



Functional Activity of Blood Eosinophils in Patients with *Opisthorchis Felineus* Invasion

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Aim: to study the functional activity of blood eosinophils in patients with *Opisthorchis felineus* (*O. felineus*) invasion.

Material and methods. A total of 328 patients with *O. felineus* invasion (120 men and 208 women, mean age — 40.3 years) and 34 practically healthy people (14 men and 20 women, mean age — 41.1 years) aged 18 to 70 years were examined. The main method for diagnosing opisthorchiasis was the determination of eggs or bodies of adult parasites in the duodenal contents and/or feces, which was used in all 328 patients with opisthorchiasis. All patients underwent a complete blood count and biochemical blood test, esophagogastroduodenoscopy and ultrasound examination of the abdominal organs. The study of the functional activity of blood eosinophils was carried out in 42 patients with opisthorchiasis and 34 healthy individuals from the control group by chemiluminescent analysis with the measurement of the intensity of production of reactive oxygen species in spontaneous and zymosan-induced reactions in lucigenin- and luminol-dependent processes.

Results. The frequency of eosinophils in the complete blood count above 5 % in the examined patients with opisthorchiasis was 19.5 %. An increase in the content of eosinophils in the blood in patients with opisthorchiasis was associated with an increase in the frequency of complaints of pain in the right hypochondrium, pruritus, skin rashes, an increase in the proportion of leukopenia and neutropenia, an increase in the level of gamma glutamyl transpeptidase in the blood, and an increase in the frequency of ultrasound signs of cholecystitis. At the same time, a pronounced increase in the functional activity of blood eosinophils, determined by the chemiluminescent method, was observed in patients with *O. felineus* invasion.

Conclusions. Patients with *O. felineus* invasion with an increase in the content of eosinophils in the blood due to the likelihood of an aggressive course of the pathology deserve close attention of practitioners with the need for a thorough comprehensive examination, including immunological methods.

Keywords: *Opisthorchis felineus*, eosinophils, functional activity, chemiluminescence

Conflict of interest: the authors declare that there is no conflict of interest.

For citation: Tsukanov V.V., Veselova N.E., Savchenko A.A., Kolenchukova O.A., Gvozdev I.I., Vasyutin A.V., Tonkikh Yu.L., Kasparov E.V., Borisov A.G., Gorchilova E.G., Olkhovskaia M.Yu., Prokopieva N.O. Functional Activity of Blood Eosinophils in Patients with *Opisthorchis Felineus* Invasion. Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2023;33(6):26–35. https://doi.org/10.22416/1382-4376-2023-33-6-26-35

Функциональная активность эозинофилов крови у больных с инвазией *Opisthorchis felineus*

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Цель исследования: изучить функциональную активность эозинофилов крови у больных с инвазией *Opisthorchis felineus* (*O. felineus*).

Материал и методы. Всего было обследовано 328 больных с инвазией *O. felineus* (120 мужчин и 208 женщин, средний возраст — 40,3 года) и 34 практически здоровых человека (14 мужчин и 20 женщин, средний возраст — 41,1 года) в возрасте от 18 до 70 лет. Основным методом диагностики описторхоза являлось определение яиц или тел взрослых паразитов в дуоденальном содержимом и/или в кале, которое применялось у всех 328 пациентов с описторхозом. Всем пациентам выполнялись клинический и биохимический анализы крови, эзофагогастродуоденоскопия и ультразвуковое исследование органов брюшной полости. Исследование функциональной активности эозинофилов крови было проведено 42 больным описторхозом и 34 здоровым лицам из группы контроля методом хемилюминесцентного анализа с измерением интенсивности выработки активных форм кислорода в спонтанной и зимозан-индуцированной реакции в люцигенин- и люминол-зависимых процессах.

Результаты. Частота выявления эозинофилии у обследованных больных описторхозом составила 19,5 %. Повышение содержания эозинофилов в крови у больных описторхозом было ассоциировано с увеличением частоты жалоб на боли в правом подреберье, кожный зуд, кожные высыпания, увеличением доли лейкопении и нейтропении, повышением уровня гамма-глутамилтранспептидазы в крови и частоты ультразвуковых признаков холецистита. Вместе с этим у пациентов с инвазией *O. felineus* наблюдалось выраженное повышение функциональной активности эозинофилов крови, определяемой хемилюминесцентным методом.

Выводы. При инвазии *O. felineus* пациенты с эозинофилией крови имеют более агрессивное течение заболевания.

