Features of vimentin autoantibodies formation in patients with pulmonary sarcoidosis*

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Sarcoidosis is suggested to be a granulomatous disease with unknown etiology and highly variable clinical manifestation.In recent years, vimentin has been considered the most possible autoantigen in sarcoidosis, as well as in the number of various "classic" autoimmune connective tissue disorders. The aim of the study is to determine the severity of the immune response to various modifications of vimentin in patients with sarcoidosis. In a prospective comparative study was were included patients with pulmonary sarcoidosis stage II (n = 93), with nonspecific lung diseases (n = 55), in which were studied patinets with chronic obstructive pulmonary disease (COPD) (n = 25), granulomatosis with polyangiitis (n = 15), alveolitis (n = 15), and healthy individuals (n = 40). Serum levels of antibodies to modified citrullinated vimentin (anti-MCV) were determined in all participants included in the study, serum of patients with elevated levels of anti-MCV was tested for antibodies to cyclic citrullinated peptide (anti-CCP) and to Sa-antigen (anti-Sa). Anti-MCV and anti-CCP were determined with ELISA. An increased level of anti-MCV was determined in 40.9 % (38/93) cases of patients with pulmonary sarcoidosis, which was significantly more frequent than in comparison and control groups. Antibodies to cyclic citrullinated peptide did not show their significance in the pathogenesis of sarcoidosis and other studied lung diseases (COPD, granulomatosis with polyangiitis, alveolitis). The absence of anti-CCP and the positive correlation between anti-MCV and anti-Sa suggest that citrullination and modification of vimentin is not a key factor in the formation of an autoimmune response to this peptide in sarcoidosis.

Keywords: sarcoidosis, autoimmunity, anti-vimentin autoantibodies

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Introduction

Sarcoidosis is suggested to be a granulomatous disease with unknown etiology and highly variable clinical manifestation. The particular antigen, that induces the immune response and inflammation is still undefined. Studies of the specificity of T-lymphocytes in sarcoidosis have shown a number of antigens, with stimulation of which peripheral mononuclear cells were activated, and various cytokines were released. Among them the leading role is played by infectious antigens (ESAT-6 proteins, KatG M. tuberculosis) and autoantigens (vimentin, lysyl-tRNA synthetase). In recent years, vimentin has been considered the most possible autoantigen in sarcoidosis [1], as well as in the number of various "classic" autoimmune connective tissue disorders, such as systemic lupus erythematosus and rheumatoid arthritis [2]. Vimentin is a the filament protein, that is presented in of mesenchymal cells of connective tissue and participates in intercellular interactions and the functioning of the immune system; determining its role in sarcoidosis may be important for understanding the pathogenesis of the disease and improving treatment [1]. The first mention of vimentin as an etiological factor in sarcoidosis was made by Cain H. et al. in 1983. It was found that the asteroid bodies in multinuclear giant cells of sarcoid granulomas consisted of vimentin filaments [3], in addition, vimentin is the main autoantigen of Kveim reagent, obtained from the lymph nodes of patients with sarcoidosis previously used as a skin allergy test for sarcoidosis, known since 1941 as a Kveim-Nickerson reaction [4]. In 2007, Wahlström et al. described possible autoantigens associated with major histocompability complex HLA-DR molecules in bronchoalveolar fluid cells in sarcoidosis patients. The expressed response of T-cells of bronchoalveolar fluid to vimentin was also demonstrated in 6 of 11 positive patients with HLA DR-B1 * 0301 with an acute course of the disease [5].

Aim

To determine the severity of the immune response to various modifications of vimentin in patients with sarcoidosis.

