



Case report

Clinical polymorphism in patients with *Opisthorchis felinus* infection in the Western Siberia



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ABSTRACT

Clinical symptoms of chronic opisthorchiasis superinvasion the inhabitants of the Western Siberia, which is hyperendemic for this parasites, are presented. The polymorphism of manifestations from many organs and systems (liver, respiratory, immune, musculoskeletal, and digestive, etc.) with the development of eosinophilic hepatitis, according to histological studies, are shown. Manifestation of the latent course of the chronic phase of opisthorchiasis in case of repeated infection was accompanied by leukemoid eosinophilia, hyperleukocytosis and severe cholestasis, which determined the difficulties of the differential diagnostic search.

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Introduction

Western Siberia is an endemic for opisthorchiasis. This disease is characterized by long-term parasitism by worms in the intrahepatic bile ducts and pancreatic ducts. There are early and late phases in the pathogenesis of opisthorchiasis. The early phase (acute opisthorchiasis) lasts from several days to 4–8 weeks. The late phase (chronic opisthorchiasis) lasts for many years with symptoms of biliary system damage, gastroduodenitis, pancreatitis [1,2]. In the pathogenesis of the chronic stage, repeated infections with subsequent fibrosis of the biliary tract, pancreas, liver steatosis, impaired tonic and motor function of the bile ducts, gall bladder and the development of cholestasis play a leading role [1,3]. In endemic foci of opisthorchiasis local residents develop immunological tolerance to helminth antigens as a result of repeated infections starting from childhood. As a result, invasion

takes on a primary chronic course without a pronounced acute phase of opisthorchiasis and for many years proceeds in an erased or asymptomatic form without classic eosinophilia on the hemogram [4–6].

Re-infection and relapse of opisthorchiasis develop a condition [1,2,6] that resembles the acute phase of the infection (fever, intoxication, a variety of clinical symptoms with eosinophilia and leukocytosis), which significantly complicates the clinical diagnosis of this disease. Here we report two clinical cases of opisthorchiasis superinvasion.

Case report 1

A 45-year-old woman (Patient V.) has been registered as outpatient since 2015 with a diagnosis of bronchial hyperreactivity. For two years periodically she was bothered by paroxysmal cough with scanty sputum, fever up to 38–39 °C, shortness of breath during exertion. Since November 2016 episodes of dyspnea were added, the body temperature rose to 37.8 °C, and the administration of Beclomethasone and Amoxicillin had no effect. In January 2017 she was admitted to the Pulmonary Department of the hospital in Barnaul with a diagnosis of nonspecific interstitial pneumonia and unspecified eosinophilia. On admission, the woman had a complaint of shortness of breath in unstable cold weather, a rare unproductive cough, flying pains and swelling of the joints (elbow, knee, wrist) which were relieved by taking NSAIDs. Diagnosis at hospital: "Community-acquired bilateral

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polysegmental pneumonia in the upper lobes, moderate severity, respiratory failure 0 stage. Unspecified eosinophilia". After an antibiotic therapy (Ceftriaxone + Azithromycin) normalization of body temperature and a chest X-ray improvement have happened. After discharge from the hospital, flying pains reappeared in joints (elbow, knee, wrist). On an outpatient basis, in blood serum the antibodies against *Opisthorchis*, *Toxocara canis*, *Giardia lamblia* was examined by ELISA and *Mycobacterium tuberculosis* by PCR –with the negative results of all tests. Multi-slice computed tomography (MSCT) revealed the multiple areas of ground-glass interstitial infiltration with indistinct contours, irregular shape, thickening of the peribronchovascular and interlobular interstitium in the form of linear cords in both lungs, mainly in the upper lobes in the cortical and subpleural regions. The patient was admitted to the Pulmonary Department.