Ключевые слова: *Opisthorchis felinus*, эозинофилы, функциональная активность, хемилюминесценция

Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования: Цуканов В.В., Веселова Н.Е., Савченко А.А., Коленчукова О.А., Гвоздев И.И., Васютин А.В., Каспаров Э.В., Тонких Ю.Л., Борисов А.Г., Горчилова Е.Г., Ольховская М.Ю., Прокопьева Н.О. Функциональная активность эозинофилов крови у больных с инвазией *Opisthorchis felinus*. Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2023;33(6):26–35. <https://doi.org/10.22416/1382-4376-2023-33-6-26-35>

Introduction

Opisthorchiasis is a global health problem. *Opisthorchis viverrini* and *Clonorchis sinensis* determined in 45 million people in the countries of Southeast and East Asia [1]. *Opisthorchis felinus* (*O. felineus*) invasion is diagnosed in 10–15 % of the endemic foci population in Russia [2]. The role of opisthorchiasis in the development of cholangiocarcinoma is currently being actively studied [5]. European Association for the Study of the Liver (EASL) emphasized the importance of *O. felineus* in the genesis of liver cirrhosis and cholangiocarcinoma in a review about the role of parasites in the development of pathology [3]. In a modern Russian study carried out in the Tomsk Oblast and Khanty-Mansi Autonomous Okrug, the authors found a strong association between *O. felineus* invasion and cases of cholangiocarcinoma ($p = 0.008$) [4].

It is known that the innate immune system, including basophils, eosinophils, dendritic cells, neutrophils, and monocytes, is a key system regulating the host's defense against helminths [6, 7]. In recent years, interest in eosinophil pleiotropism has increased sharply [8]. The role of eosinophils is noted not only in the fight against some parasitic, bacterial and viral infections, the role of these cells in the development of asthma, chronic rhinosinusitis and some gastrointestinal disorders is also discussed [9]. Considerable attention is paid to discussing the diagnosis and management of patients with eosinophilic esophagitis [10, 11].

One of the most interesting achievements at present time is the study of the eosinophils role in the pathogenesis of functional dyspepsia. The current meta-analysis identified 22 studies, including 1108 patients with functional dyspepsia and 893 control group people. There was a clear increase in the number of eosinophils ($p = 0.0001$) and mast cells ($p = 0.0001$) in patients with functional dyspepsia [12]. All of the above determines the relevance of studying the functional activity of blood eosinophils in patients with *O. felineus* invasion.

Materials and methods

The work was carried out on the basis of the therapeutic department of the clinic of the Federal Research Centre “Krasnoyarsk Science Centre” of the Siberian Branch of Russian Academy of Sciences, Scientific Research Institute of Medical Problems of the North, and the Gastroenterological Department of the Krasnoyarsk Private Clinical Hospital “Russian Railways-Medicine”. A total of 328 patients with *O. felineus* invasion (120 men and 208 women, average age — 40.3 years) and 34 practically healthy people (14 men and 20 women, average age — 41.1 years) aged from 18 to 70 years were examined.

Inclusion criteria for patients with opisthorchiasis were: 1) age from 18 to 70 years; 2) diagnosed chronic opisthorchiasis; 3) signed informed consent.

The exclusion criteria from the study were: 1) age under 18 and over 70 years; 2) HIV infection; 3) oncological diseases; 4) chronic liver diseases

of various etiologies (viral hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease, Wilson – Konovalov disease, hemochromatosis, autoimmune hepatitis, etc.); 5) tuberculosis; 6) pregnancy; 7) severe chronic diseases of various organs and systems; 8) refusal to participate in scientific research.

The control group consisted of healthy individuals who, during a preventive examination, did not present gastroenterological complaints, did not have severe chronic diseases of various organs and systems, were characterized by normal complete blood count and biochemical blood test, the absence of markers for viral hepatitis, antibodies to opisthorchiasis, and the absence of helminth eggs in stool analysis for five consecutive days, and denial of a history of alcohol abuse.

Clinical symptoms and anamnestic information were studied in all subjects using a standard questionnaire developed on the basis of current international classifications [13]. The criteria for the diagnosis of opisthorchiasis were the identification of eggs or bodies of adult parasites in the duodenal contents and/or in the feces, which was used in all 328 patients with opisthorchiasis. Chronic opisthorchiasis was determined based on the duration of *O. felineus* invasion for more than six months according to anamnestic data.