Materials and methods

A prospective comparative study was performed in 2017 — 2018 years. The following groups of patients were included in the study: with histologically verified pulmonary sarcoidosis stage II (n = 93) — group I (main); with nonspecific lung diseases (n = 55) — group II (comparison): with chronic obstructive pulmonary disease (COPD) (n = 25), granulomatosis with polyangiitis (n = 15), alveolitis (n = 15); healthy individuals (n = 40) — group III (control). Serum levels of antibodies to modified citrullinated vimentin (anti-MCV) were determined in all participants included in the study. Serum of patients with elevated levels of anti-MCV was tested for antibodies to cyclic citrullinated peptide (anti-CCP). Anti-MCV was determined with ELISA (ORGENTEC, Germany), for anti-CCP (aka: anti-Sa) determination used ELISA (EUROIMMUN, Germany). All measurements were performed using a flatbed IFA spectrophotometer BIO-TEK ELx800. For positive result the cut level of antibodies more than 19.5 U/ml was taken. Statistical analysis was performed with Statistica 10.0, the differences were considered significant with $p < 0.05$.

Results

An increased level of anti-MCV was determined in 40.9 % (38/93) cases of patients with pulmonary sarcoidosis, which was significantly more frequent than in comparison and control groups (23.6 % and 25.0 % of positive cases respectively). Increased levels of anti-CCP were determined in one patient with sarcoidosis and two patients with nonspecific lung diseases, but was not detected in the control group, that allude the presence of autoimmune inflammation in the first group (Table 1).

Table 1. **Results of anti-MCV and anti-CCP in the studied groups**

Studied groups	Anti-MCV results		CI 95 %	Anti-CCP results		CI 95 %
	High level n/%	Absolute value (M ± m)		High level n/%	Absolute value (M ± m)	
I group Pulmonary sarcoidosis, n (%) n=93	40.9 (38/93)	20.31 ± 18.34	16.97–23.64	2.6 (1/38)	0.89 ± 0.39	1.17–2.64
II group Nonspecific lung diseases, n (%) n=55	23.6 (13/55)	33.94 ± 31.47	10.53–19.12	15.4 2/13	2.43 ± 1.45	0.69–9.76

*$p < 0.01$ — significant differences between group II and group III.

The level of anti-Sa was studied in the group of patients with sarcoidosis (n = 13) and nonspecific lung diseases (n = 9). A high concentration of these antibodies was detected in 7 patients with sarcoidosis and 2 patients from group II. In 13 lung sarcoidosis patients with positive anti-MCV levels, a moderate positive correlation was found between anti-MCV and anti-Sa titers (r = 0.66) (Fig. 1).

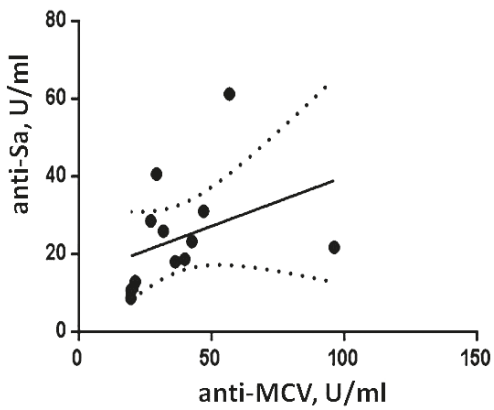

Fig. 1. Correlation of anti-MCV and anti-Sa titers in patients with sarcoidosis

Conclusion

The significance in the detection of high titers of modified citrullinated vimentin in patients with pulmonary sarcoidosis allows us to consider vimentin as one of the major targets for immunological response in this disease. Antibodies to cyclic citrullinated peptide did not show their significance in the pathogenesis of sarcoidosis and other studied lung diseases (COPD, granulomatosis with polyangiitis, alveolitis). The absence of anti-CCP and the positive correlation between anti-MCV and anti-Sa suggest that citrullination and modification of vimentin is not a key factor in the formation of an autoimmune response to this peptide in sarcoidosis. The presence of an autoimmune inflammation associated with an increase in the level of autoantibodies can be significant for the therapy appointment and in certain cases may serve as a criterion for considering the prescription of immunosuppressive therapy.

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