On admission to the pulmonary department, general condition was satisfactory. Body temperature was 36.7 °C. The skin was a normal color without rashes. Peripheral lymph nodes were not palpable. Auscultation of the lung showed vesicular breath sound with breath rate 20/min., SatO₂ – 97 %. Heart boundaries were displaced to the left by 1.5 cm lateral of the midclavicular line, the tones of heart were muffled, the rhythm was correct, heart rate was 90 per minute, blood pressure – 120/80 mm Hg. Edge of the liver was near the costal margin. There was no edema, urination was not frequent, stool was normal.

Results of the blood test presented in Table 1 and revealed some abnormalities: leukocytosis up to $12.9 \times 10^9 / L$ (reference range: $4.0-9.0 \times 10^9 / L$), 56%–24% eosinophilia (reference range: (1–5%) and ALT up to 229.2 U/L (reference range: 0–40 U/L), AST up to 110.7 U/L (reference range: 0–40 U/L), ALP up to 967 U/L (reference range: 0–130 U / L). Abdominal ultrasound showed diffuse homogeneous changes in the walls of the intrahepatic bile ducts, signs of bile thickening. X-ray examination revealed intrathoracic lymphadenopathy and bilateral areas of compaction of the lung tissue in the form of infiltrates. According to the lungs and mediastinum MSCT data, pronounced interstitial changes in the lungs which are characteristic of nonspecific interstitial pneumonia (sarcoidosis?) were revealed. No pathology was established by video bronchoscopy. Stool ova and parasite examination using concentration method (3-x negative results), studies of blood serum by ELISA (detection of IgM, IgG antibodies against *Opisthorchis*, *Toxocara canis*, *Giardia lamblia*) (Helminths-IgG-ELISA-BEST No. FSR 2009/04032, a set of reagents for enzyme detection of IgG to antigens of *Opisthorchis*, *Toxocara canis*, *Trichinella*, and *Echinococcus* in serum (plasma) of blood) (negative tests) were performed.

Multiple organ lesions: signs of allergic pneumonitis revealed by MSCT, arthralgic syndrome, hypereosinophilia (up to 56 % in the blood test), involvement of the hepatobiliary system, and

Table 1
Dynamic of the laboratory findings of patient V.

Test	On admission	At discharge	Reference range
Hemoglobin (g/L)	131	137	120–164
WBC ($10^9/L$)	12.5	12.9	4.0–9.0
RBC ($10^{12}/l$)	4.72	4.97	3.7–5.5
Platelets ($10^9/L$)	275	354	180–320
Eosinophils (%)	56	24	1–5
Band neutrophils (%)	3	2	0–3
Neutrophils (%)	19	52	50–72
Lymphocytes (%)	18	16	18–36
Monocytes (%)	4	6	2–10
ESR (mm/h)	24	17	1–15
Total bilirubin ($\mu\text{mol/L}$)	20	16	8.55–20.52
ALT (U/L)	229	110	0–40
AST(U/L)	110	82	0–40
ALP (U/L)	967	238	0–130

anamnesis (accommodation from birth to the present time in an area where opisthorchiasis is endemic, the constant use of insufficiently heat treated fish) were the basis for a targeted search for parasitic invasion, primarily opisthorchiasis, as well as the exclusion of diffuse connective tissue diseases.

When carrying out the recommended set of examinations a month after discharge from the hospital, a large number of leukocytes, epithelial cells, and *Opisthorchis felinus* eggs were found in the duodenal contents. Complex therapy aimed at deworming (Praziquantel 75 mg / kg) followed by rehabilitation (taking cholagogue drugs – Ursodeoxycholic acid 10 mg / kg per day for up to 1 month), desensitizing (Levocetirizine 5 mg per day, up to 10 days) ensured a full clinical recovery and restoration of the quality of life (18 months follow-up period).

Case report 2

A 24-year-old woman A., was taken to the surgical department of the emergency hospital in October 2017 with suspicion of a destructive process in the abdominal cavity. Her complaints on admission were sharp pain in the epigastric region and nausea. Patient fell ill three days ago with the appearance of pain in the epigastric region, nausea, labial herpes, took Omeprazole and Pancreatin without positive effect.

