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TUMOR NECROSIS FACTOR IN ACUTE LEUKEMIA PATIENTS

***Aim**: to study the tumor necrosis factor (TNF) concentration in blood plasma of the patients with acute leukemia (AL), its production by the primary culture of peripheral blood mononuclear cells (PBMC) and to estimate the relation between these rates and hematologic signs of the AL. **Material and methods**: the TNF concentration in blood plasma of 44 patients with AL was studied applying biological method based on its cytolytic effect in TNF-sensitive culture of L929 line transformed mouse fibroblasts estimated by radiometric method. **Results**: TNF concentration in blood plasma of the patients with AL is significantly higher than normal value, and its production by the PBMC increases too. But the TNF fraction produced by PBMC in TNF plasma concentration (Index I) is smaller than in healthy persons. Anemia and thrombocytopenia are accompanied by the increase of TNF concentration in blood plasma, as well as its production by PBMC. **Conclusions**: the results make it possible to consider the increase of TNF level in AL as a pro-apoptotic manifestation of changes in hematopoiesis which results in the development of anemia and thrombocytopenia.*

Tumor necrosis factor (TNF) is of special significance among cytokines since its biological characteristics and functions are extremely varied. Multiple studies have proved that TNF can both inhibit the development of some kinds of new-growths and physiologically regulate growth, differentiation and metabolism of various cell types. A lot of research has been done into the connection between TNF and individual manifestations of lymphoid neoplasm [1–4], as well as its prognostic validity in chronic lymphocytic leukemia (CLL) [5, 6] and malignant lymphomas [7, 8]. However, the number of works on changes in TNF concentration in case of acute leukemia (AL) is insufficient and their results are often contradictory [9–14].

The aim of this research is to study TNF concentration in blood plasma of patients with AL, its production by the primary culture of peripheral blood mononuclear cells (PBMC) (mixture of blasts and lymphocytes) and to estimate the relation between these rates and some clinical symptoms of the disease.

PATIENTS AND METHODS

The study includes 44 patients with AL (28 male and 16 female) from 16 to 81 years old (the median value is 57,5 years), 30 of them were diagnosed with AL for the first time, 14 were examined during first early relapse of the disease. On the basis of cytological, cytochemical and immunological analysis, 23 patients were diagnosed with acute lymphoblastic leukemia (ALL) and 21 patients were diagnosed with acute myeloid leukemia (AML). The TNF concentration was determined with the biological method [15] in blood plasma of patients with AL as well as in conditioned substrates of PBMC cultures.

The TNF concentration was examined for patients without infectious complications, before the beginning of cytostatic treatment, in blood plasma and supernatant fluid of the cultures of mononuclear cells obtained from peripheral blood in the density gradient of ficoll-verografin ($\rho = 1.077$). PBMC of the patients containing blast cells and lymphocytes were cultivated for cytokine production in the concentration of $5 \cdot 10^5$ cells/ml of substrate RPMI-1640 in the atmosphere of CO_2 with the temperature of 37 °C during 24 hours without stimulation. The plasma and supernatants before the study were kept under the temperature conditions of –30 °C.

The TNF concentration (total $\alpha + \beta$) was determined using the biological method based on the lysis level of TNF-sensitive culture of transformed mouse fibroblasts of L929 line. The experiment used trypsinized L929 line cells on the 3rd day after passage, marked by the standard method with H^3-methyl thymidine and processed with actinomycin D. The suspension of the marked L929 line cells in $8 \cdot 10^5$ cells/ml concentration of the substrate was introduced by 100 µl into a 96-well plate; 150 µl of the test samples of plasma or supernatants of PBMC cultures were added into every well; the study was done in triplets. The cytotoxic effect of TNF from the test samples on the L929 line cells was estimated by the level of spontaneous appearance of the radioactive tracer after 24 hours of incubation by the radiometric method. A calibration curve based on the results of recombinant human TNF titration (Sigma, $LD_{50} = 0.067$ ng/ml) on the L929 line cells was used to determine the TNF concentration.

Taking into account the possibility of TNF presence in blood not only from immunocompetent cells and leukemic cells of peripheral blood, a ratio of TNF production by PBMC to its concentration in blood plasma was calculated too (index I).

The control group for determining normal indicators of TNF concentration in blood and its production by PBMC consisted of 15 healthy persons, blood donors, from 21 to 39 years old, 11 of them being male and 4 female.