Duodenal intubation was carried out after a preliminary three-day preparation with restrictions in the diet of gas-forming foods, sweet, fatty foods and after a 12-hour fast. Classically, three portions of bile were obtained – “A”, “B” and “C” (duodenal, bladder and hepatic), extracted before and after stimulating the motor activity of the gallbladder. To stimulate the motor activity of the gallbladder, 30 mL of a 30 % solution of magnesium sulfate was used. The study continued throughout the expiration of the cystic portion and another 15–20 minutes after the appearance of the light hepatic portion. In each portion, the volume and color were determined, and its macroscopic description was performed. Then microscopy of native bile smears was performed, 5–10 samples from all portions. Portions “B” and “C” were considered the most informative. Also, during an in-depth search, microscopy of bile sediment after centrifugation was performed in order to increase the efficiency of searching for opisthorchis eggs.

The examination of feces for the presence of opisthorchiasis was carried out using the Kato method – the thick smear under cellophane method. A thick smear is a layer of undiluted feces on a glass slide, pressed under a sheet of thin hygroscopic cellophane, previously impregnated with glycerin.

All patients underwent complete blood count and biochemical blood test. A biochemical blood

test determined alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGTP), glucose and total bilirubin levels. All patients underwent esophago-gastroduodenoscopy and ultrasound examination of the abdominal organs.

A study of the functional activity of blood eosinophils was carried out on 42 patients with opisthorchiasis and 34 healthy individuals from the control group. The intensity of the production of reactive oxygen species (ROS) in blood eosinophil cultures was studied using chemiluminescent analysis. The activity of lucigenin- and luminol-dependent spontaneous and zymosan-induced chemiluminescence was determined. Primary ROS (superoxide anion) were studied using lucigenin, and secondary ROS (H_2O_2 , $\cdot OH$, $HClO$) were studied using luminol. Spontaneous chemiluminescence shows the basic level of functional activity of eosinophils; upon stimulation with zymosan, the reserve capabilities of the cells were determined. Chemiluminescent activity was assessed for 90 minutes on a 36-channel chemiluminescent analyzer “CL3606” (Russia). The following characteristics of the functional activity of cells were determined: time to reach maximum (T_{max}), maximum intensity value (I_{max}) and area under the curve (S) of chemiluminescence. The activation index (AI) was calculated by the ratio of S in the zymosan-induced reaction to S in the spontaneous reaction.

The study was carried out with the permission of the local ethics committee of the Federal Research Centre “Krasnoyarsk Science Centre” of the Siberian Branch of Russian Academy of Sciences (protocol No. 4 of 08.02.2019). Each participant signed an informed consent form for the examination, in accordance with the World Medical Association Declaration of Helsinki, which governs scientific research.

Statistical processing of the research results was carried out on a personal computer using the Statistica (version 7.0) and SPSS v. 12.0 application package. To analyze quantitative indicators, the median (Me) and interquartile range (C_{25} – C_{75}) were calculated. The significance of differences between the indicators of independent samples was assessed using the nonparametric Mann – Whitney U test. To analyze the statistical significance of differences in qualitative characteristics, the calculation of the odds ratio (OR) and confidence interval (CI) for the OR was used (CI was determined using the Woolf logit method). Differences were considered statistically significant at $p \leq 0.05$.

Results

As part of this work, we analyzed a fairly large number of medical records of patients with

O. felineus invasion ($n = 328$) in order to determine the relationship between increased levels of eosinophils in the blood and clinical and laboratory manifestations. The frequency of detection of blood eosinophilia (the content of eosinophils in complete blood count is higher than 5 %) in the examined patients with opisthorchiasis was 19.5 % (in men — 21.7 %, in women — 18.3 %; OR = 1.24; CI: 0.71–2.16; $p = 0.55$). We did not find an association of eosinophilia in the blood with age of patients.

In patients with a blood eosinophil content above 5 %, an increase in the frequency of pain in the right hypochondrium, skin itching and skin rashes was registered. A very interesting fact was the establishment of a relationship between eosinophilia with leukopenia and neutropenia. In our previous works, we showed that patients with *O. felineus* invasion have a decrease in the functional activity of neutrophils in the blood [14, 15]. In this work, we demonstrated for the first time the association of eosinophilia with leukopenia and neutropenia. Among other indicators, one should highlight an increase in GGTP content and a higher frequency of ultrasound signs of cholecystitis (thickening of the gallbladder wall of 4 mm or more) in patients with an increase in the content of eosinophils in the blood compared to persons with a normal leukocyte formula (Table 1).

