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The correlation between serum E-selectin levels and soluble interleukin-2 receptors in relation to nailfold capillaroscopy in localized scleroderma

Korelacja stężenia E-selektyny i rozpuszczalnego receptora interleukiny 2 w surowicy z kapilaroskopową oceną mikrokrążenia wału paznokciowego u chorych na twardzinę ograniczoną

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Słowa kluczowe

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Summary

Introduction. Localized scleroderma is an autoimmune connective tissue disease. Increased secretion of adhesion molecules by stimulated endothelial cells results in their desquamation and release into the bloodstream. E-selectin is one of the proteins expressed intensely on the surface of stimulated endothelial cells during inflammation. Elevated serum levels of soluble interleukin-2 are observed in both systemic sclerosis and localized scleroderma, which suggests their involvement in the pathogenesis of both diseases.

Aim. The aim of the study was to determine the correlation between sE-selectin and sIL-2R concentrations as well as possible abnormalities in the nailfold capillaroscopy image in various forms of localized scleroderma.

Material and methods. 42 patients diagnosed with localized scleroderma were enrolled. In both groups, sE-selectin and sIL-2R concentrations were evaluated using the ELISA immunoenzymatic method. All patients underwent nailfold capillaroscopy to assess the structural and morphological changes.

Results. The results showed no significant correlation between sE-selectin levels and capillaroscopy abnormalities in the LoS group and all patients. The correlation between sIL-2R serum levels and changes in nailfold capillaroscopy was assessed in all patients. The analysis did not show statistically significant differences in sIL-2R levels in subjects with capillary abnormalities compared with any group: the LoS patients, the control group and all patients.

Conclusions. On the basis of available reports and self-reported results, the role of nailfold capillaroscopy in the diagnosis of localized scleroderma should be emphasized. Although abnormalities in nailfold microcirculation are rarely observed in this disease, their presence has very significant clinical implications and requires further follow-up.

Streszczenie

Wstęp. Twardzina ograniczona jest chorobą tkanki łącznej. Zwiększone wydzielanie cząsteczek adhezyjnych przez stymulowane komórki śródbłonka powoduje ich złuszczanie i uwalnianie do krwiobiegu. E-selektyna jest jednym z białek intensywnie wyrażanych na powierzchni stymulowanych komórek śródbłonka podczas zapalenia. Podwyższone stężenie rozpuszczalnej interleukiny-2 w surowicy krwi obserwuje się zarówno w twardzinie układowej, jak i ograniczonej, co sugeruje ich udział w patogenezie obu chorób.

Cel pracy. Celem pracy było określenie korelacji pomiędzy stężeniem E-selektyny i sIL-2R a nieprawidłowościami w obrazie kapilaroskopowym mikrokrążenia wału paznokciowego chorych z twardziną ograniczoną.

Materiał i metody. Do badania włączono 42 pacjentów z rozpoznaną twardziną ograniczoną. W grupie badanej i kontrolnej oznaczono stężenie E-selektyny oraz sIL-2R przy pomocy metody ELISA. U wszystkich pacjentów wykonano kapilaroskopową ocenę mikrokrążenia wału paznokciowego.

Wyniki. Wyniki nie wykazały istotnej korelacji pomiędzy stężeniem E-selektyny a nieprawidłowościami w kapilaroskopii w grupie chorych oraz kontrolnej. U wszystkich chorych oceniono korelację między poziomem sIL-2R w osoczu a zmianami w mikrokrążeniu. Analiza nie wykazała statystycznych różnic w poziomie sIL-2R u osób z nieprawidłowościami naczyń włosowatych w porównaniu z obrazem w grupie chorych, grupie kontrolnej i obu grupach.

Wnioski. Na podstawie dostępnych badań oraz wyników własnych należy podkreślić rolę kapilaroskopii w diagnostyce twardziny ograniczonej. Mimo iż w tej jednostce chorobowej rzadko obserwuje się nieprawidłowości w mikrokrążeniu wałów paznokciowych, ich obecność niesie za sobą bardzo istotne konsekwencje kliniczne i wymaga dalszej obserwacji.

INTRODUCTION

Localized scleroderma is an autoimmune connective tissue disease in which excessive fibrosis concerns mainly dermis, epidermis and subcutaneous tissue. Depending on the clinical form, the lesions may also affect fascia, muscles and bones.

The processes leading to localized scleroderma remain unclear. Many argue that microvascular damage is a very important feature of the early stage that begins the cascade of processes leading to fibrosis (1). In scleroderma, the anticoagulative, vasodilating and anti-inflammatory endothelial profile is transformed into a prothrombotic, vasospastic and pro-inflammatory one (2).

Vascular abnormalities are also manifested in the increased expression of adhesion molecules which is noticeable in the affected skin, especially in perivascular infiltrates. These molecules strengthen the adhesion of leucocytes and propagate inflammation in the vascular wall (3). ICAM-1, VCAM-1, E-selectin and P-selectin are found in skin biopsies from scleroderma lesions but are absent from healthy skin (2). Increased secretion of adhesion molecules by stimulated endothelial cells results in their desquamation and release into the bloodstream. In fact, circulating blood contains soluble forms of adhesive proteins (abbreviated as 's') coming from proteolytic disconnection of their extracellular domain. They are adhesion molecule expression indicators and therefore can play an important role as inflammation indicators (3, 4).

E-selectin is one of the proteins expressed intensely on the surface of stimulated endothelial cells during inflammation. Interleukin-1, tumor necrosis factor alpha (TNF-α), interferon gamma (INF-γ), substance P, and bacterial lipopolysaccharides are inflammatory mediators which strongly induce this phenomenon. Increased E-selectin production is observed for example in inflammation-affected joints, renal and cardiac allografts during their rejection and inflammatory skin diseases including scleroderma (5).

