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DYNAMICS OF HEMATOLOGICAL PARAMETERS IN PATIENTS WITH HRTB/HIV WITH LEVELS OF CD4+LYMPHOCYTES 200-50 cells/µl IN IMUNOGLOBULIN THERAPY APPLICATION

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Abstract

Introduction. According to the World Health Organization (WHO), in 2017 about 10 million people became ill with TB in the world. Also, WHO reports that Ukraine belongs to countries where the number of patients with chemo-resistant tuberculosis (HRTB) is one of the largest in the world. In 2017, TB caused 1.6 million deaths, of which 300,000 had a combined HIV/TB infection.

The purpose and tasks of the study. To study the hematologic changes in patients co-infected HRTB / HIV at the level of CD4 + lymphocytes 200 - 50 cells/ml and evaluate the effectiveness of immunoglobulin therapy.

Materials and methods. The study involved 52 patients with combined HRTB / HIV disease, aged 20 to 55 years. The study of hematological parameters was performed on the basis of the laboratory of the Odessa regional anti-tuberculosis dispensary, the calculation was performed on the automatic hematological analyzer Sysmex XP-300 3-diff with direct counting of neutrophils (Japan).

Results and discussion. In patients with HRTB / HIV with a level of CD4 + lymphocytes below 200 cells / μl, hematological parameters before the start of anti-TB therapy were characterized by the fact that patients of both groups were more likely to have leukocytosis than leukopenia, that is: 3.5 times more often in patients in group 1 (26.9% vs. 7.7%), and 9.1 times in the 2nd group (34.6% vs. 3.8%); lymphopenia - 2 times higher than lymphocytosis in group 1 and the same expressed in group 2 (see table). Monocytopenia was noted in 3.8%, monocytosis was registered 4 times more often in group 1, and in 1.5 times - in the 2nd. The frequency of eosinophilia reached 15.4% and 11.5%, in the first and second groups, respectively. Increases in neutrophils occurred in 30.8% and 38.5% of patients in groups 1 and 2, respectively.

Lung anemia was registered more often in both groups than anemia of average grade - 2 times more often in the 1 st (46.2% vs. 23.1%), and the second group (53.8% vs. 26.9%) , and severe anemia was 3.8% in the 1st group and 7.7% in the second group of the subjects.

Thrombocytopenia was diagnosed in 23.1% and 19.2% of patients in groups 1 and 2. Increasing the rate of erythrocyte sedimentation was determined in a greater number of patients - 69.2% of the examined group 1 and 65.4% of the 2nd group.

Conclusions. After the use of intravenous IgG in the combination therapy of patients with HRTB/HIV, there was a significant reduction in the manifestations of inflammation and infectious activity compared with patients taking only anti-TB drugs and ARVT according to treatment standards.

Key words: chemo-resistant tuberculosis, HIV-infection, hematologic changes.

Introduction. The most important problem is that worldwide tuberculosis (TB) is one of the first ten causes of death [3]. According to the World Health Organization (WHO), in 2017 about 10 million people became ill with TB in the world. Also, WHO reports that Ukraine belongs to countries where the number of patients with chemo-resistant tuberculosis

(HRTB) is one of the largest in the world. In 2017, TB caused 1.6 million deaths, of which 300,000 had a combined HIV/TB infection [8].

According to the Center for Public Health of the Ministry of Health of Ukraine for the first 9 months of 2018, the highest levels of HIV infection in Ukraine were registered in Dnipropetrovsk (78.9 per 100,000 population), Odesa (74.3), Mykolaiv (55.5) Oblasts, Kyiv (48.7), Kyiv (40.1), Kirovograd (38.6), Chernihiv (37.5), Kherson (36.6) oblasts. During 9 months of 2018, 2361 cases of AIDS deaths were registered, compared to 2,248 cases for the corresponding period of last year. The AIDS mortality rate was 5.6 and 5.3 per 100,000 population, respectively. The rate of growth of the indicator was + 5.7%. The highest levels of AIDS deaths were registered in Dnipropetrovsk (18.6 per 100,000 population), Odesa (10.3), Kirovograd (9.4), Mykolaiv (8.9) oblasts and Kyiv (6.5) [1].