The functional activity of eosinophils in the luminol-dependent process was significantly higher in patients with opisthorchiasis compared to healthy individuals. The area under the curve (S) for the spontaneous reaction in patients with *O. felineus* invasion was 7.5 times higher, and for the zymosan-induced reaction it was 15.4 times higher. It should be noted that the ability of eosinophils to produce reactive oxygen species increased significantly in patients with opisthorchiasis when stimulated with zymosan (AI = 3.36) in comparison with healthy individuals (AI = 1.61; Table 2).

Similar regularities were determined in the lucigenin-dependent process. The area under the curve, which determines the total production of reactive oxygen species, in patients with opisthorchiasis in comparison with healthy individuals was 20.6 times higher in the spontaneous reaction, and 11.4 times higher in the zymosan-induced reaction (Table 3).

Thus, we obtained data according to which an increase in the content of eosinophils in the blood in patients with opisthorchiasis was associated with an increase in the frequency of complaints of pain in the right hypochondrium, skin itching, skin rashes, an increase in the proportion of leukopenia and neutropenia, an increase in the

level of GGTP in the blood and an increase in the frequency of ultrasound signs of cholecystitis. At the same time, a pronounced increase in the functional activity of blood eosinophils, determined by the chemiluminescent method, was observed in patients with *O. felineus* invasion.

Discussion

Eosinophils are myeloid cells that develop in the bone marrow in response to specific combinations of transcription factors and cytokines. After differentiation and maturation, eosinophils leave the bone marrow, enter the bloodstream, and are rapidly recruited to peripheral tissues. Less than 1 % of the body's total eosinophil pool is found in the bloodstream, where they constitute less than 5 % of white blood cells. The vast majority of eosinophils are found in the mucosa of the digestive tract [16].

Eosinophils are granulocytes and contain numerous granules of varying composition. Cationic granule proteins mediate most of the cytotoxic effects of eosinophils, play a role in host defense, and promote inflammation. Eosinophil peroxidase generates reactive oxygen species, which also contribute to cytotoxicity. Eosinophil granules contain cytokines, chemokines, growth factors and lipid mediators that are selectively released in response to various stimuli [17].

The classical function of eosinophils was considered to be the fight against helminths and participation in allergic processes [18]. When helminth larvae migrate in tissues, an immune response develops, which leads to the expansion of eosinophils and the production of IgE type immunoglobulins. IgE antibodies bind to the target antigen and activate eosinophils, which release cytotoxic substances [19].

The last 20 years have been marked by a change in ideas about the functions of eosinophils. The involvement of these cells in immune homeostasis has been described. These cells are able to modulate the functions of B cells, plasma cells and T cells, and participate in the regulation of the intestinal microbiota [20]. A number of modern studies have established the pathogenic role of eosinophils in the development of some diseases. The role of eosinophils has been studied particularly well in patients with bronchial asthma. Early studies demonstrated that total eosinophil count reflects asthmatic activity and is useful for steroid dose adjustment [21]. Subsequently, the relationship between the number of eosinophils in the blood and sputum and the severity of asthma was verified [22]. A study in 2002 showed that a therapeutic approach targeting eosinophilic inflammation resulted in optimal asthma treatment outcomes [23]. Subsequently, when studying a cohort of 130,000 patients in the UK, the authors demonstrated that the number

Table 1. Clinical and laboratory parameters in patients with opisthorchiasis depending on the content of eosinophils in the blood

Таблица 1. Клинико-лабораторные показатели у больных описторхозом в зависимости от содержания эозинофилов в крови