On admission, the condition was moderate severity. The skin was clean. Pustular eruptions on the red border of the lips were found. On auscultation there was vesicular breath sound with respiratory rate 16/min. Heart sounds were clear and rhythmic. Pulse was 78/min, blood pressure – 110/80 mm Hg. Tongue was dry and white coated. On physical examination the patient's abdomen was tense, painful in the epigastrium and right hypochondrium. The liver edge was near the costal margin, the spleen was not palpable.

In blood test a stab left shift was revealed (Table 2). On the 4th day of hospitalization, the patient's temperature rose to 40 °C, after that Ceftriaxone 2.0 IV was prescribed. Results of the biochemical analysis showed significant increase in ALT– 570 U/L (reference range: 0–40 U / L), AST – 294 U / L (reference range: 0–40 U / L), ALP up to 2373 U / L (reference range: 0–130 U / L), GGTP – 744 U / L (reference range: 0–38 U / L), Presepsin – 800 pg/mL (reference range: less than 300 pg/mL), CRP 73 g / L (reference range: 0–5 g / l) levels. In hemogram eosinophilia from 9 % with an increase to 28 % in dynamics was found (reference range: 1–5 %).

The test for viral hepatitis, RW, HIV were negative. Abdominal ultrasound showed an increase in liver size, biliary sludge. Echocardiography has not revealed any pathology. Patient was examined by a urologist and otolaryngologist. Pelvis ultrasound showed a 6–7th weeks pregnancy. On esophagogastroduodenoscopy hemorrhagic erosion in the stomach, erosive bulbitis, superficial gastritis, and cardia insufficiency were revealed. On the 11th day of hospitalization, diagnostic laparoscopy was performed. On laparoscopy multiple foci in both lobes with the size from 0.5 to 3.5 cm with dense consistency, irregular shape and a lot of small-dot whitish inclusions in the center were found. Histological examination of liver biopsy: a fragment of the liver with signs of acute hepatitis with moderate, focal polymorphic, mainly eosinophilic infiltration. Conclusion: "Eosinophilic hepatitis", or hepatitis with severe eosinophilic infiltration"

On the 12th day of hospitalization, the patient was transferred to the gastroenterology department with a diagnosis: "Nonspecific reactive hepatitis? Hemorrhagic erosive gastritis. 6–7 weeks of pregnancy".

When examined by a hematologist differential diagnosis of eosinophilic leukemoid reaction was carried out and eosinophilic leukemia was excluded. Complete blood count results on the 12th day of hospitalization: leukocytes up to $17.56 \times 10^9 / L$ (reference

Table 2
Dynamic of the laboratory findings of patient A.

Test	06.10	14.10	15.10	17.10	20.10	26.10	Reference range
Hemoglobin (g/L)	118	131	116	113	118	113	120–164
WBC ($10^9/L$)	9.0	10.2	11.78	17.56	17.53	10.84	4.0–9.0
ESR (mm/h)	16		22	24	18	24	1–15
RBC ($10^{12}/\mu$)			4.12				3.7–5.5
Platelets ($10^9/L$)	200	215		290	384	354	180–320
Eosinophils (%)	7		52	48	54	47	1–14
Band neutrophils (%)	7		2	1	3	1	0–3
Neutrophils (%)	69		30	40	28	32	50–72
Lymphocytes (%)	9		11	5	7	13	18–36
Monocytes (%)	8		5	6	8	7	2–10
MCH			28.2			28.3	27–31
MCV			90.1			94.7	82–95

Table 3
Dynamic of the biochemical parameters of patient A.