The purpose and tasks of the study. To study hematological changes in patients with co-infection of HRTB/HIV at a level of CD4 + lymphocytes 200 - 50 cells/μl and to evaluate the effectiveness of immunoglobulin therapy.

Materials and methods. The study involved 52 patients with combined HRTB/HIV disease, aged 20 to 55 years. The study of hematological parameters was performed on the basis of the laboratory of the Odessa regional anti-tuberculosis dispensary, the calculation was performed on the automatic hematological analyzer Sysmex XP-300 3-diff with direct counting of neutrophils (Japan). Use the volume of specimens of 50 μl of whole blood, or 20 μl in pre-dilution mode. For the study, DC method was used in a fixed volume: WBC, RBC / PLT, and non-cyanide hemoglobin determination (HGB). Quality control: internal (60 graphs, 6 QC files) and daily external (IQAS Online via SNCS), control blood Eightcheck-3WP. Reagents CELLPACK (diluent), volume 20 l, Stromatolyser-WH (lysis solution), 3 vials of 500 ml, Cellclean (cleansing solution), 50 ml. Control materials: EIGHTCHECK®-3WP-N, 1.5 ml, EIGHTCHECK®-3WP-L, 1.5 ml, EIGHTCHECK®-3WP-H, 1.5 ml.

To achieve the purpose of the work, patients with HRTB/HIV with a CD4 + lymphocyte level below 200 cells/μl, but above 50 cells/μl were selected, and divided into 2 groups:

- Group 1(control) - 26 patients with HRTB/HIV with a level of CD4 + lymphocytes below 200 cells/μl, but above 50 cells/μl receiving standard treatment for second-line antiretroviral therapy (ARVT);

- Group 2 (basic) 26 patients with HRTB/HIV with a level of CD4 + lymphocytes below 200 cells/μl but above 50 cells/μl receiving additional intravenous immunoglobulin IgG in a complex therapy (5% solution for intravenous infusion 50 ml, Biofarma, Ukraine).

Results of analysis of literary sources. Hematologic changes play an important role in the pathogenesis of TB/HIV co-infection, which can be one of the immediate causes of the lethal outcome of HRTB/HIV patients, and also prevent the use of ARVT in the early stages of TB treatment because it complicates its management, especially in patients with pronounced immunosuppression (with a level of CD4 + lymphocytes below 200 cells/μl) [4, 6, 9].

In late stages of HIV, in combination with HRTB, haematological changes arise due to bone marrow obesity due to the formation of its atrophy and even necrosis. There are dysplastic changes, which according to clinical and laboratory characteristics resemble myeloplasty syndrome [2, 7]. Due to severe hematological disorders, there is a need to change the treatment plan and its supplements with new pathogenetic agents that will contribute not only to the improvement of white and red blood, but also to reduce the toxicity burden in general and to reduce the risk of developing of systemic inflammatory response a syndrome (SIRS) [5, 8, 10].

Discussion of the results of their own research. In patients with HRTB/HIV with a level of CD4 + lymphocytes below 200 cells/μl, hematological parameters before the start of anti-TB therapy were characterized by the fact that patients of both groups were more likely to have leukocytosis than leukopenia, that is: 3.5 times more often in patients in group 1 (26.9% vs. 7.7%), and 9.1 times in the 2nd group (34.6% vs. 3.8%); lymphopenia - 2 times higher than lymphocytosis in group 1 and the same expressed in group 2 (see table). Monocytopenia was noted in 3.8%, monocytosis was registered 4 times more often in group 1, and in 1.5 times - in the 2nd. The frequency of eosinophilia reached 15.4% and 11.5%, in the first and second groups, respectively. Increases in neutrophils occurred in 30.8% and 38.5% of patients in groups 1 and 2, respectively.