Parameter / Показатель	Eosinophils ≤ 5.0 % Эозинофилы $\leq 5,0$ % (n = 264)		Eosinophils > 5.0 % Эозинофилы $> 5,0$ % (n = 64)		OR; CI, p ОШ; ДИ; p
	EO abs. / абс.	%	EO abs. / абс.	%	
Pain in the right hypochondrium Боли в правом подреберье	71	26.9	29	45.3	0.44; 0.25–0.78; p = 0.007
Epigastric pain Боли в эпигастрии	90	34.1	17	26.6	1.41; 0.77–2.58; p = 0.32
Pruritus Кожный зуд	64	24.2	27	42.2	0.44; 0.25–0.77; p = 0.007
Skin rashes Кожные высыпания	81	30.7	35	54.7	0.37; 0.21–0.64; p < 0.001
Overweight (BMI ≥ 30.0) Ожирение (ИМТ $\geq 30,0$)	39	14.8	6	9.4	1.58; 0.66–3.79; p = 0.36
Leukopenia ($< 4 \times 10^9/L$) Лейкопения ($< 4 \times 10^9/л$)	21	8.0	12	18.8	0.37; 0.17–0.79; p = 0.02
Neutropenia (< 47.0 %) Нейтропения ($< 47,0$ %)	67	25.4	30	46.9	0.39; 0.22–0.68; p = 0.001
Lymphocytosis (> 37.0 %) Лимфоцитоз ($> 37,0$ %)	134	50.8	28	43.8	1.32; 0.76–2.28; p = 0.39
Elevated ALT levels Повышенный уровень АЛТ	27	10.2	10	15.6	0.60; 0.28–1.30; p = 0.32
Elevated AST levels Повышенный уровень АСТ	17	6.4	7	10.9	0.54; 0.22–1.34; p = 0.33
Increased GGTP Повышенная ГГТП	24	9.1	17	26.6	0.28; 0.14–0.55; p < 0.001
Increased serum glucose (> 6.1 mmol/L) Повышенная глюкоза в сыворотке крови ($> 6,1$ ммоль/л)	15	5.7	6	9.4	0.56; 0.21–1.46; p = 0.42
Elevated total bilirubin (≥ 21.0 μ mol/L) Повышенный общий билирубин ($\geq 21,0$ мкмоль/л)	47	17.8	13	20.3	0.83; 0.42–1.64; p = 0.78
Hepatomegaly on ultrasound Гепатомегалия по УЗИ	47	17.8	16	25.0	0.64; 0.34–1.22; p = 0.26
Signs of cholecystitis on ultrasound Признаки холецистита по УЗИ	8	3.0	7	10.9	0.25; 0.09–0.71; p = 0.02
Biliary sludge on ultrasound Билиарный сладж по УЗИ	46	17.4	16	25.0	0.63; 0.33–1.19; p = 0.23
Polyps in the gallbladder on ultrasound Полипы в желчном пузыре по УЗИ	31	11.7	5	7.8	1.46; 0.56–3.77; p = 0.5
Steatosis in the liver on ultrasound Стеатоз в печени по УЗИ	21	8.0	2	3.1	2.21; 0.58–8.42; p = 0.28
Peptic ulcer Язвенная болезнь	23	8.7	2	3.1	2.43; 0.64–9.23; p = 0.21

Note: the significance of the differences in indicators was calculated using the odds ratio; EO abs. — absolute eosinophil count; OR — odds ratio; CI — confidence interval; BMI — body mass index; ALT — alanine aminotransferase; AST — aspartate aminotransferase; GGTP — gamma glutamyl transpeptidase.

Примечание: достоверность различий показателей вычислена при помощи отношения шансов; ОШ — отношение шансов; ДИ — доверительный интервал; ИМТ — индекс массы тела; АЛТ — аланинаминотрансфераза; АСТ — аспартатамино-трансфераза; ГГТП — гамма-глутамилтрансептидаза.

Table 2. Characteristics of the functional activity of eosinophils in the luminol-dependent process in patients with opisthorchiasis in comparison with healthy individuals, $Me (C_{25}-C_{75})$

Таблица 2. Характеристики функциональной активности эозинофилов в люминол-зависимом процессе у пациентов с описторхозом в сравнении со здоровыми лицами, $Me (C_{25}-C_{75})$

Parameter / Показатель		Patients with opisthorchiasis Пациенты с описторхозом (n = 42)	Healthy individuals Здоровые лица (n = 34)	p
Spontaneous reaction Спонтанная реакция	T_{max} , s / c	1154 (888–1428)	635 (307–1723)	0.04
	I_{max} , RU / отн. ед.	16 759 (2801–28 079)	2230 (977–4396)	< 0.001
	S , $\times 10^3$ RU / отн. ед.	36 260 (10 370–64 340)	4823 (1135–12 890)	< 0.001
Zymosan-induced reaction Зимозаниндуцированная реакция	T_{max} , s / c	1332 (977–1600)	848 (308–1477)	0.01
	I_{max} , RU / отн. ед.	41 879 (10 644–57 676)	5371 (1219–9459)	< 0.001
	S , $\times 10^3$ RU / отн. ед.	125 200 (30 330–137 600)	8108 (2047–21 000)	< 0.001
Activation index Индекс активации		3.36 (1.37–4.94)	1.61 (1.14–3.75)	0.01

Note: the reliability of differences in indicators was determined using the Mann – Whitney test; T_{max} – time to reach maximum; I_{max} – maximum intensity value; S – area under the chemiluminescence curve; RU – relative units; s – seconds.

