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ANALYSIS OF MORPHOLOGICAL AND FUNCTIONAL CHANGES OF KIDNEY ENDOTHELIUM IN SYSTEMIC RHEUMATIC DISEASES

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Метою роботи стала оцінка характеру морфологічних змін ендотелію судин нирок при системному червоному вовчаку, ревматоїдному артриті, геморагічному васкуліті та мікроскопічному поліангіїті, зв'язок з клініко-лабораторними чинниками перебігу захворювань і вплив системної ендотеліальної дисфункції судин. Остання в цих групах хворих бере участь в патогенетичних побудовах нефропатії, щільно пов'язана з системними проявами ангіопатії

***Ключові слова**: нирки, ендотеліум, кровоносні судини, функція, системні ревматичні захворювання*

1. Introduction

Vessels and vascular endothelium are involved in the pathogenesis of inflammatory rheumatic diseases. Systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Henoch-Schönlein purpura (HSP) and microscopic polyangiitis (MPA) combined into a group of systemic autoimmune rheumatic diseases (SRD) [1, 2], the prevalence of which is growing everywhere [3]. The commonness of these diseases is the presence of various autoantibodies in blood [4] and changes in the kidneys blood vessels [5]. Angiopathy is one of the main manifestations of SLE [6, 7] and RA [8–10], and as for patients with HSP and MPA, the vascular inflammatory process is already included in the definition of the names of diseases [11]. In patients with systemic autoimmune diseases, the prevention of kidney failure risk is now regarded as part of the global management along with controlling of disease activity and inflammation. Kidney vessels endothelial dysfunction and accelerated nephropathy are presented in the early years of the disease before nephropathy becomes apparent [12]. The widening of the mortality gap between SRD patients and the general population [13], calls for early identification of patients at higher risk in order to improve outcomes and introduce preventive and therapeutic strategies in early stages, when they are likely to be more effective.

2. Case presentation

The pathogenesis of renal damage vessels in lupus and rheumatoid glomerulonephritis (LGN, RGN) remains not adequately explored [14, 15], although the severity of the vasculopathy determines the prognosis both SLE [16] and RA [17]. The above fully applies to patients suffering from HSP and MPA [18].

It should be noted that SRD are characterized by disorders of vascular endothelial function [19] with the overproduction of vascular endothelial growth factor (VEGF) [20], endothelin-1 (ET1) [21] and E-selectin (ESel) [22]. These processes play an important role in the damage of glomerular capillaries and arterioles of the kidneys at SRD [23], which has been proved by experimental studies in animals [24]. Kidney endothelium responds to systemic vascular endothelial dysfunction (VED) firstly in the patients organism [25, 26].

At the same time, the nature of morphological changes in the endothelium of the kidneys capillaries and arterioles in SLE, RA, HSP and MPA studied insufficiently, to be elucidated the pathogenetic mechanisms of vascular deposition of immune components, the relationship with clinical and laboratory factors of the disease and the effect of systemic VED.

3. Purpose

The purpose of the work was to evaluate the nature of morphological changes in the endothelium of the kidneys capillaries and arterioles in SLE, RA, HSP and MPA, connection with clinical and laboratory factors of the disease course and the effect of systemic vascular endothelial dysfunction.

4. Materials and methods

Study was conducted on the basis of the Donetsk Regional Clinical Territorial Medical Association in Rheumatological department. Analyzed the results of kidney biopsy and laboratory studies of vascular endothelial function in 94 patients with HSP, among which 41 persons suffered from SLE, 17 – RA, 24 – SHP and 12 – MPA. In these groups ratio of men and women, respectively, was as 1: 7, 1: 2, 2: 1 and 1: 3, the average age of the patients – 37.6±1.63 years, 50.1± ±2.33 years, 27, 5±2.19 years and 40,5±3,70 years, the duration of the disease from its manifestation – 11,9± ±1,28 years, 12,4±1,99 years, 10,2±1,77 years, 4 0± ±1,02 years, distribution of patients I, II and III degree of activity of the pathological process – as a 1:2:3, 1:2:2, 2:1:1, 1:2:9. In SLE chronic course of the disease met 5 times more often than subacute, the RA ratio of I: II: III: IV disease stages was as 2:9:5:1, the rate of DAS arthritis activity was 4,9±0,30 r.u., and Lansburi index – 155,8±13,35 points; in SHP purely renal form of the disease, skin – joint – renal, skin – renal, joint-renal, skin – joint – abdominal – kidney, skin – abdominal – renal, joint – abdominal – renal; abdominally – renal forms correlated in frequency 20:13:11:8:6:3:2:1. We studied the clinical course of the index angiopathy (Ω) the formula: $\Omega=(\Sigma:E)\times\Omega=(\Sigma:E)\cdot\sqrt{Y}$, where Σ – sum of points of all clinical signs of SRD, E – the number of features, Y – the degree of disease activity.