Lung anemia was registered more often in both groups than anemia of average grade - 2 times more often in the 1 st (46.2% vs. 23.1%), and the second group (53.8% vs. 26.9%), and severe anemia was 3.8% in the 1st group and 7.7% in the second group of the subjects.

Thrombocytopenia was diagnosed in 23.1% and 19.2% of patients in groups 1 and 2. Increasing the rate of erythrocyte sedimentation was determined in a greater number of patients - 69.2% of the examined group 1 and 65.4% of the 2nd group.

During treatment, the following hematologic dynamics was observed (see table).

Table

Dynamics of hemogram index of patients with HRTB/HIV with CD4+ <200 cells/µl but >50 cells/µl in intensive phase

Indicator / A group of patients		0 month		2 weeks		1 month		2 month /3 month		4 month		5 month		6/7/8 month	
		abs	$Q\pm m_q$ %	abs	$Q\pm m_q$%	abs	$Q\pm m_q$%	abs	$Q\pm m_q$%	abs	$Q\pm m_q$%	abs	$Q\pm m_q$%	abs	$Q\pm m_q$%
Leuko-cytosis	TG-1 (n=26)	7	26,9 ±1,77	10	38,5 ±1,95	12	46,2 ±1,99	11/13	42,3±1,98/ 50,0±2,02	8	30,8 ±1,85	6	23,1 ±1,69	3/1/1	11,5±/ 1,28/ 3,8±0,76/ 3,8±0,76
	TG-2 (n=26)	9	34,6 ±1,90	3	11,5** ±1,28	3	11,5** ±1,28	1/1	3,8±0,76***/ 3,8±0,76***	0	0±0***	0	0±0***	0/0/0	0±0***/0±0**/ 0±0**
Leukopenia	TG-1 (n=26)	2	7,7 ±1,58	4	15,4* ±1,77	3	11,5** ±1,85	2/0	7,7±1,07***/ 0±0***	0	0±0***	0	0±0***	0/0/0	0±0***/0±0*/ 0±0*
	TG-2 (n=26)	1	3,8* ±0,76	8	30,8 ±1,85	14	53,8 ±1,99	12/10	46,2±1,99/ 38,5±1,95	7	26,9 ±1,77	4	15,4 ±1,44	2/1/1	7,7±1,07/ 3,8±0,76/ 3,8±0,76
Lympho-cytosis	TG-1 (n=26)	1	3,8* ±0,76	3	11,5* ±1,28	2	7,7*** ±1,07	5/4	19,2±1,58*/ 15,4±1,44**	3	11,5 ±1,28	2	7,7 ±1,07	1/1/0	3,8±0,76*/ 3,8±0,76/ 0±0
	TG-2 (n=26)	2	7,7 ±1,07	9	34,6 ±1,90	11	42,3 ±1,98	10/13	38,5±1,95/ 50,0±2,02	5	19,2 ±1,58	3	11,5 ±1,28	2/0/0	7,7±1,07/ 0±0**/ 0±0
Lympho-penia	TG-1 (n=26)	2	7,7 ±1,07	7	26,9 ±1,77	9	34,6 ±1,90	9/12	34,6±1,90/ 46,2±1,99	8	30,8 ±1,85	7	26,9 ±1,77	4/ 4/1	15,4±1,44/ 15,4±1,44/ 3,8±0,76
	TG-2 (n=26)	2	7,7 ±1,07	1	3,8 ±0,76***	1	3,8 ±0,76***	1/0	3,8±0,76***/ 0±0**	0	0 ±0***	0	0±0***	0/0/0	0±0***/0±0***/ 0±0*
Mono-cytosis	TG-1 (n=26)	4	15,4 ±1,44	4	15,4 ±1,44*	6	23,1* ±1,69	7/9	26,9±1,77*/ 34,6±1,90*	4	15,4* ±1,44	2	7,7* ±1,07	1/0/0	3,8±0,76*/ 0±0*/ 0±0
	TG-2 (n=26)	3	11,5 ±1,28	8	30,8 ±1,85	10	38,5 ±1,95	11/14	42,3±1,98/ 53,8±1,99	6	23,1 ±1,69	4	15,4 ±1,44	2/1/0	7,7±1,07/ 3,8±0,76/ 0±0
Monocyto-penia	TG-1 (n=26)	1	3,8* ±0,76	3	11,5 ±1,28	4	15,4 ±1,44	4/7	15,4±1,44/ 26,9±1,77	5	19,2 ±1,58	3	11,5 ±1,28	3/2/1	11,5±1,28/ 7,7±1,07/ 3,8±0,76
	TG-2 (n=26)	2	7,7 ±1,07	2	7,7 ±1,07	1	3,8** ±0,76	1/0	3,8±0,76**/ 0±0***	0	0±0***	0	0±0***	0/0/0	0±0***/0±0***/ 0±0*

