Case Report

Paradoxical coexistence of atopic asthma and Human T-Lymphotropic Virus Type I (HTLV-I) infection: a case report

A. Souza-Machado[1], Á. A. Cruz[1], T. Sena Galvão[1], André Muniz[2], A. Porto[2], S. Braga (Pharm), E. Marcelino Carvalho[2]

Center for Respiratory Diseases (CER)[1] and Immunology Department[2] of Professor Edgard Santos University Hospital, Faculty of Medicine, Federal University of Bahia, Salvador, Bahia, Brazil.

Abstract. In this case report, the authors report the presence of two supposedly antagonic immune diseases in the same patient. The patient is a 45-year-old white woman with a history of asthma and allergic rhinitis for the last 10 years. Asthmatic symptoms were present and were triggered after exposure to dust and mold. Her Human T-Lymphotropic Virus Type I (HTLV-I) seropositive status was detected by chance five years ago during a routine screening for blood donation. Skin prick tests were positive for *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* and *Blomia tropicalis*. Cytokine levels in unstimulated cultures were: IFNγ = 1195 pg/ml, TNF∝ = 460 pg/ml, IL5 = 41 pg/ml and IL10 = 265 pg/ml.

Key words: asthma, interferon, allergy and retrovirus.

Introduction

The functional classification of murine $CD4^+$ T-helper cell clones into distinct subtypes, called Th1 and Th2, based primarily on the pattern of their cytokine production, has enhanced our understanding of T-cell biology [1]. Th1 cells are characterized by the production of IL-2, IFNγ and TNF-α, whereas Th2 cells produce IL-4, IL-5, IL-6 and IL-13 [1-2]. Previous studies have shown that Th1/Th2 cells play different roles in infectious and allergic diseases [3-6].

With respect to human retroviruses, it has been observed that individuals infected with HTLV-I virus have spontaneous T-cell proliferation and high levels of IFN production, which are immunological functions associated with a Th1 type immune response [6-11]. Allergic diseases, on the other hand, are associated with higher levels of IL-4, IL-5 and IL-13, which promote IgE production. Distinct patterns of immune regulation in different illnesses, particularly in allergic and autoimmune diseases, have been observed and implicated in the immune deviation toward the strongest stimulus [11-13]. Previous studies in patients infected with HTLV-I and *Strongyloides stercoralis* have shown that this virus induces high levels of IFN production and a suppression of Th2 cytokines [4-5]. Based on this information, milder or no clinical manifestation of allergic asthma would be expected in HTLV-I infected subjects.

In this case study, the authors report on the presence of two supposedly antagonic immune diseases in the

same patient, a 45-year-old white female with allergic asthma and rhinitis, infected with the HTLV-I virus, resulting in high IFN γ production but no changes in the course of asthma.

Case report

The subject is a 45-year-old white woman with a history of asthma and allergic rhinitis over the past 10 years. Asthmatic symptoms such as dyspnea, coughing and wheezing were present and were triggered after exposure to domestic dust and mold. Nocturnal asthmatic symptoms were observed once a week. Nasal itching and lacrimation were associated with the asthmatic complaints. The patient had experienced atopic symptoms with no remission periods since childhood and she required treatment with an inhaled steroid (budesonide; 800 mcg daily) and a long-acting β2 agonist (formoterol, 12mcg bid).

Her HTLV-I seropositivity was detected by chance five years ago during a routine screening for blood donation and was confirmed by ELISA (Cambridge Biotech Corporation, Wocester, MA, USA.) and Western-blot assays (Genelabs, Singapore). The patient reported having received a blood transfusion ten years ago.

Physical examination revealed that the patient was apparently in good health. Her blood pressure was normal. Her nasal passages were moderately blocked by turbinate hypertrophy and swelling of the mucosa, which was congested and humid. Lung auscultation revealed a bilateral reduced murmur and wheezing. No arrhythmias or any other heart disturbances were detected on chest examination. No abnormalities were found in the extremities. A complete neurological exam searching for mild manifestations of HTLV-I-related myelopathy revealed no abnormalities.

Spirometry [14] showed a severe obstruction with a significant response after use of a bronchodilator (salbutamol 400 mcg) - FEV_1 = 45% and 64% of the predicted values, respectively (Table 1). Chest radiography was normal. White blood counts revealed 7,800 leukocytes and 2% eosinophils. Skin prick tests (15) were positive for *Dermatophagoides pteronyssinus* (4 mm), *Dermatophagoides farinae and Blomia tropicalis* (3 mm). Negative control with saline did not elicit any skin reaction. Histamine positive control led to a 5 mm flare.