Patients underwent echocardiography («Acuson-Aspen-Siemens», Germany, and «HD-11-XE-Philips», the Netherlands), Doppler ultrasonic investigation of blood vessels («Aplia-XG-Toshiba», Japan) and biomicroscopy of vessels of the conjunctiva (slit lamp "Haag-Streit-Bern-900", Switzerland). Determined also instrumental vascular index (Ψ), wherein each average indicator in patient (X) with its standard deviation (ς) were evaluated in 1 point in case of <X+ς, when X+ς↔X+2ς – in 2 points, when X+2ς↔X+3ς – in 3 points, at>X+3ς – in 4 points. Calculated Ψ per patient according to the formula: Ψ=(A+2B+3Γ+4Δ): E, where «A, B, Γ, Δ» – the number of patients accordingly to the 1, 2, 3 and 4 points, «E» – the number of indicators.

Using biochemical analyzer «Olympus-AU-640" (Japan) were investigated the creatinine, immunoglobulin (Ig) A and rheumatoid factor (RF) concentrations in serum, examined levels of antibodies to native deoxyribonucleic acid (aDNA), cardiolipin (aCL), anti-cyclic citrullinated peptide antibody (aCCP), VEGF indicators, ET1, thromboxane-A2 (TxA2), homocysteine (hCys), prostacyclin (PgI2), cyclic guanosine monophosphate (cGMP), ESel, P selectin (PSel), using the immune-enzyme analysis (reader «PR2100 Sanofi diagnostic pasteur», France), and by immunoblotting method (apparatus «Euroline-Euroimmun», Germany) determined antinuclear factor (ANF) and anti-neutrophil cytoplasmic antibody (ANCA) – to myeloperoxidase (aMP) and proteinase-3 (aP3).

Seropositivity of SLE by ANF presence was met in 85.4 % of patients, by aDNA – in 68.3 % and aCL – in 31.7 %; seropositivity of RA by RF (>14 IU/mL) – in 53.0 % and aCCP (>17 U/ml) – in 94.1 %; seropositivity of HSP by IgA (>3 mmol/l) – in 41.7 % and by RF – in 29.2 %; MPA seropositivity by ANCA was in all cases, and the ratio aMP to aP3 was as a 5: 1. For the evaluation of renal function was used defining glomerular filtration rate (GFR) using CKD-EPI formula. To study the integral index of VED (Θ) was calculated the degree of vasoconstrictor indicators changes (Δ) – VEGF, ET1 and TxA2 and vasodilator PgI2 using formula: $X=[(I_1–I_2):ς]^2$, where I_1 and I_2 – indicators at sick and healthy, ς – the standard deviation of the healthy. Θ determined by the formula:

$$\Theta = \sqrt{(K + \Lambda + M) : N},$$

where «K» – VEGF, «Λ» – ET1, «M» – TxA2, «N» – PgI2 (VED diagnosed in Θ>5 r.u). As a control, laboratory parameters were studied in 30 healthy subjects (13 men and 17 women aged 18–65 years).

