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Случай сочетанного течения брюшного тифа и лептоспироза

Т.В. Харламова[1], И.В. Барышева[1], Н.А. Половинкина[1], Е.Ю. Бурдова[1], М.В. Богданова[2]

[1] Российский университет дружбы народов имени Патриса Лумумбы, Москва, Российская Федерация;
[2] Инфекционная клиническая больница № 2, Москва, Российская Федерация

АННОТАЦИЯ

Сочетанные инфекции становятся всё более актуальной проблемой и требуют срочного изучения. Развитие международного туризма является причиной быстрого распространения инфекционных заболеваний из стран с неблагоприятными санитарно-гигиеническими условиями. В данной статье представлен клинический случай пациентки, недавно вернувшейся из Индии, у которой развилось сочетанное течение брюшного тифа и лептоспироза на фоне астровирусной инфекции и бластоцистоза. Заболевание характеризовалось признаками энтерита, лихорадкой низкой степени тяжести и лёгкой интоксикацией. Пациентка неоднократно обращалась за медицинской помощью. В результате были диагностированы острая респираторная вирусная инфекция и кишечная инфекция неизвестной этиологии. Симптоматическая терапия не дала положительного результата, лихорадка и выраженный астенический синдром сохранялись. Пациентка была госпитализирована на 18-й день с момента заболевания в состоянии средней тяжести. С учётом клинических, анамнестических, эпидемиологических данных и результатов лабораторного исследования был диагностирован брюшной тиф. Методом полимеразной цепной реакции в кале была выявлена РНК астровируса, при исследовании кала на наличие паразитов — *Blastocystis hominis*. Несмотря на проводимую патогенетическую и антибактериальную терапию с учётом чувствительности возбудителя к антибиотикам, состояние пациентки ухудшалось. На 23-й день заболевания были отмечены желтуха, геморрагический синдром, признаки острой почечной недостаточности. После изучения изменений клинико-лабораторных показателей и с учётом данных эпидемиологического анамнеза (пребывание в эндемичном по лептоспирозу регионе) был поставлен диагноз «лептоспироз» и проведена антибактериальная терапия. Комплексная интенсивная терапия с использованием экстракорпоральных методов лечения позволила предотвратить развитие неблагоприятных исходов сочетанной патологии. Данный клинический случай подчеркивает, что врачи должны с осторожностью относиться к завозным инфекциям и проводить дополнительное комплексное обследование при подозрении на них.

Ключевые слова: сочетанные инфекции; завозные инфекции; брюшной тиф; лептоспироз.

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A case of a combined course of typhoid fever and leptospirosis

Tatiana V. Kharlamova[1], Irina V. Barysheva[1], Nadezhda A. Polovinkina[1], Elena Yu. Burdova[1], Mariya V. Bogdanova[2]

[1] Peoples' Friendship University of Russia named after Patrice Lumumba, Moscow, Russian Federation;
[2] Infectious Diseases Clinical Hospital No. 2, Moscow, Russian Federation

ABSTRACT

Coinfections are becoming increasingly relevant and urgently require research. The development of international tourism has caused the rapid spread of infectious diseases from countries with unfavorable sanitary and hygienic conditions. This article analyzes the clinical case of a patient who recently returned from India and developed a combined course of typhoid fever and leptospirosis due to astrovirus infection and blastocystosis. The disease was characterized by symptoms of enteritis, low-grade fever, and mild intoxication. The patient repeatedly sought medical help. Diagnoses of "acute respiratory viral infection" and "intestinal infection of unknown etiology" were established. Symptomatic therapy was performed without a positive effect; fever and severe asthenic syndrome persisted. The patient was hospitalized on the 18th day of illness with moderate severity. Taking into account clinical, anamnestic, and epidemiological data and laboratory examination results, typhoid fever was diagnosed. A polymerase chain reaction (PCR) test identified astrovirus RNA in the stool, and *Blastocystis hominis* was detected during stool examination. Despite the ongoing pathogenetic and antibacterial therapy, considering the determination of the pathogen's sensitivity to antibiotics, the patient's condition worsened. On day 23 of the illness, jaundice, hemorrhagic syndrome, and signs of acute renal failure were noted. Through in-depth analysis of changes in the clinical and laboratory findings, considering epidemiological history data (stay in a region endemic for leptospirosis), leptospirosis was diagnosed and treated with antibacterial therapy. Complex intensive therapy using extracorporeal treatment methods helped prevent the development of unfavorable outcomes of combined pathology. This clinical case emphasizes that doctors must be wary of imported infections and conduct additional comprehensive investigations of suspected cases.