Statistical summarizing of obtained data has been performed using application programs Statistica 6.0 and

MS Excel with program maintenance Attestat. Parametrical criteria (the mean and its standard error) were used after proving normal (Gaussian) distribution of the data applying Epps — Pally test. The difference among the compared groups using *t*-test was considered to be significant if the error probability was < 5%. Pearson's correlation coefficient (r) was applied for correlation analysis.

RESULTS AND DISCUSSION

Values of TNF concentration in blood plasma of patients with AL depending on demographic indicators and some hematological parameters are presented in the Table. In the general group of patients with AL, TNF concentration in blood plasma was on average 0.971 ± 0.136 ng/ml, which is more than 10 times as much as that in the group of healthy individuals (0.089 ± 0.017 ng/ml; $p < 0.001$). TNF concentration in blood plasma did not depend on the AL variant: TNF in the plasma of the patients with ALL was 1.065 ± 0.242 ng/ml, while that of the patients with AML was 0.908 ± 0.163 ng/ml ($p > 0.05$).

Table

Concentration of TNF in blood plasma of patients with AL and its production by PBMC depending on age, sex and hematological parameters (M ± m)

Indicant	TNF, ng/ml	TNF of PBMC, ng/ml	Index (I)**
Control group	0.089 ± 0.017	0.070 ± 0.002	0.768 ± 0.046
Patients with AL	0.971 ± 0.136*	0.292 ± 0.072*	0.379 ± 0.080*
ALL	1.065 ± 0.142	0.360 ± 0.030	0.605 ± 0.116
AML	0.908 ± 0.163	0.219 ± 0.056*	0.232 ± 0.063*
Age, years:			
< 60	1.016 ± 0.164	0.306 ± 0.100	0.389 ± 0.101
> 60	0.893 ± 0.148	0.258 ± 0.066	0.356 ± 0.135
Sex:			
male	0.882 ± 0.165	0.273 ± 0.099	0.435 ± 0.116
female	1.104 ± 0.137	0.330 ± 0.092	0.290 ± 0.096
Blast cells in bone marrow, %:			
< 75	0.980 ± 0.178	0.200 ± 0.040	0.326 ± 0.086
> 75	0.953 ± 0.111	0.497 ± 0.110*	0.489 ± 0.172
Hemoglobin, g/l:			
> 100	0.721 ± 0.233	0.176 ± 0.061	0.356 ± 0.223
< 100	1.033 ± 0.149	0.349 ± 0.103	0.385 ± 0.085
Erythrocytes, $\times 10^{12}$/l:			
> 3	0.858 ± 0.172	0.166 ± 0.053	0.303 ± 0.128
< 3	1.027 ± 0.156	0.370 ± 0.101*	0.409 ± 0.092
Platelets, $\times 10^{9}$/l:			
> 100	0.930 ± 0.174	0.203 ± 0.048	0.360 ± 0.123
< 100	1.053 ± 0.189	0.430 ± 0.104*	0.411 ± 0.114
Leukocytes, $\times 10^{9}$/l:			
< 4	0.796 ± 0.153	0.456 ± 0.197	0.534 ± 0.133
4–9	1.090 ± 0.129	0.423 ± 0.120	0.365 ± 0.143
> 9	0.940 ± 0.195	0.193 ± 0.045*	0.358 ± 0.104
Erythrocytes sedimentation rate, mm/h:			
< 20	0.772 ± 0.189	0.125 ± 0.057	0.418 ± 0.134
> 20	1.031 ± 0.155	0.328 ± 0.086*	0.368 ± 0.083

*$p < 0.05$ – statistical significance of differences compared to the figures of the previous group.

**Ratio of TNF production by PBMC to its concentration in blood plasma.

TNF concentration in blood plasma in age and gender groups of patients with AL in statistical terms was significantly higher ($p < 0.001$) than the corresponding value in the control group; however it showed no dependence on the age and sex of patients.

TNF concentration in plasma did not depend on degree of leukemic infiltration in bone marrow. TNF concentration in AL patients with more significant (> 75% blasts) bone marrow infiltration was an average 0.953 ± 0.211 ng/ml and did not differ from corresponding value in patients with lower amount of blasts (< 75%) in bone marrow (0.980 ± 0.178 ng/ml; $p > 0.05$).

To determine the relation between TNF concentration in plasma and erythrocyte number in the patients' peripheral blood, they were divided into two groups: those with erythrocyte level at least $3 \cdot 10^{12}$/l and below $3 \cdot 10^{12}$/l. TNF concentration in blood plasma of patients with the erythrocyte number < $3 \cdot 10^{12}$/l turned out to be more intense (1.027 ± 0.156 ng/ml) than that of patients with the number of erythrocytes > $3 \cdot 10^{12}$/l (0.858 ± 0.172 ng/ml; $p > 0.05$). Patients with hemoglobin concentration < 100 g/l also manifested statistically unconfirmed high TNF concentration (1.033 ± 0.149 ng/ml) compared to the corresponding indicator for patients whose hemoglobin level was > 100 g/l (0.721 ± 0.233 ng/ml).