Kidney biopsy was performed on the background of ataralgesia by controlling of kidney ultrasound. We used the technique of «True-Cut» («the present cut-off») with «Biopty-Bard» high-speed gun. Histological sections of the kidneys were stained with hematoxylin-eosin, alcian blue (on glycoproteins) and Van Gieson (collagen and elastic fibers), becoming the PAS-reaction. In addition, the enzyme immunoassay (with peroxidase labele) and immunofluorescence methods of kidney tissue research were performed. IgA, IgG, IgM deposits, C3- and Cq1- complement components were studied. Microscopic examination was performed on a microscope «Olympus-AX40» and «Olympus-AX70-Provis» with a digital video camera «Olympus-DP50». Renal failure of individual structures (glomeruli, tubules, stroma and vessels) were scored (from 0 to 3). Also there was calculated average damage indicator (θ) according to the formula: θ=(α+2β+3γ):(α+β+γ+δ), where «α, β, γ» – the number of patients correspondingly with 1, 2 and 3 points and «δ» – the number of patients with the absence of this sign.

Kidney biopsy is performed only in patients with the presence of proteinuria; nephrotic syndrome had 4 patients with SLE, 2 with RA and 2 with HSP. Ratio of CKD I, II, III and IV stages in SLE was as 10:7:2:1, in RA – 9:5:2:1, in HSP – 4:4:1:1, MPA – 5:4:2:1, and the average GFR in these groups was about the same, amounting to 96,1±4,17 ml/min/1.73 m^2, 97,0±7,35 ml/min/ 1.73 m^2, 100,7±3,61 ml/min/1.73 m^2, 88,4±7,12 ml/min / 1.73 m^2. In RA, patients with secondary AA-amyloidosis of the kidneys were excluded. In the survey group consisted of persons suffering from RGN the ratio of mesangioproliferative to mesangiocapillary RGN was as 2:1. Ratio of II:III:V:IV class of LGN frequency was as 1:2:4:13, and V:VI: IV:III:II type of Henoch-Schönlein purpura nephritis (HSPN) – 1:3:4:6:10. It should be emphasized that all 94 examined patients with SRD had tubulointerstitial changes in their kidneys.

Statistical analysis of the results of research was conducted by computer variation, correlation, regression, single-factor (ANOVA) and multivariate (ANOVA/ MANOVA) analysis of variance (program «Microsoft Excel» and «Statistica-Stat-Soft», USA). Assessed mean values (X), their standard deviations (ς) and error rates (μ), coefficient of parametric Pearson correlation (r) and nonparametric Kendall (τ), regression criteria (R), dispersion Brown-Forsythe (BF) and Wilcoxon-Rao (WR), McNemar-Fisher criteria, Student's test (t) and the probability of statistical indicators (p).

5. Results

Noteworthy the fact definite quantified differences of kidneys vascular lesions nature in the individual SRD. So, θ in RA patients was 0,43±0,050 r.u., in cases HSP – 0,69±0,059 r.u., SLE – 0,89±0,043 r.u., MPA – 1,01±0,130 r.u. VED established in 35.3 %, 51.9 %, 39.0 % and 100.0 % of those surveyed, and Θ was 4,5±0,36 r.u., 5,3±0,35 r.u., 4,8±0,14 r.u. and 6,5±0,55 r.u.

The frequency of certain morphological characters of vascular endothelium at SRD is presented in Table. 1.

According to performed ANOVA/MANOVA, SRD nosological forms have a highly significant (p<0,001) influence on the integral state of capillary endothelium (WR=3,60) and arterioles (WR=2,29). In multivariate Wilcoxon-Rao analysis, the lesion of the capillaries endothelium and arterioles of the kidneys depend on the cutaneous syndrome severity (consequently WR=2,49, p=0,002 and WR=2,05, p=0,027), as well as peripheral neuropathy (WR=1,92, p=0,022 and WR=1,97, p=0,035).

Table 1

The frequency of the certain features of vascular endothelium lesion and the accuracy of the impact on them the integrated clinical and instrumental indicators of vascular disease in patients with SRD

