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Drug-induced urticaria – activity of selected cytokines and acute phase proteins in plasma

Drug-induced adverse skin reactions are connected with various forms of inflammatory and immune responses, the nature of which is not entirely elucidated yet. Cell-mediated response seems to be involved in some of them (erythema fixum, erythema multiforme, maculopapular exantems, Lyell's syndrome), circulating immune complexes in another (hyperergic vasculitis), and humoral IgE-related response in urticaria/angioedema. In recent years, however, elevated levels of some cytokines being the correlates of cell-mediated immunity were observed in drug-induced urticaria (2,3,5,6,7,8). Release of MIF (macrophage migration inhibition factor) as well as other Th1 cytokines including interferon-γ (IFN-γ), has been reported in drug-induced immediate hypersensitivity reactions, such as diclofenac-induced urticaria, allergy to penicillin manifested by urticaria, angioedema and macular exanthem (1,3,8). It suggests more complex character of pathogenic phenomena in cutaneous adverse drug reactions that do not allow to distinguish clearly between humoral and cellular immune responses. Drug-induced urticaria is one of the most common type of cutaneous adverse drug-reactions (8). It seems interesting to examine the activity of cytokines connected with promotion of T cell-mediated response (IL-2, sIL-2R) or exerting the moderatory influence upon cellular/humoral responce balance (IL-10, p55TNF-R) in disease in which mostly immediate hypersensitivity is engaged. Some cytokines can influence mobilization (IL-6, TNF-α) and extinguishing (IL-10, p55TNF-R) of the acute phase reaction.

The aim of the present study was to evaluate plasma activity of some cytokines, their receptors and induced by them acute phase proteins in drug-induced urticaria.

MATERIAL AND METHODS

33 adult patients with drug-induced urticaria were included into the study. Among them were 17 women and 16 men. The mean age of the group was 40 years, the range between 18–74 years. All the patients took the culprit drugs several hours to 4 days before their urticaria appeared. 13 patients received only 1 drug (antibiotic or analgetic/antipyretic), 9 patients 2 drugs simultaneously (two analgetics) and 11 persons took 3 and more drugs (most frequently analgetics with nonsteroidal antiinflammatory drugs). Among the causative drugs in all group of 33 patients the most common were: analgetics/antipyretics; antibiotics (especially penicillin, amoxicillin); nonsteroidal antiinflammatory drugs (especially piroxicam).

Blood samples were taken from all the patients: a) during the acute stage of disease, before the treatment was administered; b) after clearing of skin lesions following the effective treatment. Duration of treatment was 5–10 days, but repeated measurements were done 14 days after the previous ones. The control group consisted of 30 healthy volunteers in appropriate age. Plasma concentrations of the following proteins were examined: interleukin-2 (IL-2), soluble interleukin-2 receptor (sIL-2R), interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor-α (TNF-α), p55 soluble TNF receptor (p-55sTNF-R), C-reactive protein (CRP), α-2 macroglobulin (α-2 MG).

Measurements of protein concentrations. An enzyme-linked immunosorbent assay (ELISA) was used to detect and quantify the presence of selected proteins in plasma. The kits for ELISA were provided by Endogen Inc.USA (cytokines and receptors); Eucardio Laboratory Inc.USA (CRP); Immunodiagnostik GmbH Germany (α-2 MG). The measurement were done in duplicates according to the instructions included in the assay. The data were put to statistical analysis. Average (M), median (Me), standard deviation (SD), the mean error of the average (SE) and variation coefficient (V%) were evaluated. Significance of differences between the average values was tested by Student's t-test, Cochran's-Cox's test and Mann-Whitney's test.

RESULTS

In a group of 33 patients with drug-induced urticaria the acute symptoms of disease were followed by considerable elevation of plasma levels of examined proteins ($p<0.001$) in comparison to the controls (Tab.1, Fig.1). After clearing of skin lesions the proteins' concentrations were distinctly lowered in comparison with the active stage ($p<0.001$) and it is worth to stress that mean plasma levels of sIL-2R, IL-10, TNF-α and CRP despite their deep decrease were still significantly higher than in the healthy control ($p<0.001$). Moreover, mean concentration of IL-2 receptor after clearing of lesions was still high, despite the fact that the level of cytokine came back to the control values and reversely: prolonged increased concentration of TNF-α was found out although its receptor level returned to normal values. It is specially interesting because these proteins can partially block each other's activity. Appart from this, TNF-α can induce releasing of inflammatory mediators from cutaneous mast cells in hypersensitivity IgE-related reactions (4). It seems that especially IL-10 activity in the examined patients may have some clinical implications. Elevated concentrations of IL-10, cytokine connected with promotion of humoral type response, persisting after total regression of clinical symptoms in drug-induced urticaria, can indicate a possibility of disease recurrence after re-exposure to the same or chemically related drug.