Keywords: co-infections; imported infections; typhoid fever; leptospirosis.

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BACKGROUND

The problem of combined infectious diseases associated with two or more pathogens is one of the leading topics in modern infectology because of emerging difficulties not only in clinical and laboratory diagnostics but also in treating such patients and prevention of fatal outcomes. The issues of the pathogenesis of such diseases, nature of the relationship of pathogens among themselves, and their effect on the human immune system remain insufficiently examined.

Recent domestic and foreign publications have described clinical and epidemiological descriptions of combined human infectious diseases caused by pathogens of different biological species (viruses, bacteria, helminths, protozoa, and fungi). The leading coinfectious agents are bacteria (53.4%) and viruses (34.7%) [1, 2].

Acute intestinal infections occupy a significant place in the structure of infectious diseases. According to the WHO, more than 1 billion cases are registered annually worldwide [3]. In domestic publications, the incidence of intestinal infections caused by several pathogens can reach 48.9±3.3% [4,5]. The associations of pathogens are interconnected primarily by the commonality of the mechanisms and methods of their transmission.

Most studies have demonstrated that combined intestinal infections are more severe than monoinfections, which have complications, a protracted course, and prolonged bacterial and viral excretion [5, 6].

Various combinations of typhoid fever with other infectious nosologies, such as dysentery, viral hepatitis A, malaria, and helminthiasis, have been reported in Russia. The analysis of these cases outlined a change in the clinical picture of the disease, a high risk of severe diseases, and occurrence of complications (septic shock, intestinal perforation, and intestinal bleeding). Invasion of several parasites (*Ascaris lumbricoides* and *Ancylostoma*) in patients with typhoid fever increases the number of complicated diseases by eight times and deaths by seven times [4].

Currently, the incidence of typhoid fever in the Russian Federation has decreased significantly, and only sporadic cases of infection have been recorded, mainly due to importation from regions where this disease endemic. According to the Russian Federal Service on Surveillance on Consumer Rights Protection and Wellbeing, approximately 40% of typhoid fever cases in the Russian Federation are attributed to tourists who have visited tropical countries, particularly in India and Thailand, and migrants from Central Asia [7, 8]. Countries with tropical and subtropical climates have a high incidence of leptospirosis (10–100 cases per 100,000 population) [9].

Herein, we present a clinical case of a combined course of typhoid fever and leptospirosis in a patient who returned from a tourist trip to India.

DESCRIPTION OF THE CASE

Anamnesis

Patient A (29 years old) was admitted to the infectious diseases department on January 29 with complaints of an increase in body temperature to 39.5°C, chills, weakness, dizziness, and loose stools. From anamnesis, she was in India from January 5 to January 12. She considered herself sick on January 10 when she experienced feeling hot, weakness, general malaise, and pain in the epigastric region, and she had a single mushy stool without pathological admixtures. She did not seek medical help. She took polymethylsiloxane polyhydrate without any effect. In the following days, weakness increased and mushy stools persisted 1–2 times a day without mucus or blood. She did not measure her body temperature.