Morphological signs of vascular endothelial lesion		Groups of patients with SRD			Integrated indicators		
	SLE	RA	HSP	MPA	Ω	Ψ	
	frequency of symptoms, (%)				degree of impact, (p BF)		
Endothelium proliferation	capillaries	97,6	17,7	33,3	91,7	0,461	0,555
	arterioles	29,3	17,7	54,2	83,3	0,629	0,509
Deposits in capillaries	IgA	90,3	82,4	100,0	100,0	0,048	0,124
	IgG	92,7	94,1	91,7	91,7	0,792	0,572
	IgM	95,1	88,2	75,0	91,7	0,493	0,295
	C3	65,9	54,0	41,7	50,0	0,451	0,831
	C1q	48,8	11,9	25,0	58,3	0,724	0,529
Deposits in arterioles	IgA	22,0	23,5	54,2	33,3	0,019	0,364
	IgG	29,3	23,5	37,5	33,3	0,036	0,709
	IgM	29,3	5,9	16,7	25,0	0,635	0,536
	C3	22,0	5,9	12,5	25,0	0,614	0,509
	C1q	19,5	5,9	4,2	25,0	0,545	0,115

The presence of VED has an impact on the nature of arteriolar endothelial changes (WR=1,47, p=0,046). In patients with SLE indicators of system VED effect on capillary endothelial damage (WR=2,95, p=0,042), which is confirmed by the direct dependence of integrated morphological parameters of Θ (R=+7,42, p<0,001). In addition, multiple regression analysis set positive relationship Θ with changes of capillaries endothelium and arterioles at HSP (correspondingly R=+2,98, p=0,008 and R=+9,73, p<0,001) and MPA (R=+6, 81, p=0,001 and R=+6,50, p=0,002).

Indicators of vascular endothelial function in healthy subjects in the control group and patients with SRD reflected in the Table 2.

Table 2

Indicators of endothelial vessels function in serum of healthy and SRD patients (M±m)

Indicators	Groups of patients with SRD				
	Healthy (n=30)	SLE (n=41)	RA (n=17)	HSP (n=24)	MPA (n=12)
VEGF, pg/ml	90,0±5,28	534,3±11,63*	109,2±8,60	515,5±12,98*	545,0±22,46*
ET1, pg/ml	4,0±0,10	7,8±0,36*	5,7±0,43*	7,9±0,48*	7,7±0,55*
TxA2, ng/ml	8,0±1,56	9,5±0,47	9,6±0,79	10,1±0,57	10,9±1,28
HCys, mcmol/l	9,3±0,48	16,0±0,66*	16,2±0,86*	16,5±0,76*	16,9±1,17*
PgI2, ng/ml	72,6±9,01	18,4±1,06*	18,8±1,66*	17,7±1,19*	19,1±1,93*
cGMP, pmol/ml	11,2±0,20	13,6±0,48*	13,4±0,70*	12,8±0,55*	12,9±0,66*
ESel, ng/ml	246,7±12,12	230,1±6,30	211,9±3,18*	227,7±6,27	214,1±8,88
PSel, ng/ml	41,1±1,41	48,9±1,54*	47,9±1,82*	47,6±1,79*	49,1±2,96*

*Note: * – the differences between similar indeces of ill and healthy patients are statistically significant (p<0,05)*

The similarity for all SRD was significantly higher parameters of ET1, HCys, cGMP and PSel in the blood on background of unchanged concentration of TxA2. However, only for the RA proved atypical elevated levels of VEGF and only in this group stated reduction of ESel.

In patients with LGN Θ index affects the proliferation of capillaries and glomerular endothelium (BF=3,38, p=0,028), and arterioles (BF=3,25, p=0,033), which demonstrates the Brown-Forsythe variance analysis. In turn, in RGN such connection concerns only arteriolar endothelium (BF=10,81, p=0,002), while the MPA – capillaries (BF=5,29, p=0,027).

6. Discussion

The least significant vascular changes observed in RA, and the most pronounced – in MPA. The same results was got by Koseki at all during a 42-month observation period in prospective study of renal disease in patients with early rheumatoid arthritis: only in 7 % of the patient with RA was developed persistent proteinuria and 6 % presented elevated serum creatinine with or without proteinuria. [27]. These abnormalities were mostly drug-related and reversible after discontinuation of the treatment [8, 10]. On renal biopsy, MPA typically presents as a pauci-immune (devoid of immune complexes), necrotizing and crescentic glomerulonephritis – which is why renal MPA often presents as a rapid progressive disease with advanced stage of renal failure [12]. Only the group of patients with SLE and MPA did not differ in frequency of immune deposits in the kidneys blood vessels that demonstrate fulfilled McNemar-Fischer analysis. Lupus and necrotizing nephritis determines long-term morbidity and mortality in SLE and MPA because renal failure in SRD is associated with a large number of secondary and tertiary complications [12, 16].

