic areas with different rates of atopy and sarcoidosis but which use similar methodology, including the definition of atopy, could answer some of the questions raised by this case study.

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