Similar character of changes in IL-6 activity and induced by this cytokine α-2 MG are also worthy to stress. Both these proteins are highly elevated in peripheral blood during the acute stage of disease and both returned towards control values after clearing of urticaria. Increase of CRP and α-2 MG plasma levels observed in this study indicate that in drug-induced urticaria the acute phase response can be mobilized. Some of the examined cytokines take part in the control of this dynamic process as its positive (IL-6, TNF-α) or negative (IL-10, p55 TNF-R) regulator.

Elevated α-2 MG levels in plasma were also observed by the Finnish authors in patients with drug-induced urticaria (9). It is striking that the majority of the examined patients confirmed the use of more than one drug before their urticaria appeared. In this study, analgetics appeared to be most frequently culprit drugs. Although other authors acknowledge the role of this group of drugs in inducing urticaria, they regard antibiotics as the most common causative agents (10, 11). In recent years, the participation of large group of drugs applied in cardiovascular system diseases still increases in the adverse drug-induced cutaneous reactions,

including urticaria. Disorders of urticaria/angioedema type were observed as caused by angiotensin convertase inhibitors, e.g. captopril, enalapril (8,10).

Table 1. Plasma concentration of measured proteins in patients with drug-induced urticaria and control group

Protein	Group	Statistical characteristics							Comparison with control	
		n	M	SD	SE	Min	Max	V%	p	lg%
IL – 2 pg/mL	C	30	2.08	1.95	0.36	0	8.00	93.9		
	P_1	33	14.93	8.62	1.50	0	35.80	57.76	$p < 0.001$	2.85
	P_2	33	2.48	2.87	0.50	0	12.40	115.48	$p > 0.05$	2.07
sIL - 2R U/mL	C	30	253.33	106.35	19.42	96.0	420.0	41.98		
	P_1	33	1839.61	1057.10	184.02	245.00	5520.00	57.46	$p < 0.001$	2.86
	P_2	33	758.70	452.88	78.83	234.00	2402.00	59.69	$p < 0.001$	2.47
IL – 6 pg/mL	C	30	1.83	1.34	0.25	0	5.6	73.21		
	P_1	33	11.72	16.58	2.89	0.30	67.00	141.51	$p < 0.001$	2.80
	P_2	33	2,04	2.52	0.43	0	12.80	123.55	$p > 0.05$	2.04
IL – 10 pg/mL	C	30	3.14	1.80	0.33	0.60	7.60	57.35		
	P_1	33	22.97	14.65	2.55	4.60	65.20	63.77	$p < 0.001$	2.84
	P_2	33	10.98	9.90	1.72	0.90	42.50	90.15	$p < 0.001$	2.54
TNF – α pg/mL	C	30	2.57	3.03	0.55	0	10.20	117.80		
	P_1	33	19.59	10.32	1.78	0	38.70	52.70	$p < 0.001$	2.88
	P_2	33	6.46	4.66	0.81	0	14.30	72.10	$p < 0.001$	2.40
p55 TNF – R pg/mL	C	30	210.50	73.97	13.50	52.00	352.00	35.14		
	P_1	33	322.85	183.75	31.99	168.00	1170.00	56.92	$p < 0.001$	2.18
	P_2	33	208.70	82.17	14.30	48.00	472.00	39.37	$p > 0.05$	1.99
CRP mg/L	C	30	0.29	0.30	0.05	0	0.86	102.46		
	P_1	33	8.53	5.44	0.95	1.38	20.00	63.73	$p < 0.001$	3.46
	P_2	33	1.85	1.48	0.26	0.24	6.22	79.99	$p < 0.001$	2.80
α - 2MG mg%	C	30	129.53	42.87	7.82	30.00	190.00	33.10		
	P_1	33	528.30	196.54	34.21	106.00	740.00	37.20	$p < 0.001$	2.61
	P_2	33	176.97	105.72	18.40	42.00	560.00	59.74	$p > 0.05$	2.13

C – control, P_1 – patients before treatment, P_2 – patients after treatment

The mechanism of urticaria, disease connected basically with immediate-type reaction, is not quite clear in case of drug-induced urticaria, which may be suggested by increased activity of cytokines, being cell-type immune mediators observed in this study. It seems that other various mechanisms also take part, which results in releasing of histamine and other active mediators causing increased permeability and vasodilatation in skin (11).

CONCLUSIONS

1. In drug-induced urticaria plasma concentrations of examined cytokines, receptors and acute phase proteins are highly elevated and they can change with the disease activity.