The proliferation of capillary endothelium to a greater extent has been characteristic of SLE and MPA, and arteriolar endothelium – only of the MPA, whereas these changes were not characteristic for RA. Despite some differences in the clinic of primary systemic necrotizing vasculitis – MPA and systemic autoimmune diseases – SLE, they share a number of common pathogenetic mechanisms, which are based on immunological process [15, 16].

As expected, IgA deposits in the blood vessels were the most typical to Henoch-Schönlein purpura nephritis, because its a small vessel vasculitis mediated by IgA-immune complex deposition [11], and C1q – for LGN and MPA, C1q deposits are usually found in association with other complement components and immunoglobulins in proliferative glomerulonephritis and may predominate in SLE

and MPA [7]. C1q deposits were quasi-constantly found in SLE patients with or without skin lesions (90 %).

The clinical vascular manifestations of SRD are considered with the presence of skin purpura, telangiectasia, capillaritis of hands and feet, antiphospholipid syndrome, Raynaud's syndrome, uveitis, cheilitis, leukocytoclastic enantemy, peripheral vasoneuropathy, vascular encephalopathy and pulmonary hypertension.

With Ψ index at SRD weakly related morphological characteristics of renal endothelium lesion. The vascular lesion confirm extensive previous data that immune complexes in vessels do not bind significantly to unstimulated endothelial cells [17].

In turn Ω has a significant impact on IgA deposition in the glomerular capillaries (BF=2,78, p=0,048) and arterioles (BF=3,49, p=0,019) as well as deposits IgG in arterioles (BF=2,99, p=0,036) that showed with Brown-Forsythe variance analysis. According to the analysis Kendall, there are direct correlations Ω indices with IgA deposition rate in capillaries (τ=+0,187, p=0,005), and in renal arterioles (τ=+0,141, p=0,036). With that said, the rate of Ω>1,5 r.u. (>X+ς patients SRS) is a risk factor for high level of IgA deposits in the renal vascular endothelium. The pathogenesis of immune complex mechanism is characterized by the deposition in the different structure of the kidney tissue of immune deposits and Ig. As part of the deposited immune complexes is most often defined "full house" – the entire set of Ig and complement components. Immune complexes can be deposited not only in the glomeruli, but also in the tubular basement membrane and into the vessel walls. Different types of angiopathy can be observed in the glomerular aparatus at SRD [19].

In LGN Θ index closely related with deposition in glomerular capillary endothelium of C3 (BF=3,96, p=0,015), in HSGN- IgM (BF=3,19, p=0,048), and with MPA – IgA (BF=7 99, p=0,010), IgG (BF=4,42, p=0,041), IgM (BF=4,26, p=0,045), C1q (BF=20,24, p<0,001). The co-localization of Ig isotypes IgG, IgA and IgM with C1q, C4 and C3 (the so called 'full house' pattern) in the glomeruli is almost exclusively present in glomeruli of patients with lupus nephritis [20]. Given that C3 is the common point connecting all three pathways in complement activation and is tightly regulated naturally, many of the studies in lupus mice have concentrated on activators and regulators of C3 [14].

Deposits in the kidneys arterioles in SLE concern C1q (BF=23,63, p<0,001), in HSP – IgA (BF=6,84, p=0,002), IgG (BF=9,76, p<0,001) and C1q (BF=24,48, p<0,001), in RA – IgA (BF=4,47, p=0,032), IgG (BF=3,39, p=0,048), IgM (BF=19,74, p=0,001), C3 (BF=9,65, p= =0,007) and C1q (BF=9,65, p=0,007).

Renal vascular endothelium synthesizes vasoactive hormones such as endothelin, NO, prostacyclin, thromboxane, participating in vascular endothelial function, as well as factors of coagulation and inflammation that cause endothelial participation in the processes of regulation of renal function, inflammation, possible further sclerosis and destruction of nephrons [2]. Thus, VED is involved in the processes of deposition of immunoglobulins and complement components in the endothelium of the kidney vessels at all SRD, but RA characterized by deposits exclusively in the arterioles, and MPA – in glomerular capillaries, that is likely due to the nature of renal tissue destruction.

