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**IMPROVING THE DIAGNOSIS AND TREATMENT OF TUBERCULOUS
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Summary: Presents the results of treatment of patients with TB of the peripheral lymph nodes. Lymphotropic administration of isoniazid for one month on a background of standard TB treatment leads to a rapid clinical benefit, which developed against the background of significant reduction in immune status and persisted until the end of the observation with the manifestation of the change in the ratio in the number of subpopulations of T-lymphocytes. Thus, compared with the control group, the experimental group of patients within a month after the start of lymphotropic therapy appeared stable positive clinical and laboratory dynamics, which gradually increased until the end of follow-up. However, it should be noted that the positive clinical effect was developed against the backdrop of significant low immune status, which lasted until the end of the observation and manifest change in the ratio in the number of subpopulation of T-lymphocytes (CD4+ и CD8+ cell). Since the role of intercellular mediators that regulate the immune response in the body perform cytokines, the existence of an imbalance in tuberculosis of peripheral lymph nodes was one pathophysiological basis, which is the development and progression of specific inflammation. Comparative observation in experimental and control group showed that the targeted delivery of isoniazid at lymphotropic therapy has a positive effect on the dynamics of local inflammation: in patients of the experimental group was noted faster resorption local inflammatory changes and in any case was not observed in the control, development of fluctuations in the lymph nodes. The latter may have been due to the cytokine imbalance that patients in the control group had not normalized until the end of treatment. Patients test group, by contrast, the quantity of cytokines in the treatment normalized by IL-1 β and FNO α , while the content of IFN γ and IL-2 remains significantly below normal.

Keywords: lymphatic system, extrapulmonary tuberculosis, lymphotropic administration isoniazid, tuberculosis of peripheral lymph nodes, treatment tuberculosis, immune status, cytokines, CD4+ / CD8+.

Резюме: Представлены результаты комплексного лечения больных туберкулеза периферических лимфатических узлов. Лимфотропное введение изониазида в течение одного месяца на фоне стандартного противотуберкулезного лечения приводит к быстрому положительному клиническому эффекту, который развивался на фоне достоверного снижения иммунного статуса и сохранялось до конца наблюдения с проявлением изменением соотношения в количестве субпопуляций Т-лимфоцитов. Так, по сравнению с контрольной группой, у больных опытной группы уже через месяц после начала лимфотропной терапии появилась стабильная положительная клинико-лабораторная динамика, которая постепенно нарастала до конца наблюдения. Однако надо отметить, что положительный клинический эффект развивался на фоне достоверного низкого иммунного статуса, который сохранялся до конца наблюдения и проявлялся изменением соотношения в количестве субпопуляций Т-лимфоцитов (CD4+ и CD8+

клеток). Так как роль межклеточных медиаторов, регулирующих иммунный ответ, в организме выполняют цитокины, то наличие их дисбаланса при туберкулезе периферических лимфоузлов являлось той патофизиологической основой, на которой происходило развитие и прогрессирование специфического воспаления. Сравнительные наблюдения в опытной и контрольной группах показали, что адресная доставка изониазида при лимфотропной терапии положительно отражалась на динамике локального воспаления: у больных опытной группы отмечалось более быстрое рассасывание локальных воспалительных изменений и ни в одном случае не было отмечено, как в контроле, развития флюктуации в лимфоузлах. Последнее, возможно, было связано с цитокиновым дисбалансом, который у больных контрольной группы не нормализовался до конца лечения. У больных опытной группы, наоборот, количество цитокинов в процессе лечения нормализовалось за счет $IL-1\beta$ и $FNO\alpha$, тогда как содержание $IFN\gamma$ и $IL-2$ так и осталось достоверно ниже нормы.

Ключевые слова: лимфатическая система, внелегочный туберкулез, лимфотропное введение изониазида, туберкулез периферических лимфатических узлов, лечение туберкулеза, иммунный статус, цитокины, $CD4+$ / $CD8+$.

Diseases caused by *Mycobacterium tuberculosis* continue to have a significant negative impact for the health care system. According to the statistics of the World Health Organization, more than 10 million people fall ill with tuberculosis every year, and, despite the fact this is a preventable and curable disease, mortality reaches 1.5 million people per year, which makes it the main infectious cause of death in the world.