Eosino-philia	TG-1 (n=26)	4	15,4 ±1,44	6	23,1 ±1,69	7	26,9 ±1,77	7/8	26,9±1,77/ 30,8±1,85	5	19,2 ±1,58	3	11,5 ±1,28	2/2/1	7,7±1,07/ 7,7±1,07/ 3,8±0,76
	TG-2 (n=26)	3	11,5 ±1,28	1	3,8*** ±0,76	1	3,8*** ±0,76	0/0	0±0***/ 0±0***	0	0±0***	0	0±0***	0/0/0	0±0***/0±0***/ 0±0*
Neutro-philia	TG-1 (n=26)	8	30,8 ±1,85	13	50 ±2,02	15	57,7 ±1,98	14/17	53,8±1,99/ 65,4±1,90	10	38,5 ±1,95	6	23,1 ±1,69	4/3/2	15,4±1,44/ 11,5±1,28/ 7,7±1,07
	TG-2 (n=26)	10	38,5 ±1,95	3	11,5 ±1,28**	2	7,7 ±1,07***	2/1	7,7±1,07***/ 3,8±0,76***	1	3,8*** ±0,76	0	0±0***	0/0/0	0±0***/ 0±0***/0±0***
Anemia light weight	TG-1 (n=26)	12	46,2 ±1,99	11	42,3 ±1,98	8	30,8 ±1,85	7/5	26,9±1,77/ 19,2±1,58	6	23,1 ±1,69	5	19,2±1,58	4/3/3	15,4±1,44/ 11,5±1,28/ 11,5±1,28
	TG-2 (n=26)	14	53,8 ±1,99	10	38,5 ±1,95	7	26,9 ±1,77	2/1	7,7±1,07**/ 3,8±0,76**	2	7,7 ±1,07**	1	3,8 ±0,76***	1/0/0	3,8±0,76**/ 0±0***/0±0***
Anemia medium	TG-1 (n=26)	6	23,1 ±1,69	7	26,9 ±1,77	9	34,6 ±1,90	9/8	34,6±1,90/ 30,8±1,85	4	15,4 ±1,44	2	7,7 ±1,07	0/0/0	0±0/ 0±0/0±0
	TG-2 (n=26)	7	26,9 ±1,77	5	19,2 ±1,58	3	11,5 ±1,28**	3/1	11,5±1,28**/ 3,8±0,76***	0	0±0***	0	0±0***	0/0/0	0±0/ 0±0/0±0
Anemia heavy	TG-1 (n=26)	1	3,8 ±0,76*	1	3,8 ±0,76	2	7,7 ±1,07	2/1	7,7±1,07/ 3,8±0,76	1	3,8 ±0,76	0	0 ±0	0/0/0	0±0/ 0±0/0±0
	TG-2 (n=26)	2	7,7 ±1,07	1	3,8 ±0,76	1	3,8* ±0,76	0/0	0±0***/0±0*	0	0±0*	0	0±0	0/0/0	0±0/0±0/0±0
Thrombo-cytopenia	TG-1 (n=26)	6	23,1 ±1,69	8	30,8 ±1,85	8	30,8 ±1,85	10/ 11	38,5±1,95/ 42,3±1,98	7	26,9 ±1,77	4	15,4 ±1,44	2/1/1	7,7±1,07/ 3,8±0,76/ 3,8±0,76
	TG-2 (n=26)	5	19,2 ±1,58	3	11,5 ±1,28**	4	15,4 ±1,44*	2/1	7,7±1,07**/ 3,8±0,76***	1	3,8 ±0,76***	0	0±0***	0/0/0	0±0***/ 0±0*/0±0*
Increased ESR	TG-1 (n=26)	18	69,2 ±1,85	19	73,1 ±1,77	21	80,8 ±1,58	21/22	80,8±1,58/ 84,6±1,44	20	76,9 ±1,69	15	57,7 ±1,98	12/11/ 8	46,2±1,99/ 42,3±1,98/ 30,8±1,85
	TG-2 (n=26)	17	65,4 ±1,90	18	69,2 ±1,85	14	53,8 ±1,99*	10/11	38,5±1,95*/ 42,3±1,98*	8	30,8 ±1,85*	6	23,1 ±1,69*	4/3/3	15,4±1,44*/ 11,5±1,28**/ 11,5±1,28*