On January 12, she returned to Moscow, and her physical state remained the same. On January 15, she started having a dry cough, and her body temperature increased to 37.3°C. The patient went to the local polyclinic at her place of residence, where she was diagnosed with acute respiratory viral infection. Symptomatic treatment was prescribed; however, the patient's condition did not improve, and she still had mushy stool without admixtures 1–2 times a day and subfebrile body temperature. On January 18, her body temperature increased to 38°C; however, she still had increased weakness, nausea, and a mushy stool that persisted up to 3–4 times a day. She did not seek medical help. On January 23, her condition worsened: feeling of chills, fever, a body temperature of 39.5°C, repeated vomiting >10 times, multiple liquid stools without admixtures, and episodes of clouding of consciousness. On January 24, the patient was examined by a district doctor, and she was diagnosed with an intestinal infection of uncertain etiology. She was prescribed with nifuroxazide, *Enterococcus faecium* ENCfa-68 and *Bifidobacterium longum* BB-46, and polymethylsiloxane polyhydrate, without a positive effect: her body temperature remained at approximately 39°C; weakness, nausea, and abdominal pain persisted, and stool became more abundant. Because her health deteriorated on January 29, the patient was hospitalized by an ambulance team in the Infectious Diseases Hospital No. 2 in Moscow with a directional diagnosis of gastroenteritis of unspecified etiology.

The epidemiological history revealed that the patient was in India (Delhi, Agra) from January 5 to 12. She lived in a hotel, ate in public catering places (fresh fruits, smoothies, and cocktails), and drank bottled water. She denied insect bites and contact with patients having infections. Anamnesis revealed acute respiratory viral infections and whooping cough. She had allergy to cat hairs. The patient denied the presence of chronic somatic pathology.

Upon admission on January 29 (day 18 of the disease), the condition was of moderate severity. Complaints included increased body temperature up to 40°C, weakness, and loose stools. The skin was pale, and single roseolous elements

were observed on the anterior surface of the abdominal wall. She had dry lips, normal color of the sclera, hyperemic oropharyngeal mucosa, and absence of no raids. The lymph nodes were not enlarged. In the lung examination, breathing was bilaterally normal, wheezing was absent, and the respiratory movement was 22 per minute. The heart tones were rhythmics, the heart rate was 88 beats/min, and the blood pressure was 100/65 mmHg. The tongue was dry and thickly overlaid with a white coating. The stomach was painful and rumbling along the course of the intestine. Ascites was not observed. The liver protruded from under the costal edge by 1 cm. The spleen was not enlarged. The stool was liquid without admixtures up to 5 times per day. Urine (from the words of the patient) was dark. Focal and meningeal neurological symptoms were not detected.

Taking into account the gradual increase in body temperature, duration of fever, pronounced symptoms of intoxication, diarrheal syndrome, skin pallor, roseolous elements of a rash on the anterior surface of the abdominal wall, moderate bloating, relative bradycardia, liver enlargement, rumbling in the ileocecal region, and staying in an area endemic to typhoid fever, typhoid-paratyphoid disease was suspected.

Diagnostic assessment

A comprehensive laboratory and instrumental examination was conducted. In a clinical blood test, leukocytosis of 10.9×10^9/L with a left shift and lymphopenia (lymphocytes, 10%) were noted. Biochemical analysis of blood revealed a slight increase in aminotransferases (alanine aminotransferase [ALT], 74.6 U/L [N, 10–45 U/L]), aspartate aminotransferase (AST, 75.2 U/L [N 10–45 U/L]), and the levels of urea and creatinine remained within the reference values (urea, 4.7 mmol/L [N 1.7–8.3]; creatinine, 75 mmol/L [N 62–98]). Markers of viral hepatitis were negative.

General urinalysis: proteinuria (protein, 1.21 g/L [N 0.00–0.14 g/L), leukocytes 10–12 in the field of vision (N 0–5), and erythrocytes 5–7 in the field of vision (N 0–2). Urine analysis according to Nechiporenko revealed leukocytes of 25000 (N 2000) and erythrocytes of 7000 (N 1000), and the cylinders loosely covered all fields of vision (N 20). Chest X-ray imaging showed enhancement of the pulmonary pattern. During ultrasound examination of the abdominal organs, an increase in mesenteric lymph nodes was noted.