Примечание: достоверность различий показателей определена с помощью критерия Манна – Уитни; T_{max} – время выхода на максимум; I_{max} – максимальное значение интенсивности; S – площадь под кривой хемилюминесценции; отн. ед. – относительные единицы; с – секунды.

Table 3. Characteristics of the functional activity of eosinophils in the lucigenin-dependent process in patients with opisthorchiasis in comparison with healthy individuals, $Me (C_{25}-C_{75})$

Таблица 3. Характеристики функциональной активности эозинофилов в люцигенин-зависимом процессе у пациентов с описторхозом в сравнении со здоровыми лицами, $Me (C_{25}-C_{75})$

Parameter / Показатель		Patients with opisthorchiasis Пациенты с описторхозом (n = 42)	Healthy individuals Здоровые лица (n = 34)	p
Spontaneous reaction Спонтанная реакция	T_{max} , s / c	1472 (1250–1598)	888 (492–1846)	0.03
	I_{max} , RU / отн. ед.	4576 (925–11 712)	227 (72–1461)	< 0.001
	S , $\times 10^3$ RU / отн. ед.	9674 (1947–31 570)	470 (322–3555)	< 0.001
Zymosan-induced reaction Зимозаниндуцированная реакция	T_{max} , s / c	1420 (1277–1661)	707 (282–1353)	0.001
	I_{max} , RU / отн. ед.	6893 (1419–9400)	612 (128–1072)	< 0.001
	S , $\times 10^3$ RU / отн. ед.	18 540 (3566–26 570)	1633 (511–2973)	< 0.001
Activation index Индекс активации		1.92 (0.64–4.46)	3.41 (0.83–6.02)	0.04

Note: the reliability of differences in indicators was determined using the Mann – Whitney test; T_{max} – time to reach maximum; I_{max} – maximum intensity value; S – area under the chemiluminescence curve; RU – relative units; s – seconds.

Примечание: достоверность различий показателей определена с помощью критерия Манна – Уитни; T_{max} – время выхода на максимум; I_{max} – максимальное значение интенсивности; S – площадь под кривой хемилюминесценции; отн. ед. – относительные единицы; с – секунды.

of eosinophils in the blood is a biomarker of severe asthma exacerbation [24]. Recently, the significant role of eosinophilic inflammation has been established for a number of other diseases, which include chronic rhinosinusitis with nasal polypsis, eosinophilic granulomatosis with polyangiitis, gastrointestinal pathology (eosinophilic esophagitis and dyspepsia) and hypereosinophilic syndrome, in connection with which the term “eosinophilic immune dysfunction” was proposed [8, 25]. The significance of the problem of diseases associated

with hypereosinophilia was drawn attention by the World Health Organization, which in 2022 published recommendations for the diagnosis and management of patients with this pathology [26].

Our results, on the one hand, confirm the concept of the protective role of eosinophils in the fight against parasitic diseases, on the other hand, they suggest that some patients with *O. felinus* invasion exhibit manifestations of probable “eosinophilic immune dysfunction”, consisting of an association of hypereosinophilia with a more aggressive course of pathology.

Conclusion

A clinical and laboratory study of 328 patients with *O. felinus* invasion in combination with determination of the functional activity of eosinophils using the chemiluminescent method in 42 patients with opisthorchiasis and 34 practically healthy controls made it possible to establish the presence of an association of blood eosinophilia with increased frequency of pain in the right hypochondrium complaints, skin itching, skin rashes, increased proportion of leukopenia and neutropenia, an increase in the blood GGTP level and increased frequency of cholecystitis ultrasound signs. A chemiluminescent

study showed an increase in the functional activity of blood eosinophils in luminol- and lucigenin-dependent processes. From our point of view, patients with *O. felinus* invasion with an increase in the content of eosinophils in the blood deserve the close attention of practitioners with the need for a thorough comprehensive examination, including immunological methods. Interesting aspects of this problem include the search for effective methods of treating such patients and the advisability of organizing new studies to answer the question: are manifestations of "eosinophilic immune dysfunction" possible in patients with opisthorchiasis?

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Submitted: 23.06.2023 Accepted: 15.09.2023 Published: 29.12.2023
Поступила: 23.06.2023 Принята: 15.09.2023 Опубликовано: 29.12.2023