Based on the indirect estimates, about a quarter of the world's population may be "carriers" of *Mycobacterium tuberculosis*, but most of these people do not have any clinical manifestations. However, tuberculosis is more likely to infect those ones who has a compromised immune system, chronic malnutrition, or diabetes.

Tuberculosis of the peripheral lymph nodes is the most common extrapulmonary manifestation of tuberculosis. This illness frequently mimics other illnesses and gives contradictory physical and laboratory results, and therefore it remains problematic both in terms of diagnosis and in terms of choosing treatment tactics. Distinguishing between tuberculous and non-tuberculous mycobacterial cervical lymphadenitis is crucial since their treatment protocols differ. Making an accurate diagnosis is challenging and frequently necessitates a biopsy.

Numerous harmful substances originating from the inflammatory focus are known to be blocked by lymphatic capillaries, arteries, and lymph nodes. There is widespread blockage of lymphatic transit through the lymph nodes and microlymphatic outflow of tissues. All of this paralyzes the lymphatic system's immunological and barrier functions, making it a source of toxemia and septicemia [6].

Levin Yu.M. (1986) developed a method for lymphotropic administration of drugs. In contrast to direct endolymphatic therapy, the medication is injected subcutaneously into the lower thigh region while also promoting lymphotropism, or enhanced lymphatic system flow. [2].

The publications of Rakhmetov N.R. (1989) are related to the use of lymphological methods of therapy in clinical practice as pathogenetically substantiated components of treatment in the complex therapy of non-specific and specific purulent-inflammatory diseases [5].

Following the directive №19 of the Ministry of Health and Social Development of the Republic of Kazakhstan dated August 22, 2014 [4], tuberculosis of the peripheral lymph nodes is treated

according to the standard regimens depending on the drug sensitivity of MBT according to category I or II (sensitive forms) or according to category IV (resistant forms). However, a number of circumstances, including the existence of gastrointestinal tract disorders can limit the flow of drugs into the area of specific inflammation during standard treatment [3, 7]. As an example, the publications of O.E. Dogorova and M.K. Vinokurova (2015) shows better effectiveness of treatment of various forms of pulmonary tuberculosis using targeted anti-tuberculosis drugs delivery [1].

Targeted delivery of anti-tuberculosis medications to the site of tuberculous inflammation is a critical issue in this context, particularly in peripheral lymphadenitis, because the surrounding lymph node tissue is quickly implicated in the inflammatory process.

Objective: to create novel techniques for detecting and treating peripheral lymph node tuberculosis by delivering anti-tuberculosis medications to the lymphoid tissue specifically.

Research objectives: to develop a method for increasing the effectiveness of treating tuberculosis of the axillary peripheral lymph nodes by targeted delivery of anti-tuberculosis drugs.

Materials and methods: Criteria for inclusion and exclusion of patients from the study were developed to form identical groups during the study. According to them, the experimental and control groups included patients 1) with a histologically and bacteriologically confirmed tuberculous process in the axillary lymph nodes with preserved drug sensitivity; 2) with 1-2 stages of specific inflammation (hyperplastic, granulomatous, and caseous without decay); 3) with no tuberculous lesions in other organs, in particular in the lungs; and 4) newly ill patients, typed as a "new case". Inclusion in the observation of patients with lesions of only the axillary lymph nodes was explained by the fact that the greatest clinical effect in lymphotropic therapy was achieved if drugs were administered into the zone located near the affected organ. The axillary lymph nodes were the closest zone into which lymph with the drug flowing from the arm could reach. Therefore, the choice of patients was limited to forms of the disease with tuberculous lesions of the axillary lymph nodes.