Serum total IgE was 147 KUI/L (MEIA) and specific IgE to *D. pteronyssinus, D. farinae* and *B. tropicalis* were 1,520 KU/L, 2,100 KU/L and 2,100 KU/L, respectively. Peripheral blood mononuclear cells (PBMCs) were isolated from heparinized peripheral blood by a Ficoll-Hypaque gradient as previously described [16]. IFN-γ (Genzyme Corp., Cambridge, MA, USA), TNF-∝, IL-5 and IL-10 (PharMingen, San Diego, USA) levels in supernatant of unstimulated cultures were measured by ELISA sandwich technique and the results were expressed in pg/ml based on a standard curve generated using recombinant cytokines [10]. Cytokine levels in the PBMC supernatant were compared with a control group of healthy (n=15) and allergic asthmatic patients (n = 9): IFN-γ = 1,195 pg/ml (healthy controls: 1 ± 4 pg/ml; asthmatic patients: 414 ± 204 pg/ml), TNF-∝ = 460 pg/ml (healthy controls: 60 ± 63 pg/ml), IL-5 = 41 pg/ml (healthy controls: 2 ± 2 pg/ml; asthmatic patients: 85 ± 44 pg/ml) and IL-10 = 265 pg/ml (healthy controls: 2.6 ± 10 pg/ml; asthmatic patients 20 ± 7 pg/ml).

Table 1. Patient's lung function.

	Before bronchodilator use (B-bd)			**After bronchodilator use (A-bd)**		
	Predict parameter	Basal parameter	Predict (%)	A-bd parameter	Predict (%)	Change (%)
FVC (liters)	2.98	1.98	66	2.67	90	23
FEV_1 (liters)	2.59	1.16	45	1.67	64	20
FEV_1/FVC	83	59	-	63	-	-
$MMEF_{25-75\%}$ (liters/min)	3.92	0.57	15	0.97	25	10

¶ Lung function was performed according to standard technique (ATS, 1994). Maneuvers repeated 15 minutes after inhaled albuterol use (400 mcg).

Discussion

Atopy is the single strongest risk factor for the development of asthma. From an immunological standpoint, allergic diseases are characterized by a Th2 cytokine profile, increased IL-4 and IL-5, and activation of mast cells and basophils.

There is evidence that high IFN-γ production suppresses the allergic immune response and may protect against asthma [2, 4-8]. Shirakawa and colleagues evaluated the effect of repeated Th1 stimuli through BCG vaccination (at 5 and 12 years of age) on cytokine profiles in atopic Japanese schoolchildren. They observed an inverse correlation between tuberculin reactions and atopy [17].

The human T lymphotropic virus, type I, is a retrovirus linked to hematological and neurological disorders. It has T-cell tropism ($CD4^+$ and $CD8^+$), which causes T-cell proliferation and establishes persistent infection [9]. It also stimulates the production of high levels of IFNγ MIP-1α, -1β and IL-16 [7-8]. The increased levels of IFNγ, produced by HTLV-I-infected T-cells may down-regulate a Th2 immune response. Porto et al. have observed an inverse correlation between IFNγ, IgE and IL-5 and a direct relationship between IFNγ response and IL-10 in HTLV-I seropositive patients co-infected with *Strongyloides stercoralis* [4]. The HTLV-I infection decreases the sensitivity of *S. stercoralis*-specific IgE, the size of the immediate hypersensitivity skin reaction and the sensitivity of these tests in the diagnosis of strongyloidiasis [5]. IgE and IL-5 suppression was not observed in the present case although a moderate decrease in IL-10 level was observed.

Th1 and Th2 responses have often been viewed as being mutually exclusive. However, it has recently been shown that Th1 and Th2 may coexist in the lungs and can cooperate to generate eosinophilic inflammation. Furthermore, Th1 cells may induce alterations in the lung microenvironment such as secretion of chemokines and adhesion molecule expression that may potentiate Th2 cell recruitment to the airways [18].

In this case report, despite the strong Th1 immune response with increased IFNγ production (in PBMC non-stimulated culture supernatant), no suppression of the Th2 response or of the clinical manifestations of asthma was observed.

In conclusion, the high IFN-γ production observed in this asthmatic subject, found to be HTLV-I seropositive after a blood transfusion ten years before, interfered neither with her atopy markers, such as specific IgE or SPT reactivity, nor with the intensity of her asthma manifestation or her level of IL-5. It seems that in special situations Th1 and Th2 cytokine profiles may coexist in the same patient. This co-existence suggests that atopy and its immune regulation is not an all-or-nothing condition but that a spectrum of situations may exist, ranging from non-atopic with normal T-cell IFN-γ production to highly atopic with high impairment of T-cell IFNγ production. In addition, many different factors such as genetic background, environment, route and timing of exposure to antigens and infections may regulate the expression of atopic disorders.

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Adelmir Souza-Machado

Centro de Enfermidades Respiratórias (CER),
Hospital Universitário Professor Edgard Santos
Rua Augusto Viana s/n Canela, 3º andar
CEP: 40.110-160 Salvador BA, Brazil
Phone: + (5571) 203 2749
Fax: + (5571) 237 6679
E-mail: adelmirm@terra.com.br