In the fecal analysis by polymerase chain reaction (PCR) of the intestinal group of microorganisms, DNA of *Salmonella* spp. and RNA of *Astrovirus* were detected in the coprological study of *Blastocystis hominis*. Microbiological fecal culture of an intestinal group of microorganisms detected *Salmonella typhi* gr. D. Microbiological blood culture in bile broth detected Salmonella typhi gr. D.

The diagnosis

Because of the obtained laboratory data, the following clinical diagnosis was made:

1. Typhoid fever, moderate severity.
2. Astrovirus gastroenteritis, moderate severity.
   Background diagnosis: Blastocystosis, intestinal form.
   Concomitant diagnosis: Urinary tract infection, unspecified.

Interventions

The patient was prescribed the following treatment: parenteral ciprofloxacin 800 mg/day, metronidazole 1.5/day, and ceftriaxone 4 g/day; infusion detoxification therapy.

Despite the treatment given, on February 3 (day 23 of the disease), the patient's condition worsened. During the examination, the skin was pale, petechial rash elements appeared on the neck and chest, and the sclera was icteric. The patient had difficulty breathing, single wheezes were heard on the right, the respiratory rate was 22–24/min, and the SpO_2 was 90%. The heart tones were rhythmic, the pulse was 83 beats/minute, and the body temperature was 38°C. The blood pressure was 85/55 mmHg. The tongue was dry and overlaid with a whitish coating in the center. The abdomen was soft, slightly swollen, and painless. Intestinal peristalsis was heard during auscultation. During palpation, the liver protruded 4.0 cm from under the edge of the costal arch. The patient had a single, watery stool without pathological admixtures. Urination was painless. Diuresis was reduced. No focal or meningeal symptoms were noted. In laboratory blood parameters from February 3 (day 23 of illness), significant changes were detected: in the clinical blood test, the erythrocyte count decreased to 3.43×10^{12}/L (N 3.9–5.6×10^{12}/L), hemoglobin to 105 g/L (N 120–160 g/L), leukocytes to 3.4×10^9/L (N 4.0–10.0×10^9/L), and platelets to 23×10^9/L (N 150–50×10^9/L). In the biochemical blood analysis, total protein significantly decreased to 47.8 g/L (N 65–85 g/L) and albumin to 21.4 g/L (N 35–50%), total bilirubin increased to 24.9 mmol/L (N 8–20.5 mmol/L), increased ALT (104.6 U/L; (N 10–45 U/L) and AST (187 U/L; N 10–45 U/L), alkaline phosphatase (811 U/L; N 40–150 U/L), increased urea and creatinine (12.3 and 125.5 mmol/L; N 3.2–8.2 and 53–115 mmol/L, respectively). In the coagulogram, the prothrombin index decreased to 60% (N 80–100%), and the activated partial thromboplastin time was prolonged to 38 s (N 24–35 s). Ultrasound investigation of the abdominal cavity revealed negative dynamics: increased and diffuse changes in the liver and spleen parenchyma and moderate diffuse changes in the kidney parenchyma. Mesenteric lymph nodes were enlarged. A small amount of free fluid was detected in the abdominal cavity. Chest X-ray imaging revealed bilateral bronchopneumonia and hydrothorax.

Taking into account the presence of intoxication, febrile fever, hepatosplenomegaly, thrombohemorrhagic syndrome, decreased diuresis, changes in laboratory blood and urine tests, ultrasound data of the abdominal cavity and kidneys, and epidemiological history, an examination for leptospirosis was conducted. Blood tests for leptospirosis by micro-agglutination reaction (MAT) and enzyme immunoassay

(ELISA) were positive. Antibacterial therapy was drastically changed: meropenem 3 g/day and vancomycin 2 g/day parenterally.

