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Research Article

Do Anti-Vimentin Antibodies Play a Role in Psoriasis?

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Abstract

Antibodies against Citrullinated Proteins/Peptides (ACPAs), and especially antibodies targeting citrullinated vimentin (anti-Sa), are novel biomarkers of Rheumatoid Arthritis (RA) and also in Psoriatic Arthritis (PsA). The aim of the present study was to investigate the prevalence of anti-Sa in 54 PsA and PsO patients aged 20-69 years (22 F and 32 M). Each patient was assessed with Psoriasis Area and Severity Index - PASI score (severity of psoriasis), the presence of antibodies against vimentin (anti-Sa) and Antinuclear Antibodies (ANA) on HEp-2 cells. There were no statistically significant differences between the mean values of the PASI and the presence of antibodies to vimentin or the antinuclear antibodies. Additionally analysis showed that the incidence of antibodies against vimentin (anti-Sa) in patients with plaque psoriasis was similar for patients with also psoriatic arthritis (65.115% *vs.* 62.5%). On the other hand, it can be concluded that the presence of them is much more common in patients with psoriasis than healthy controls - the highly significant statistical differences ($p = 0.003$). Our results suggest that the presence of anti-Sa in psoriasis confirm the autoimmune nature of this disease.

Introduction

Vimentin is one of five major groups of intermediate filaments (58 kDa), a form of the cytoskeleton of cells (fibers, microfibers). Using monoclonal antibodies we can find vimentin in mesenchymal cells (fibroblasts, endothelial cells, chondrocytes), lymphoid tissues, melanocytes, and also in pathological cells of sarcomas, melanomas, lymphomas and their metastases [1,2]. Vimentin can only be expressed by posttranslational modification that is enzymatic citrullination of arginine residues, catalyzed by the enzyme peptidylarginine deiminase found in monocytes and macrophages. Moreover vimentin is associated with macrophage differentiation, phagocytosis and ROS production. Vimentin is expressed on activated macrophages and is secreted in response to pro-inflammatory stimuli. Inflammation and cell apoptosis lead to changes in the structure of the protein by citrullination and result in the increased production of auto antibodies to citrullinated peptides [3].

Anti-vimentin auto antibodies are a subtype of ACPA (Anti-citrullinated Protein/Peptide Antibodies) group, which also includes: Anti-Cyclic Citrullinated Peptides antibodies (anti-CCP), antibodies against citrullinated peptides of type II collagen, Anti-Perinuclear Factor (APF), Anti-Keratin Antibodies (AKA), Anti-Filaggrin Antibodies (AFA). These antibodies are mainly IgG class and are determined in laboratory tests using a peptide rich in citrulline. Antibodies against citrullinated peptides are found in many autoimmune diseases, especially in rheumatoid arthritis, where the anti-CCP is recognized as a specific and sensitive marker of the disease. In RA citrullination takes place in the synovium, periodontal tissue and lungs [1-4]. Although citrullinated proteins and antibodies against these citrullinated proteins are known to have an important role in the pathogenesis of RA, they can also be found in systemic lupus erythematosus, juvenile idiopathic arthritis, Sjögren's syndrome, Crohn's disease, amyotrophic lateral sclerosis and even Alzheimer's disease [5,6]. It is interesting to observe the strong relationship the presence of antibodies against vimentin in patients with rheumatoid arthritis with concomitant diseases of the cardiovascular system [6].

Anti-vimentin was firstly described by Despres, et al. in 1994. Citrulline is a transient form of the protein vimentin filaments, a mass of 48-50 kDa [1]. The presence of antibodies to vimentin can be assessed in the serum of patients by immunoblotting (anti Sa) or by enzyme-linked immunosorbent assay (Anti-mutated citrullinated vimentin, MCV) [7]. Tests for the determination of anti-Sa/anti-MCV have a wide sensitivity (31-84%) and specificity 83-98% in the diagnosis of RA. Additionally, anti-vimentin antibodies may be an early marker of rapid joint destruction in the disease and may be particularly useful in monitoring the effectiveness of therapy [1,8]. A recent study emphasizes their supportive role in the diagnosis of antiphospholipid syndrome, especially in seronegative forms [9]. Furthermore, it is possible that the anti-vimentin cross-react with an epitope of streptococcal M protein in rheumatic fever [10].