No statistically significant difference was found between TNF concentration in blood plasma and number of platelets of patients with AL. The content of TNF in case of patients with thrombocytopenia (< $100 \cdot 10^{9}$/l) was 1.053 ± 0.189 ng/ml and was insignificantly higher than that in the group of patients with the normal number of platelets (0.930 ± 0.274 ng/ml).

Depending on the number of leukocytes in the peripheral blood, the patients were divided into the group with leukopenia (number of leukocytes < $4 \cdot 10^{9}$/l), group with the normal number of leukocytes and group of those with leukocytosis (number of leukocytes > $9 \cdot 10^{9}$/l). TNF concentration in blood plasma was the lowest in the group of patients with leukopenia, though it did not vary significantly in different groups being equal to 0.796 ± 0.253, 1.090 ± 0.229 and 0.940 ± 0.195 ng/ml, respectively.

In ALL patients, we established low grade direct correlation between absolute blast cell number in peripheral blood and TNF level ($r = 0.34$). The same correlation in AML had lower expression ($r = 0.22$).

TNF concentration in the blood plasma of the patients with raised (> 20 mm/h) erythrocyte sedimentation rate is somewhat higher (1.031 ± 0.155 ng/ml), than that of the patients with the normal erythrocyte sedimentation rate.

In the general group of patients with AL, TNF production by PBMC was four times ($p < 0.01$) as high as the corresponding estimate in the control group and reached 0.292 ± 0.072 ng/ml. The index of ratio between the TNF concentration produced in PBMC culture and its content in peripheral blood (Index I) of the patients amounted to 0.379 ± 0.080, which is less than that of healthy individuals — 0.786 ± 0.046 ($p < 0.001$). PBMC of patients with ALL produce more TNF (0.360 ±0.130 ng/ml) than that of patients with AML (0.219 ± 0.056 ng/ml; $p < 0.05$). The index of TNF production was also significantly higher in patients with ALL. Thus, the ratio of TNF production by PBMC to its concentration in the plasma of patients with ALL amounted

to 0.605 ± 0.160 and significantly differed from the rate of patients with AML (0.232 ± 0.063; $p < 0.05$).

TNF production by PBMC for patients with AL did not depend on their age and sex. Similarly, the relation between TNF production by PBMC and its concentration in blood plasma (Index I) in age and gender groups did not differ significantly.

On the other hand, TNF production by PBMC in case of AL patients with more significant bone marrow infiltration (> 75% blasts) was approximately 2.5 times as high as corresponding estimate in patients with lower (< 75%) percent of blasts in bone marrow (0.497 ± 0.110 ng/ml *vs* 0.200 ± 0.040 ng/ml, respectively; $p < 0.02$). However, the fraction of TNF produced by PBMC in TNF content in plasma did not differ considerably between these groups of AL patients (see the Table).

TNF production by PBMC of the patients with low hemoglobin level was two times higher than that of patients without symptoms of anemia; however, the difference is statistically negligible (see the Table). In case of patients with low number of erythrocytes ($< 3 \cdot 10^{12}$/l), TNF production by blood cells was statistically significantly more intensive than that of the patients with the normal level of erythrocytes (0.370 ± 0.101 and 0.166 ± 0.053 ng/ml, respectively; $p < 0.05$). The fact that patients had anemia did not have significant effect on the proportion between TNF production by PBMC and its content in blood plasma (Index I), which, however, was lower than that in the control group.

Thrombocytopenia ($< 100 \cdot 10^9$/l) in patients with AL was accompanied by twice as high a capability of MCBP to produce TNF (0.430 ± 0.104 ng/ml) as that of the patients with the platelet level of at least $100 \cdot 10^9$/l (0.203 ± 0.048 ng/ml; $p < 0.05$). In case of thrombocytopenia, the ratio of TNF production by PBMC to its concentration in blood plasma is somewhat higher. The index of proportion (I) in case of thrombocytopenia amounts to 0.411 ± 0.114, while for patients with the normal number of platelets it was 0.360 ± 0.123 ($p > 0.05$).

