

## CASE REPORTS

# Sarcoidosis following specific immunotherapy: more than just coincidence?

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### ABSTRACT

Although not yet clear, the etiology of sarcoidosis may be linked to seasonal, environmental and genetic factors; mycobacterial or other infections. To the best of our knowledge there is no data suggesting any connection between the onset of sarcoidosis and specific allergen immunotherapy in the medical literature. During the 11-year period between 1993 and 2005, a total of 91 sarcoidosis cases have been diagnosed at our institution. Out of these, here we present 3 cases of de novo sarcoidosis occurring after receiving specific immunotherapy (SIT) at the same institution (two of which had acquired the disease in Sweden where they had resided for a short time). We suggest that sarcoidosis may occur in patients following (SIT) probably via an abnormal immunological host response to an unknown antigenic trigger.

**Key words:** Etiology. Sarcoidosis. Specific Immunotherapy.

### INTRODUCTION

Although not yet clear; acute sarcoidosis may be considered to be related to some seasonal, environmental, genetic and infectious factors. Specific immunotherapy (SIT) has been known to cause some side effects as aggravation of connective tissue and autoimmune diseases, and allergic reactions<sup>1</sup>. However, to the best of our knowledge there is no data suggesting any connection between sarcoidosis and SIT. Here we present 3 atopic patients who had received SIT in the same institution and had had sarcoidosis within time, afterwards. The similarities between these three patients have been summarized in table I.

### CASE REPORTS

#### Case 1

A 38-year-old female had been diagnosed with persistent allergic rhinitis and asthma at 5, and had received SIT for house dust mite and grass pollen allergy starting at 12 for 4 years after which she had had significant regression of symptoms. A year after the end of therapy her symptoms had gradually relapsed and at age 33 she had been diagnosed with asthma for which she had received beclomethasone dipropionate and montelukast. On successive follow-up visits her symptoms had resolved.

At age 34 the patient had traveled to Uppsala, Sweden where she had resided for a total of 6 months and had suffered symptoms of fever and arthralgia. Chest-X-ray had revealed hilar prominence suggesting sarcoidosis and she had received intra-articular corticosteroids for her arthralgia. Upon her return to Turkey, her thoracic computed tomography

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**Table I**  
**Demographic and clinical data of the cases**

		Case No	
		1	2
			3
Age of onset	34	30	18
Comorbidity	Asthma, persistent rhinitis	Persistent rhinitis	Asthma, persistent rhinitis
SIT (age/length of treatment)	12 years old/4 years	25 years old/4 years	16 years old/1 year
Clinical findings	Erythema nodosum arthralgia, fatigue	Erythema nodosum arthralgia, fatigue	Dyspnea, arthralgia, fatigue
Length of stay in Sweden (months)	9	24	–
*Exposure period (year)	22	1	4
Method of diagnosis	TBNA	Clinical and radiological findings	TBNA
Treatment	Intra-articular corticosteroid	Oral steroid	Oral steroid
Familial history of sarcoidosis	No	Yes	No
PPD	Negative	Negative	Positive
Tissue typing	HLA-ABC: A02, A24, B4901 HLA-DR: DR10, DR11	HLA-ABC: A01, A24 B08, B13 HLA-DR: DR03, DR07	HLA-ABC A24, A30 B2716, B3547 HLA-DR: DR03, DR14

\*The time period between the administration of SIT and development of sarcoidosis.  
TBNA: Transbronchial lymph node aspiration.

(CT) scan has revealed mediastinal and hilar lymphadenopathies and transbronchial lymph node aspiration from these has showed granulomatous inflammation compatible with sarcoidosis. She has been diagnosed as Loeffgren's syndrome and nonsteroid antiinflammatory treatment has been administered. Her follow-up thoracic CT has showed decrease in the size of the hilar and mediastinal lymph nodes and since her general status has seemed well no further treatment has been initialized, and her clinical status have improved spontaneously.

## Case 2

A 46-year-old male had been diagnosed with seasonal rhinoconjunctivitis and pollen asthma at age 16 and underwent 4 years of specific immunotherapy for grass pollen hypersensitivity starting at 25. He had also resided in Uppsala at 30 for two years. At the end of 8 months of stay, he had developed symptoms of bilateral erythema nodosum, general weakness, arthralgia and fever. Chest X-ray had showed bilateral hilar lymphadenopathy. He had been started a 3 month tapering off dose regimen of oral prednisolone starting with 40 mg/day due to arthritis. A few months later he had suffered another attack of arthralgia and myalgia for which he has been treated with oral prednisolon for a total of 6 months. He is now 46 years old, healthy and has not suffered any

other attack. In addition, his sister has also been diagnosed with Loeffgren's syndrome at age 28 and has recovered with oral corticosteroid therapy.