Some studies confirm over expression of vimentin in psoriatic epidermal cells, which take part into Epithelial-Mesenchymal Transition (EMT), a process of epithelial cells transformed into fibroblast-like cells [11].

Aim of the Study

The aim of the study was to evaluate the presence of antibodies against vimentin (anti-Sa) and antinuclear antibodies in patients with plaque psoriasis. In addition, the dependence of their occurrence is comparable to the severity of psoriasis (PASI).

Material and Methods

The study included 54 patients with plaque psoriasis who were treated in the Dermatology Outpatient Clinic and Department of Dermatology, Sexually Transmitted Diseases and Clinical Immunology, Municipal Hospital in Olsztyn. We excluded patients who had other inflammatory conditions, diabetes, cardiovascular complications, heart, kidney and liver failure, and a history of cancer.

Each patient was assessed with PASI score (severity of psoriasis) and identified with the presence of antibodies against vimentin (anti-Sa) by indirect immunofluorescence using commercially available anti nuclear antibody (ANA/Hep-2) test (Euroimmun, Germany). All 54 whole blood samples were collected from individual patients in tubes with anticoagulant, centrifuged (4000 rpm/ 10 min) and stored at -25°C until analysis. Each serum sample was diluted to 1:100 and incubated

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according producer procedure with two substrates of human epithelial cells (Hep-2) and monkey liver, and visualised by goat anti human IgG antibodies conjugated with fluorescein (FITC). The result of the study was read on fluorescence microscope (EUROStar III Plus, Euroimmun, Germany) at ×400 magnification. Statistical analysis was performed using descriptive statistics module and a non-parametric Kruskal-Wallis test.

Results

The study included 54 patients aged 20-69 years (22 F and 32 M). The severity of psoriasis PASI averaged 15.0 + 9.6 (standard deviation) (Table 1) (Figure 1).

Statistical analysis was performed using descriptive statistics module and a non-parametric Kruskal-Wallis test. They showed that the incidence of antibodies against vimentin (anti-Sa) in patients with plaque psoriasis was similar to that in patients with psoriatic arthritis also (65.1% *vs*. 62.5%) - no statistically significant differences. On the other hand, on the basis of the test for the two indicators of the structure, it can be concluded that the presence of them is much more common in patients with psoriasis than lack of them - the highly significant statistical differences (p = 0.003) (Table 2).

The results of the Kruskal-Wallis test (p = 0.2096) and median (p = 0.2020) revealed no statistically significant differences between the mean values of the PASI and the presence of antibodies to vimentin or the antinuclear antibodies.

Result	**Anti-Sa (+) ANA (-)**	**Anti-Sa (-) ANA (-)**	**Anti-Sa (+) ANA (+)**	**Anti-Sa (-) ANA (+)**	**Anti-Sa (+) cytopl (+)**
Patients	15	11	17	7	2
%	28,84	21,15	32,69	13,46	3,84

Table 1: Results of anti-Sa and ANA antibodies in patients by indirect immunofluorescence.

	PASI	Standard deviation	Variation [%]
Anti-Sa(+) ANA(-)	12,49	9,1083	72,93
Anti-Sa(-) ANA(-)	20,37	11,6432	57,16
Anti-Sa(+) ANA(+)	16,21	9,2783	57,24
Anti-Sa(-) ANA(+)	18, 86	10,6789	56,62
Anti-Sa(+) cytopl(+)	8,20	5,6569	68,99

Table 2: The average value of the standard deviation ratio PASI variation [%].