When the number of leukocytes was rising, TNF synthesis by PBMC was appreciably decreasing. For patients whose leukocyte number was $4–9 \cdot 10^9$/l, this figure amounted to 0.423 ± 0.120 ng/ml, while in case of leukocytosis $> 9 \cdot 10^9$/l, it was statistically significantly lower than in the previous groups (0.193 ± 0.045 ng/ml; $p < 0.05$). Similarly, in these groups of patients most TNF production rate by PBMC (Index I) was found in the blood plasma of patients with leukopenia (0.534 ± 0.133 *vs* 0.365 ± 0.143 and 0.358 ± 0.104, respectively), however, the differences were statistically negligible.

In ALL, we observed low grade negative correlation between absolute blast cell number in peripheral blood and TNF production by PBMC ($r = –0.27$). That correlation was characterized as middle grade positive in AML patients ($r = 0.38$).

Statistically significant changes in TNF production of PBMC culture in patients with AL were found to be related to the erythrocyte sedimentation rate which may bear some relation to tumor intoxication syndrome. In case of higher erythrocyte sedimentation rate (> 20 mm/h) PBMC synthesized more TNF (0.328 ± 0.086 ng/ml) than in case of patients with erythrocyte sedimentation rate < 20 mm/h (0.125 ± 0.057 ng/ml; $p < 0.05$). However, the indicators of TNF production in PBMC culture ratio to its concentration in plasma (I) did not change significantly depending on the erythrocyte sedimentation rate.

TNF synthesis in PBMC culture of the patients whose clinical course of the disease was accompanied with symptoms of tumor intoxication (such as fever without signs of infection, unmotivated loss of weight, sweating and fatigue) was somewhat lower being equal to 0.195 ± 0.05 ng/ml, while in case of patients without clinical symptoms of intoxication TNF production by PBMC was equal to 0.346 ± 0.108 ng/ml ($p > 0.05$). In case of patients with intoxication caused by the disease, the relation of TNF production by PBMC to its concentration in the plasma (I) was significantly ($p<0.02$) lower than that of patients without these symptoms.

The relation between the TNF concentration in blood plasma and TNF production by PBMC of patients with AL was subjected to correlation analysis. It was found out that the TNF concentration in blood plasma increased if TNF production in PBMC culture rose. A statistically significant ($p < 0.05$), average in its power, direct correlative relation ($r = 0.39$; see the Figure) was established between these factors. Link between the values can be expressed in logarithmic equation of regression:

$$y = 0.118e^{0.119x}$$

where: x — TNF production by PBMC in AL patients, y — TNF concentration in blood plasma of AL patients.

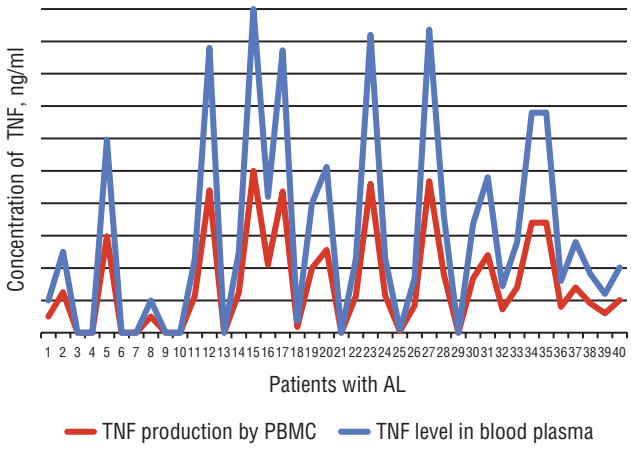

Figure. Relation between TNF concentration in blood plasma of patients with AL and TNF production by PBMC

Research into the role of TNF in patients with AL is mostly focused on children with ALL [11, 12]. Different authors point out the increase in TNF concentration of patients with AL; however, information on other cytokines is not so unambiguous [9, 10, 11, 13]. In this examination of adult individuals with AL, we have also found statistically significant increase in TNF concentration independent of the patients' age and sex. Like Potapnev et al. [11], we did not find any relation between TNF concentration and the number of blast cells in the bone marrow. But we

ascertain positive correlation of TNF level with blast cell number in peripheral blood, more distinct in ALL than in AML. The increased concentration of TNF in case of AL as well as in other lymphoid neoplasm determines concrete clinical symptoms of a pathological process — constitutional symptoms, anemia and even depressive syndrome [10, 13, 14]. This research has also established a relation between TNF and anemia as well as leukopenia but these data were statistically negligible.