2. Elevation of plasma levels of some proteins being the cellular immunity correlates, supports the belief of more complex character of

pathogenic phenomena than immediate response taking part in drug-induced urticaria.

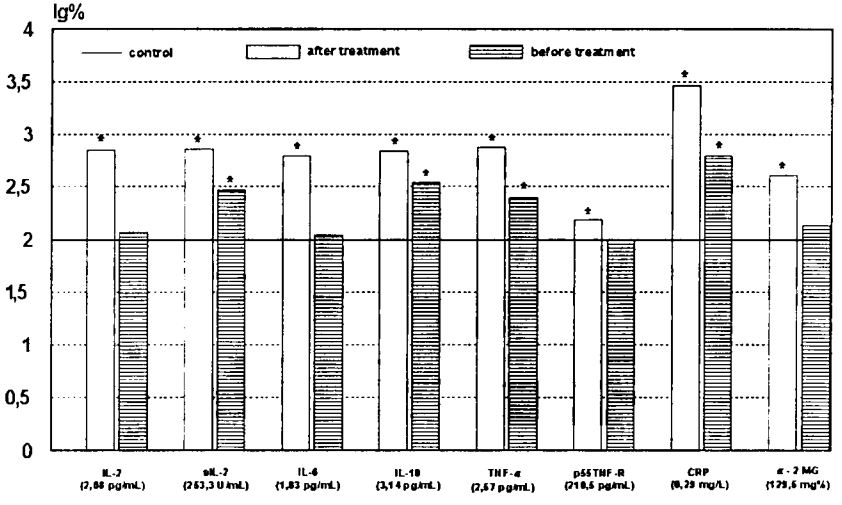

Fig. 1. Plasma concentrations of examined proteins in patients with drug-induced urticaria before and after treatment expressed as lg% of the control values;1) control values are expressed below respective bars 2) significance of differences in comparison with control expressed as * $p < 0.001$

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SUMMARY

Plasma concentrations of 8 proteins, including cytokines: interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor-α (TNF-α), receptors: soluble IL-2 receptor (sIL-2R), p55 soluble TNF receptor (p55 sTNF-R) and acute phase proteins: α-2 macrogloulin (α-2 MG), C-reactive protein (CRP) were examined in 33 patients with drug-induced urticaria. The activity of selected proteins was measured using the immunoenzymatic ELISA method: a) in the acute stage of disease before treatment was administered, and b) after clearing of skin lesions, after treatment. In the acute stage of disease elevated concentrations of the examined proteins ($p<0.001$) in comparison to the control were found. After clearing of clinical symptoms the concentrations of IL-2, IL-6, p55TNF-R and α-2 MG were not significantly different from the control values. But despite deep decrease, sIL-2R, IL-10, TNF-α and CRP levels were still significantly elevated ($p<0.001$) when compared to the control. Results of this study indicate complex character of pathogenic phenomena in drug-induced urticaria in which elevated activity of mediators acting as promotors and modulators of cellular immune response can be found.

Pokrzywka polekowa - osoczowa aktywność wybranych cytokin i białek ostrej fazy

Badano stężenia osoczowe 8 białek, w tym cytokin: interleukiny-2 (IL-2), interleukiny-6 (IL-6), interleukiny-10 (IL-10), czynnika martwicy nowotworów-α (TNF-α); receptorów: rozpuszczalnego receptora IL-2 (sIL-2R), rozpuszczalnego receptora p55 TNF (p55TNF-R) oraz białek ostrej fazy: α-2 makroglobuliny (α-2 MG) i białka C-reaktywnego (CRP) u 33 chorych z ostrą pokrzywką polekową. Aktywność wybranych białek oznaczano w osoczu przy pomocy metody immunoenzymatycznej ELISA: a) w ostrym okresie choroby przed rozpoczęciem leczenia oraz b) po ustąpieniu zmian chorobowych i zakończeniu leczenia. Stwierdzono znaczne podwyższenie stężeń badanych białek przed leczeniem ($p<0,001$) w porównaniu z grupą kontrolną. Po ustąpieniu objawów klinicznych stężenia IL-2, IL-6, p55TNF-R i α-2 MG nie różniły się od wartości obserwowanych w grupie kontrolnej, natomiast poziomy osoczowe sIL-2R, IL10, TNF-α i CRP, pomimo znacznego obniżenia, pozostały nadal wysoce istotnie podwyższone w porównaniu z grupą kontrolną. Uzyskane wyniki wskazują na złożony mechanizm patogenetyczny pokrzywki polekowej, w której przebiegu można obserwować podwyższone wartości także mediatorów związanych z promowaniem oraz modulowaniem odpowiedzi immunologicznej typu komórkowego.