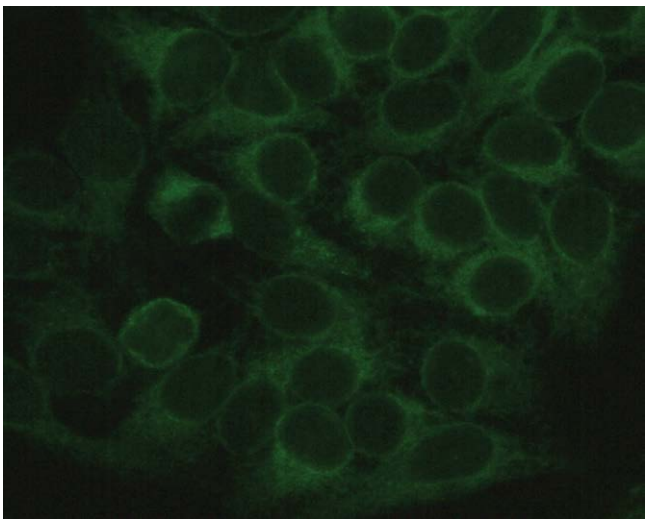

Figure 1: Anti-Sa antibodies in HEp-2 cytoplasma (magnification X 400).

Discussion

There are only a few studies which analyzed the role of vimentin in psoriasis to confirm the autoimmune nature of this disease. Somewhat unexpectedly our results showed the common presence of antibodies against vimentin in patients with psoriasis, both PsO and PsA (65.1% *vs*. 62.5% respectively). Anti-Sa antibodies were found to be specific in RA with the high degree of RA specificity, which exceeds 95% in several studies [12,13], and with relatively low sensitivity ranging from 20-25% in early in the course of RA to 47% in patients in established disease [13]. The diagnostic value of anti-Sa and widely used anty-CCP in RA is similar for both antibodies. However, the sensitivity of anti-CCP detection is higher than that of anti-Sa. Despite this the presence of anti-Sa antibodies in serum may be useful as a complementary assay in seronegative RA [14]. It has also been demonstrated an association between the anti-Sa and disease severity. Hayem et al. showed that patients with destructive disease were three times more likely to be anti-Sa positive than patients without destructive disease [15]. Boire, et al. demonstrated erosions in anti-Sa-positive patients in early RA [16]. These data indicate that anti-Sa antibodies are present early in the disease and are markers of a destructive form of RA. In our study we found no association between the anti-Sa and skin disease severity assessed with PASI score.

It is difficult to compare our results with previous studies due to the methodology. We have used indirect fluorescence method to detect of the antibody against citrullinated vimentin (anti-Sa), while other researches ELISA to assess anti-mutated citrullinated vimentin (Anti-MCV).

Samond, et al. showed the prevalence of anti-MCV antibodies in all 52 patients with PsO (25 with severe disease PASI > 20 and 27 with mild) and in only in 2 out of 30 healthy controls with low titer. It was also observed that the titer increased with duration of the disease [17].

However Dalmady, et al. demonstrated significantly higher anti-MCV titers in 42 PsA patients than in 46 PsO patients and comparing to 40 healthy controls. Additionally, PsA patients are anti-MCV positive, there was a special connection with the knee joints involvement and the presence of nail psoriasis. In patients with PsO, higher anti-MCV was found in more severe course of the disease and early onset of skin symptoms [18].

Tesija-Kun, et al. presented different results. The presence of anti-MCV was evaluated in 56 patients PsA, taking into account the activity of the disease and compared the titers of sera from 92 patients with RA and 107 healthy subjects. Anti-MCV was found only in two PsA patients (3.6%) with a polyarticular subtype, but in patients with RA it was 63% [7].

Other studies indicate the incidence of anti-MCV antibodies in patients with PsA from 5.9% to 15.7% and emphasize the correlation with more severe disease (DAS 28) [7,9]. They are more often found in the form of polyarticular PsA, a certain similarity to the RA, which may indicate the coexistence of the disease. Beyond that the anti-MCV is strongly correlated with clinical improvement under the DMARD therapy [19,20].

Summary

- Antibodies to vimentin are an expression of the autoimmune process in psoriasis and psoriatic arthritis.
- Exposing hidden antigens (hidden epitopes) in the damaged cells is a result of the inflammatory process, and may lead to the production of autoantibodies.

- The interaction of antigen with antibody and the formation of immune complexes may play a significant role in the persistence of disease processes, by direct damage to fibroblasts, myofibroblasts, or by activation of macrophages.
- Macrophages in psoriasis (main sources of MCV) play an important, but it needs further researches.

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