Research of the TNF production by PBMC can improve the understanding of its pathogenic role in AL. It was found out that concentration of TNF and interleukin-1β *ex vivo* is positively correlated to the number of monocytes and concentration of intercellular TNF [16], which attests to the normal capacity of monocytes of patients with ALL to produce cytokines *ex vivo*. Potapnev et al. [11] and Mazitova [12] demonstrated that children with ALL initially preserve the capacity of lymphocytes to produce TNF. We observed a statistically significant raise of TNF production by PBMC in the adult patients. Its association with the development of anemia, thrombocytopenia and percent of blast cells in bone marrow, correspondingly, was also confirmed. These results prove that increase in TNF production plays a certain role in suppressing erythro- and thrombocytopoesis as leukemia progresses. The relation between TNF and symptoms of intoxication was demonstrated when examining its production by PBMC. Apparently, cultivating PBMC we determine in supernanant not only the concentration of TNF produced by immune competent cells (remaining monocytes, lymphocytes). The high level of TNF in PBMC culture of AL patients also attests to the fact that it is produced by tumor cells. The decrease of index (I) that partly reflects TNF produced by PBMC in the general level of TNF in blood plasma of patients bears out this theory as well. These data may be suggestive of the presence of other significant sources of TNF in AL patients.

Two main sources of high TNF production could be ascertain in AL: immune system as manifestation of common patients' response on tumor and malignant (leukemic) cells. Most likely, the first source prevails because TNF blood levels in ALL and AML practically do not differ. At the same time, ability of lymphoid and myeloid lineage blasts to produce TNF and its influence on a growth of the blast cells remarkably differ. TNF production by lymphoblasts in ALL is quite higher, than its production by myeloid blasts in AML. These results of our study correspond to experimental data that mouse ALL cells of L1210 line are capable to constitutive expression of TNF mRNA and TNF secretion into medium destroying blood vessels endothelium and correlating with leukemia expansion rate [17]. In contrast to L1210 cells, in human AML cells of K526 line TNF genes are repressed, the cells do not express TNF mRNA and do not secrete the cytokine into medium. But K526 cells might obtain TNF by paracrine way from other cells using specific receptors [18]. Our study shows, that TNF is inhibiting growth factor for lymphoblasts in ALL, what is proved by negative correlation between blast number and TNF production by PBMC. Such correlation is positive in AML and could indicate that the TNF stimulates of myeloid blasts proliferation.

Thus, increased TNF level in AL patients may be viewed as a proapoptotic manifestation of changes in hematopoiesis and as one of factors that contribute to the development of anemia and thrombocytopenia as well as possibly to intoxication symptoms.

CONCLUSIONS

1. TNF (α + β) concentration in blood plasma of patients with AL is significantly increased as results of patient's immune system response on tumor and raised TNF production by leukemic cells.

2. TNF production by lymphoblasts in ALL is quite higher than its production by myeloid blasts in AML, and besides TNF could be considered inhibiting growth factor for lymphoblasts in ALL and it stimulate myeloid blasts proliferation in AML.

3. Increased TNF concentration in blood and raised TNF production by PBMC in AL patients are accompanied by higher number of blast cells in bone marrow and peripheral blood, anemia, thrombocytopenia and increase in erythrocyte sedimentation rate, what makes a possibility to use of TNF values as prognostic indices in AL.

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ФАКТОР НЕКРОЗА ОПУХОЛЕЙ ПРИ ОСТРОМ ЛЕЙКОЗЕ

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Резюме. ***Цель****: изучить уровень фактора некроза опухоли (ФНО) в плазме крови больных острым лейкозом (ОЛ), его продукцию в первичной культуре мононуклеарных клеток периферической крови (МКПК) и выяснить связь между этими показателями и гематологическими проявлениями ОЛ.* ***Материал и методы:*** *концентрацию ФНО исследовали в плазме крови 44 больных ОЛ биологическим методом, основанным на его цитолитическом эффекте в чувствительной к ФНО культуре трансформированных мышиных фибробластов линии L929, определяемом радиометрическим методом.* ***Результаты****: концентрация ФНО в плазме крови больных ОЛ существенно превышает нормальные значения, его продукция МКПК также возрастает. Анемия и тромбоцитопения сопровождаются повышением концентрации ФНО в плазме крови, как и его продукции МКПК.* ***Выводы****: результаты исследования позволяют расценивать повышенный уровень ФНО при ОЛ как проапоптотическую манифестацию изменений гемопоэза, приводящую к развитию анемии и тромбоцитопении.*

Ключевые слова: фактор некроза опухолей, острый лейкоз, острый лимфобластный лейкоз, острый миелобластный лейкоз, анемия, тромбоцитопения.

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