* - significant difference indices 1 and 2 groups ($p < 0.05$)
** - significant difference indices 1 and 2 groups ($p < 0.01$)
*** - significant difference indices 1 and 2 groups ($p < 0.001$)

In 38.5% (± 1.95) of patients in group 1 (control) who received standard treatment with second-line anti-TB drugs with ARVT, a gradual increase in the frequency of leukocytosis, which in 1 month. registered at 46.2%, after 3 months - at 50%, but after 4 months. there was a steady decrease of it by 1.6 times to the level of 30.8% and after 5 months in 2 times - to 23.1%). At the end of 8 months the treatment of leukocytosis was maintained in 3.8% of patients (see table).

In patients with 2 groups who additionally received intravenous IgG in combination therapy, after 2 weeks of treatment the frequency of leukocytosis decreased 3-fold and amounted to 11.5% ($p < 0.01$) with a stable decrease in this index after the 1, 2, 3 month. to 3.8% and absence of signs of leukocytosis during the last 4 to 8 months of surveillance, which was a sign of early decline in the activity of the inflammatory process.

At the same time, after 2 weeks of treatment, the frequency of leukopenia in patients of the 1st group increased almost 2 times (from 7.7% to 15.4%) and gradually decreased after the 1 st month of treatment with 11.5% to 6% in the 3rd month, since the 4th month was not noted in any of the patients (see tab.).

However, the frequency of leukopenia in patients from the 2nd group from the 2nd week was significantly more frequent than in the control (8 times versus 2 in 1 group) and reached 30.8% of cases and remained at a high level (53.8% 46.2%) to 3rd month. surveillance inclusive. Studies conducted after the 3rd and 5th months showed a marked rate of decrease in the frequency of leukopenia from 38.5% to 15.4%, and after 6 - 8 months. - from 7.7% to 3.8%, respectively.

Lymphocytosis increased ($p < 0,05$) simultaneously in patients of both the 1st and 2nd groups, but from the 1st month. treatment - more progressively in patients in the 2nd group, which reached the values of 42.3%, while in the control - 7.7% (table 2).

It should be emphasized that in patients with the first group, the high frequency of lymphopenia was maintained throughout the observation time (7.7 - 26.9 - 34.6 - 34.6 - 46.2 - 30.8 - 26.9)%, and only after the 8th month. this indicator dropped to 3.8% (one case remained) (see tab.).

In patients of the 2nd group there was an early and rapid decrease in the frequency of lymphopenia: from the end of the 2nd week to the 2nd month of observation in 2 times ($p < 0.001$), with the remainder only 1 case (3.8%), but with 3 months later limfopenia was not determined.