Test	14.10	15.10	17.10	20.10	26.10	Reference range
Total bilirubin ($\mu\text{mol/L}$)	21	18	11	12	11	8.55–20.52
Conjugated bilirubin ($\mu\text{mol/L}$)	14	13	5	7	3	1–5.1
ALT (U/L)	570	384	204	107	47	0–40
AST(U/L)	294	131	69	42	30	0–40
GGTF (U/L)	526	689	744	700	456	0–38
ALP (U/L)	2072	2373	1038	943	633	0–130
Total protein (g/L)	69					65–85
Albumin (g/L)			39	38	37	30–55
Urea (ммол/л)	2.4		1.6	1.5	1.5	2.5–8.3
Creatinine (mmol/L)	65		69	70	64	50–110
Glucose (mmol/L)	4.4					4.5–6.5
Prothrombin time (%)	92	67	99	56	98	80–100
International normalized ratio	1.12	1.49	1			

range: $4.0\text{--}9.0 \times 10^9 / L$), eosinophils - 54 % (reference range: 1–5 %). Additional studies were performed: Wright serology was positive with a titer of 1: 400; the ELISA testing for IgM and IgG against *Brucella* spp. and *Yersinia* spp. were negative (kits D-3204, D-3206, D-3202, D-3658, Vector-best, Russia), sterility testing of blood showed an absence of microbial growth.

Dynamic abdominal ultrasound revealed an increase in the size of the liver right lobe, diffuse heterogeneous changes in the hepatic structure, diffuse changes in the structure of the walls of the gallbladder and intrahepatic bile ducts in the form of linear hyperechoic striation, moderate diffuse heterogeneous changes in the structure of the pancreas, free fluid in the abdominal cavity and in the pleural cavities. As an infectious disease specialist recommended a fecal microscopic examination was carried out where the eggs of *Opisthorchis felineus* were found. On the 18th day of hospitalization, the diagnosis of “Opisthorchiasis, chronic phase. Secondary bacterial cholangitis. Hepatitis. Eosinophilic leukemoid reaction” was made.

From the epidemiological history, it was established that two months before the disease onset, a large number of river fish of the carp family were consumed without sufficient heat treatment. Repeated results of the Wright serology, Hedelson’s reaction, ELISA testing for Brucellosis and *Yersinia* were negative. Antibacterial (Ertapenemum, 1g – once a day i.v., during 5 days) and desensitizing Llevocetirizine, 5 mg per day) therapy resulted in positive effect of the treatment – normalization of body temperature, pain disappearance. There was a decrease in the number of leukocytes, eosinophils, normalization of the level of ALT, AST, a significant decrease in ALP, GGTP (Tables 2 and 3) enzyme activity. The patient was discharged under the supervision of an obstetrician-gynecologist at the place of residence. Treatment of opisthorchiasis (Praziquantel) was planned after delivery and completion of breastfeeding.

Conclusion

The given clinical cases illustrate a complex differential diagnostic challenge in patients with hypereosinophilia in endemic areas of *Opisthorchis felineus*. In the first case, damaging of the bronchopulmonary system, arthralgia (flying pain in large and small joints) in combination with high eosinophilia (from 56 % to 14 %) prevailed, which made it possible to suspect and confirm the parasitic infection with *Opisthorchis*. In the second case, opisthorchiasis with cholangitis was accompanied by intoxication, liver damage with cytolysis and eosinophilic infiltration, hypereosinophilia up to 54 %, where pregnancy could be a trigger factor for the manifestation of a superinvasion process. It should be especially noted the low informativeness of serological studies for *Opisthorchis felineus* which determines the mandatory repeated fecal microscopic examination in case of this invasion is suspected.

In conclusion, in patients from areas endemic for opisthorchiasis with the disease characterized by symptoms of damage a lot of organs and systems (liver, kidneys, immune, cardiovascular, respiratory, endocrine, digestive systems, etc.) and eosinophilia it is necessary to exclude the *Opisthorchis felineus* infection, and to carry out a comprehensive laboratory examination of not only serum, but also stool samples.

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