Elevated serum levels of soluble interleukin-2 and -6 receptors are observed in both systemic sclerosis and localized scleroderma, which suggests their involvement in the pathogenesis of both diseases. They are associated with the activation of T-lymphocytes, promote their involvement in the disease progression and cause an imbalance between Th1 and Th2 cells (6). IL-2Rα appears on the surface of activated lymphocytes and its fragment, the soluble IL-2 receptor (sIL-2R), is released into the circulation. sIL-2R also demonstrates biological action by binding free IL-2, thus contributing to the immunomodulating function of this interleukin. High serum concentration of sIL-2R are also observed in diseases associated with T-lymphocyte activation, including autoimmune diseases, lymphatic proliferative processes and infections (7). Studies show a correlation between sIL-2R as an immune system activity indicator and the severity of lesions in systemic sclerosis and localized scleroderma (6).

To evaluate disease activity, one performs capillaroscopy, which can show microvascular irregularities, often before the first clinical symptoms. It is a simple, safe, non-invasive and cheap evaluation of the structure and morphology of a selected microcirculation fragment of the skin or mucous membranes. It also has prognostic significance because it correlates with the duration and activity of the disease as well as plasma markers of systemic sclerosis (E-selectin, VCAM, ICAM, VEGF or ET-1) (8-10). Elevated levels of E-selectin, produced in excessive amounts by damaged endothelial cells during the initial phase of the disease, apparently correlated with an "early" capillaroscopic pattern. At the same time, the described microcirculation pattern was absent in patients with increased sIL-2R plasma concentrations, which illustrated the immunomodulatory response of the immune system, characteristic of the later phase of the disease (11).

AIM

The aim of the study was to determine the correlation between sE-selectin and sIL-2R concentrations as well as possible abnormalities in the nailfold capillaroscopy image in various forms of localized scleroderma (LoS).

In addition, the presence of capillary changes in different LoS subtypes in the study group was assessed.

MATERIAL AND METHODS

42 patients diagnosed with localized scleroderma were enrolled. The study group consisted of 35 women and 7 men aged from 21 to 65 (mean age: 49.0 ± 14.4). In the control group consisting of 41 respondents (28 women and 13 men), the age range was 23-65 years (mean age: 46.3 ± 12.6). Patients with histopathologically confirmed localized scleroderma who did not meet the exclusion criteria were included.

The clinical form of the disease (plaque, linear, generalized) was assessed in the study group. In both groups, sE-selectin and sIL-2R concentrations were evaluated using the ELISA immunoenzymatic method. All patients underwent nailfold capillaroscopy to assess the structural and morphological changes.

RESULTS

Nailfold capillaroscopy was performed in all patients. Structural and morphological abnormalities of nailfold microcirculation were found in 21.4% of the study group (9 cases) and 17% of the control group (7 cases). Widened and twisted blood vessels were the most common changes. Single petechiae were also seen. Because of the small number of deviations and their diversity, all participants in both the scleroderma and control group were divided into two categories: with or without microcirculation deviations (individual abnormalities falling within the normal limits). All the identified changes were isolated and were within the broadly defined standard and their prevalence was similar in the study and control group (no statistically significant differences were found in this parameter, $p = 0.615$).

The study analyzed the correlation between nailfold microcirculation abnormalities and the serum levels of sE-selectin and sIL-2R in the LoS group, the control group as well as all patients. The results showed no significant correlation between sE-selectin levels and capillaroscopy abnormalities in the LoS group and all patients. Only the control group of healthy subjects showed a near-significant difference ($p = 0.064$) between the sE-selectin levels in patients with capillary changes compared with those who presented a normal image of microcirculation in the nailfold.

In the study, the correlation between sIL-2R serum levels and changes in nailfold capillaroscopy was assessed in all patients. The analysis did not show statistically significant differences in sIL-2R levels in subjects with capillary abnormalities compared with those presenting a normal image of nailfold microcirculation in any group: the LoS patients, the control group and all patients.

DISCUSSION

The correlation between capillaroscopy changes and disease severity (including internal organs) as well as vascular damage markers and immune system activity has been confirmed in many studies concerning systemic sclerosis (7, 12).

Valentini et al. reported significantly higher levels of sE-selectin in early SSc patients presenting microvascular changes characteristic of this phase compared to those with positive antinuclear antibodies only. In the same study, there was no correlation between abnormalities in capillaroscopy and sIL-2R concentrations, but there was a significant correlation between the concentration of this molecule and the presence of autoantibodies (12). Valim et al. also confirmed the correlation of sE-selectin concentrations with microvascular depletion that was most apparent during the first 48 months of systemic sclerosis (13). Lis-Święty et al. determined sE-selectin levels in patients with SSc and Raynaud's disease, with statistically significantly higher values in both groups compared to control groups of healthy subjects. However, sE-selectin levels in Raynaud's disease were statistically significantly lower than in systemic sclerosis (14).

In own studies there was no significant relationship between sE-selectin levels, sIL-2R levels and capillary abnormalities observed in LoS patients. It is interesting to note that higher levels of sE-selectin were observed in the control group with concurrent presence of nailfold capillaroscopy changes compared to those with the normal capillary image, and the difference was close to significance ($p = 0.064$).

CONCLUSIONS

On the basis of available reports and self-reported results, the role of nailfold capillaroscopy in the diagnosis of localized scleroderma should be emphasized. Although abnormalities in nailfold microcirculation are rarely observed in this disease, their presence has very significant clinical implications and requires further follow-up. Given the possibility of LoS coexistence with systemic sclerosis and the probability of progression to SSc, each patient with localized scleroderma, especially with concurrent non-dermal symptoms, should undergo capillaroscopic evaluation.

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