The content of monocytes in patients from the 2nd group from the second week to the end of the third month increased by 4.8 times, and after 3rd month. it was gradually decreasing, and amounted to 15.4% for the 5th month and 3.8% for the 7th month (see table).

The high frequency of monocytopenia (26.9%) was observed in patients of the 1st group until the 3rd month of treatment, and decreased after the 4th month to 19.2%, the 7th - to 7.7% and the 8th - to 3.8% (1 case).

The number of eosinophils increased up to 3 months of treatment, including 30.8% of patients in group 1, while among patients in the second group of eosinophilia after the first 2 weeks, significantly (to 3.8%) decreased, and after 1 month was absent in the future (by the end of 8 months) was not registered (see table).

Frequency of neutrophilia in patients in the control group remained stable throughout the entire period of observation. In patients of the 2 nd group - this figure has decreased already after 2 weeks in 3,3 times, after the first month of treatment - in 5, and 3rd month. - 10 times ($p < 0,001$).

On the part of red blood, the majority of patients in both groups experienced anemia (73.1% to 88.4% of the 1st and 2nd groups). The performed treatment showed that anemia of mild grade in patients of group 1 was determined in 46.2% and remained until the end of 6 months. at the level of 15.4% and only after 8 months. decreased to 11.5%.

At the same time, patients in the 2nd group experienced a decrease in the frequency of anemia of mild degree from 53.8% to 38.5% after the first month. therapy with subsequent reduction of cases at the end of the 2nd month. and absence after 7th month ($p < 0.001$). The incidence of middle-level anemia in the continuation of treatment was more active ($p < 0.01$) also decreased in patients in the second group (see table).

Severe anemia regressed in patients with 2nd group 2 times faster (according to results of studies after 1-2-th and 3rd months of observation) than in patients with control group ($p < 0,05$).

Thrombocytopenia also longer recorded in the patients of group 1 and after 3 months of treatment was maintained in 42.3% of subjects.

In patients of the 2nd group, thrombocytopenia was noted with each month in a significantly smaller number of patients, and after the 2nd and 3rd months. was $7.7 \pm 1.07\%$ and $3.8 \pm 0.76\%$ respectively, which is 5 and 11 times lower than in the control group. Subsequently, starting with 6 months of treatment, thrombocytopenia was not registered in any patient (see table).

The increase in ESR was registered in more than 2/3 patients in both groups of observation. Treatment for 4 months of patients in group 1 (according to the standard scheme) did not lead to a positive dynamics of elevated ESR. However, in patients with 2 groups, in the 2 weeks of treatment, a decrease in the number of cases of elevated ESR (to 57.7%) was noted, with a progressive reduction of its percentage with each month (up to 23.1%); at the 5th month of treatment, this figure was 2.5 times lower than in group 1 (see table).

Thus, the results reflected a significant decrease in the activity of an infectious inflammation in patients who used additionally Ig G compared with patients treated by commonly accepted standard method (anti-TB drugs and ARVT) therapy in patients with HRTB/HIV.

Conclusions

1. In patients with HRTB/HIV with a level of CD4 + lymphocytes 200 - 50 cells/μl,

systemic haematological changes were detected: leukocytosis was determined more often (from 3.5 to 9 times) than leukopenia; lymphopenia - 2 times higher than lymphocytosis; monocytosis was registered 4 times more often than monocytopenia; neutrophilosis was present in 1/3 of cases with not frequent eosinophilia (11.5 - 15.4%); thrombocytopenia was diagnosed in 23,1% of cases; anemia of mild degree - in 1/2 patients, the average degree - in 2 times less often and only in one patient - severe form; in 2/3 of patients, an increase in ESR was determined.

2. Following the use of intravenous IgG in the combination therapy of patients with HRTB / HIV, there was a significant reduction in the manifestations of inflammatory process and infectious activity compared with patients taking only anti-TB drugs and ARVT according to treatment standards.

Conflict of interest. The authors did not find any conflicts of interest.

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