It is also noteworthy that in SLE patients, anti-C1q antibodies are associated with proliferative lupus nephritis, and anti-C1q antibody levels may indicate renal disease activity decreased C3 and C4 levels have been found in about 75 % of SLE patients with focal nephritis and 90 % in patients with diffuse nephritis [26]. Additionally, the co-localization of Ig isotypes IgG, IgA, and IgM with C1q, C4 and C3 (and C5b-9) (the so called "full house" pattern) in the glomeruli is almost exclusively present in glomeruli of patients with lupus nephritis and necrotising vasculitis in MPA [11]. Finally, complement split products such as C3d and C5b-9 can also be detected in the urine of SLE patients[16]. Impaired immune complexes handling plays an important role in the pathogenesis in LGN. Since the complement system is required at all steps of normal immune complexes metabolism, any number of alterations can lead to pathological glomerular immune complexes accumulation, particularly in conditions of immune complexes excess, as in SLE and MPA [26].

In addition to the dispersion relation, deposition C3 in the endothelium of the capillaries in SLE patients and C1q – in patients with MPA directly correlates with Θ parameter that reflects Kendall analysis (respectively τ=+0,224, p=0.045 and τ=+0,464, p=0.036). It can be considered in this regard that Θ>4 r.u. in cases of LGN and Θ>8 r.u. in cases of MPA (>X+ς appropriate patients) are prognosis negative criteria of deposition of complement components in the glomerular capillaries.

We have selected those indicators of endothelial function of blood vessels, with which some morphological characteristics of vascular endothelial kidney changes at the same time had both dispersion, and correlation relations. Thus, in LGN the degree of proliferation of glomerular capillaries endothelium directly depends on the content of ET1 (BF=3,06, p=0,040; τ=+0,234, p=0,031), and arteriolar endothelium – from ESel (BF=3,06, p=0,040; τ=+0,234, p=0,0311). IgG deposition in capillaries and arterioles in patients with RGN closely linked to the concentration of PSel (respectively BF=9,84, p=0,002; τ=+0,389, p=0,029 and BF=16,66, p<0,001; τ=+0,369, p=0,039), and IgA in HSPN – with level of HCys (BF=7,78, p=0,003; τ=+0,449, p=0,002 and BF=4,05, p=0,033; τ=+0,390, p=0.030). Patients with MPA on proliferation of glomerular endothelial affect the values of VEGF (BF=27,64, p <0,001; Θ=+0,436, p=0,049). We can assume that these factors of VED are involved in the pathogenesis of renal vascular damage constructions in different SRD. VED is considered as the consequence of a combination of elements including genetic predisposition, traditional cardiovascular risk factors and systemic inflammation. Therefore it is striking that in RA the contribution of systemic mediators of inflammation to VED is not yet elucidated [22]. VED is also associated with vascular complications in several

systemic autoimmune diseases. Several published studies have demonstrated that VED from the sera of patients with MPA, HSP, SLE and RA was able to modulate endothelial cell function and activate endothelial cells, leading to the production of pro-inflammatory cytokines together with a pro-adhesive phenotype [28]. Likewise whether such circulating indices of systemic inflammation could be used as biomarkers of VED.

7. Conclusions

1. VED like an imbalance of vasoconstrictors VEGF, ET1, TxA2 and vasodilator PgI2 occurs in 35 % of RA patients with renal lesion, in 39 % of SLE, 52 % with VSHG and 100 % with MPA, participating in the pathogenesis of endothelial changes in glomerular arterioles and capillaries.

2. The morphological lesion of the endothelium of renal vessels are closely linked with the severity of clinical and instrumental signs of extrarenal systemic angiopathy (with skin lesions, mucous membranes and the peripheral nervous system, with parameters biomicroscopy of vessels of the conjunctiva and vasodilation of the brachial artery).

3. The proliferation of glomerular endothelium of patients with MPA determines serum concentration of VEGF, and in the development of renal endothelial immune deposits (IgA, IgG, IgM, C3, C1q) in LGN involved ET1 and ESel, in RGN – PSel, when HSPN – HCys.

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