According to the described criteria, we formed 2 groups of patients. The first (experimental) group included 58 patients, of whom 34 were women (58.6%) and 24 were men (41.4%). The second (control) group included 55 patients, of whom 31 were women (56.4%) and 24 were men (43.6%). Due to clearly developed selection criteria, the composition of patients in the groups was identical in terms of clinical, age, and gender characteristics. After a complete clinical and laboratory examination, all patients in the hospital were prescribed treatment in the intensive phase according to category I. In this case, patients in the control group received treatment according to the standard treatment regimen, while in patients in the experimental group, peros isoniazid administration was replaced by lymphotropic. The method of lymphotropic administration of the drug was carried out as follows: a solution of lidase in a dose of 64 U, diluted in a 0.5% solution of novocaine (at the rate of 1-2 ml per injection), was injected subcutaneously into the inner surface of the upper third of the arm of the right or left upper limb (depending on the side of the lymph node lesion). After 3-4 minutes, without removing the needle, a 10% solution of isoniazid was injected in an amount of 3.0 ml. The duration of the course of lymphotropic administration of the drug was one month. After this, the patients were again transferred to taking isoniazid per os until the end of the intensive phase of treatment.

Results and discussions:

Indicators	Normal rate	Experimental Group n=58	P value	Control Group n=55	P value
		M±m (pg/L)		M±m (pg/L)	
IL-1β	353,4±84,9	654,72±76,32	p≤0,05	713,58±59,13	p≤0,05
IL-2	28,1±1,7	9,23±2,41	p≤0,05	9,01±1,87	p≤0,05
IFNγ	9,87±1,23	3,56±1,21	p≤0,05	2,69±1,96	p≤0,05
FNOα	2,55±0,87	1,99±0,10	p≥0,05	1,95±0,09	p≥0,05

The study of the immune status showed that upon admission to the hospital, the subpopulation composition of T-lymphocytes in the peripheral blood of patients was significantly altered in both control and experimental groups (Table 1).

Table 1
Indicators of immune status in patients of the experimental and control groups before the start of treatment

Indicators	Normal rate	Experimental Group n=58		Control Group n=55		P
		M±m %	infelicity %	M±m %	infelicity %	
CD4+ клетки	55–80%	30,7±28,9	1,8–59,6	34,8±12,8	22,0–47,6	p≥0,05
CD8+ клетки	19–37%	54,9±13,0	41,9–67,9	52,3±13,4	38,9–65,7	p≥0,05
CD4+ / CD8+	1–2,0	0,6		0,7		p≥0,05

Table 2
Cytokine content in the peripheral blood of patients in the experimental and control groups before treatment

Table 1 data show that changes in CD4+ and CD8+ cells in patients of both groups had opposite directions: the number of T-helpers in comparison with the norm in the experimental group was significantly reduced to 30.7±28.0% (p≤0.05), while the number of T-killers, on the contrary, was significantly increased to 54.9±13.0% (p≤0.05). In the control group, the trend was the same, while the indicators of both groups did not differ significantly (p≥0.05). Changes in the ratio between individual fractions of T-lymphocytes also led to a decrease in the immunoregulatory index CD4+/CD8+, which in both groups before the start of treatment was reduced to 0.6 in the experimental group and to 0.7 in the control (p≥0.05). Changes in cytokines were also practically the same in the groups of patients (Table 2).

From the data in Table 2, we see that before treatment, patients in both groups showed a significant decrease in IFN γ content compared to the reference values (up to 3.56 ± 1.21 in the experimental group and up to 2.69 ± 1.96 in the control group ($p \leq 0.05$)), while not differing significantly from each other ($p \geq 0.05$). In contrast, although the FNO α content was below normal in both groups (0.69 ± 0.10 and 0.55 ± 0.09 , respectively), these differences were insignificant ($p \geq 0.05$) and reflected fluctuations in the value of the indicator, but not its true decrease. Changes in the content of interleukins were different: the content of both IL-1 β and IL-2 was significantly increased compared to the norm (654.72 ± 76.32 and 732.58 ± 59.13 , respectively) ($p \leq 0.05$) but was almost the same in both groups ($p \geq 0.05$). This pattern is clearly visible in Figure 1.