## Case 3

A 27 year-old male had been diagnosed with asthma and allergic rhinitis at 5. At age 16, he had received SIT for grass pollen, house dust mites, and moulds for 1 year, which had been stopped upon no benefit to him. He had been referred to the chest diseases department for his asthma at 18. In the same year, the patient had been diagnosed with sarcoidosis after hilar and mediastinal transbronchial lymph node aspiration samples had been interpreted as granulomatous inflammation compatible with sarcoidosis, and had been treated with oral steroids for 6 months. Successive control visits has showed clinic and radiologic recovery.

## DISCUSSION

The formation of a granuloma in sarcoidosis results from the interaction between activated macrophages and T cells in addition to fibroblasts regulated by IFN $\gamma$ , IL-12, TNF- $\alpha$ , IL-6 and other cytokines resulting in cell activation, proliferation, and recruitment<sup>2</sup>. Patients with allergic diseases secrete



IL-4 (Th2) and nonallergic subjects secrete IFN $\gamma$  (Th1) in response to allergen stimulation. There was no difference in secretion of IL-2 or IFN- $\gamma$  between patients treated with SIT and those not<sup>3</sup>. Skin biopsy samples of 10 subjects treated with grass pollen immunotherapy protocol for 4 years provided evidence of an increase in IL-12 which correlated positively with IFN- $\gamma$  and negatively with IL-4, suggesting allergen specific Th1 activation in those treated with SIT<sup>4</sup>.

A study suggested that sarcoidosis is a disease which may be induced by infective agents that have not yet been identified, which is more prevalent in cold places, becomes influential with ecological change and affects persons with predispositions<sup>5</sup>. Thus, even though there is no certain data implicating that traveling abroad to countries of harsher climates may trigger sarcoidosis, the fact that these two patients acquired the disease when they were abroad may be worth paying attention.

Environmental stimuli, abnormal immunological host response to common antigenic triggers and genetic susceptibility have been proposed in the pathogenesis of sarcoidosis. It was shown that atopy rate was lower in patients with sarcoidosis<sup>6</sup>. Development of pulmonary sarcoidosis following hematopoietic stem cell transplantation (HSCT) has been reported; and suggested that pulmonary sarcoidosis may develop following autologous or allogenic HSCT<sup>7</sup>. Although which genes confer genetic susceptibility have not been confirmed yet; human leukocyte antigen (HLA) genes have been studied the most and HLA-B8 locus has shown a risk ratio between 2.2 and 4.4. However, associations between HLA and sarcoidosis are not strong enough to clarify ethnic or familial clustering<sup>8</sup>. Interestingly, we confirmed HLA-A24 locus positivity in all three patients, HLA-DR03 in both male patients and HLA-B08 in the patient who had a family history of sarcoidosis.

In the first two cases there was no available clinical record clarifying the content of the immunotherapy they had taken due to loss of SIT files during hospital restoration. According to these two patients' recall, which was later confirmed by the physicians still working in the same clinic since then, the first patient had received grass pollen and house dust extracts and the second one grass pollen and mould ex-

tracts. All of the data about the content of the SIT (grass pollen, house dust mite and mould extracts) for the third patient was obtained from the clinical records in his file. The time intervals between the ceasement of the SIT and appearance of sarcoidosis were variable for all the patients, but quite short and close to each other in cases 2 and 3 compared to case 1. There may be some explanations for this relationship. Maybe they had subclinic sarcoidosis which has been precipitated by SIT, although their routine blood analysis were normal when the hospital files other than SIT files are reviewed which may also be normal in a patient with sarcoidosis. Other possibilities are that either SIT caused sarcoidosis, or sarcoidosis coincidentally appeared in a short time after the end of SIT.

In conclusion, our cases may be more than just a mere coincidence. Although only three cases are not enough for a detailed discussion on this topic, the fact that all three patients had received immunotherapy at the same institution may suggest some antigenic trigger in the immunotherapy solutions that had been prepared in the clinic. Further studies must be carried out to confirm this possible relation.

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