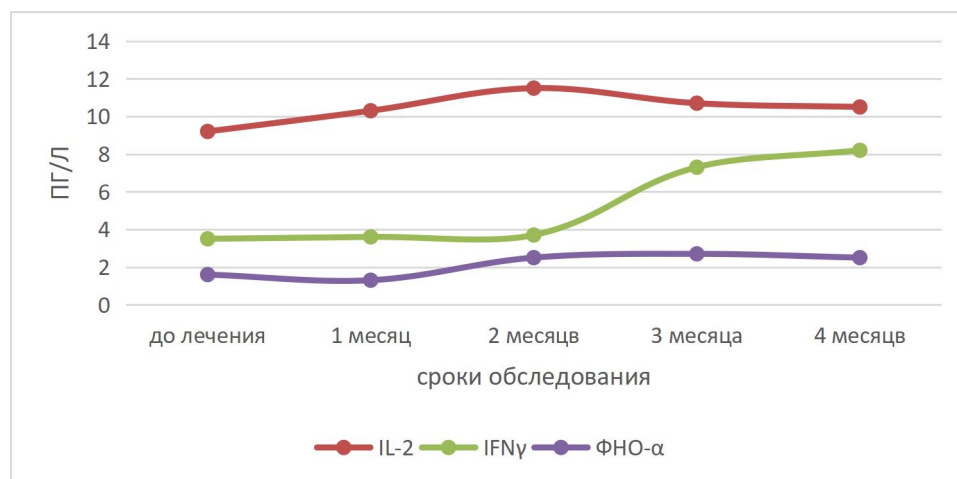


Figure 1. Cytokine content in the peripheral blood of patients in the experimental group.

Thus, it can be stated that before treatment, patients of both groups showed the same reliable changes in the content of T-lymphocyte subpopulations in the peripheral blood (a decrease in the number of CD4 $^+$ and an increase in CD8 $^+$ cells) and in the change in the cytokine status - a reliable decrease in the amount of interleukin-2 and an unreliable decrease in the tumor necrosis factor, with a reliable increase in the content of interferon-gamma and interleukin-1 β .

Anti-tuberculosis treatment received by patients of the experimental and control groups had a positive effect on clinical and laboratory parameters. By the end of the month, intoxication symptoms disappeared in patients of both groups (100% of patients in both groups), local pain in the axillary region on the side of the affected lymph nodes significantly decreased (16.4% in the experimental group) or completely ceased to be determined (100% in the experimental group and 65.5% in the control group). However, 19 patients (34.5%) in the control group developed fluctuations in the affected axillary lymph nodes, which could be regarded as progression of a specific process. In the experimental group, none of the patients developed fluctuations. In this group, on the contrary, a significant decrease in the size of the affected lymph nodes was recorded already one month after the start of treatment. Thus, in 14 patients out of 22 (63.3%) in the experimental group, the lymph nodes decreased from V to III size, and in 9 out of 20 (45.0%) from IV to III, while in the control group the size of the lymph nodes in patients remained the same.

Conclusion: The observations showed that lymphotropic administration of isoniazid for one month against the background of standard anti-tuberculosis treatment leads to the development of a rapid positive clinical effect. Thus, in comparison with the control group, whose patients received treatment according to the standard scheme, the patients of the experimental group showed stable positive clinical and laboratory dynamics already one month after the start of lymphotropic therapy, which gradually increased until the end of the observation. However, it should be noted that the positive clinical effect developed against the background of a reliable low immune status, which persisted until the end of the observation and was manifested by a change in the ratio of the number of T-lymphocyte subpopulations (CD+4 and CD+8 cells). Since the role of intercellular mediators regulating the immune response in the body is performed by cytokines, the presence of their imbalance in tuberculosis of the peripheral lymph nodes was the pathophysiological basis on which the development and progression of specific inflammation occurred. Comparative observations in the experimental and control groups showed that targeted delivery of isoniazid during lymphotropic therapy had a positive effect on the dynamics of local inflammation: patients in the experimental group showed faster resorption of local inflammatory changes and in no case, as in the control, was the development of fluctuations in the lymph nodes noted. The latter was possibly associated with cytokine imbalance, which did not normalize in patients in the control group until the end of treatment. In patients in the experimental group, on the contrary, the amount of cytokines normalized during treatment due to IL-1 β and FNO α , while the content of IFN γ and IL-2 remained significantly below normal.

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