The patient was further monitored in the intensive care unit, where etiotropic treatment was continued (vancomycin 2 g/day, meropenem 6 g/day, clarithromycin 1 g/day); detoxification, hepatoprotection, and hemostatic therapies were enhanced, disseminated intravascular coagulation syndrome and hypoproteinemia were corrected (albumin 25% 50 mL/day for 5 days and transfusion of fresh frozen plasma 600 mL/day for 3 days). Because of the persistent intoxication syndrome and progressive immunosuppression, immune therapy was added (human normal immunoglobulin 50 mL/day for 3 days intravenously), and extracorporeal detoxification methods were employed.

Given these treatments, a significant positive dynamic was observed. On February 9, the patient was transferred to the boxed infectious disease department.

During the control blood tests, hemogram parameters and biochemical analysis results were normal. No focal or infiltrative shadows over both pulmonary fields were noted on chest X-ray imaging. The pulmonary pattern was enhanced. During repeated stool examination, *Blastocystis hominis* was not detected. The results of a three-time microbiological examination of feces and urine for typhoid–paratyphoid diseases were negative.

On February 20 (day 40 of the disease), the patient was discharged in a satisfactory condition under the supervision of an infectious disease specialist to a polyclinic at the place of residence with a final clinical diagnosis:

Main diagnosis:

1. Typhoid fever, severe course.
2. Leptospirosis, icteric form, severe course.

Complication of the underlying disease: Bilateral pneumonia of unspecified etiology and multiple-organ dysfunction syndrome.

Concomitant diagnosis: Intestinal blastocystosis and Astrovirus gastroenteritis and convalescence.

DISCUSSION

The presented clinical case draws attention to the problem of imported coinfections that can remain unrecognized for a long time, leading to severe disease and death. The urgency of the problem of imported infections is associated with a significant increase in the popularity of tourist holidays in tropical and subtropical countries.

Given that the sporadic incidence of typhoid fever in Russia, doctors have shown decreasing attention to it, and the wrong prescription of antibiotics and poor adherence to the regimen mask the typical clinical picture of the disease, which makes its recognition at the early stages difficult. In these situations, patients stay at home, as in the present case, and are treated on an outpatient basis with erroneous diagnoses of "acute respiratory viral infection" or "intestinal infection of unclear etiology," without receiving adequate etiotropic therapy.

At present, a change in the classical clinical picture of typhoid fever has been noted. The onset with acute gastroenteritis or enteritis with moderate general intoxication, followed by the appearance of characteristic clinical symptoms of the disease, is possible [10].

In the presented clinical case, the onset of typhoid fever was characterized by manifestations of enteritis, subfebrility, and mild symptoms of intoxication, which could be a manifestation of not only typhoid fever but also intestinal infections of a different etiology. The combination of nosologies is associated with a common fecal–oral transmission mechanism. The probability of developing such an invasion increases significantly among people traveling to tropical countries; therefore, such patients must be further examined to exclude parasitic and viral intestinal infections, as we observed in the patient. Because of a comprehensive examination, the patient was diagnosed with astrovirus infection and intestinal blastocystosis.

It was difficult to suspect leptospirosis in the presence of clinical typhoid. High fever, severe intoxication syndrome, and liver and spleen enlargement are common symptoms characteristic of both diseases. However, the development of jaundice and hemorrhagic syndromes and oliguria are reasons to assume the possibility of typhoid fever combined with another disease (Table 1).

Epidemiological history data (stay in a tropical region endemic to typhoid fever and leptospirosis), changes in the clinical picture of the disease, and laboratory parameters (increase in thrombocytopenia, cytolysis, urea, and creatinine levels) became the basis for the appointment of an additional examination to exclude leptospirosis. According to clinical recommendations, a blood test for leptospirosis was performed using MAT and ELISA, which confirmed this infection.

Pathological inflammatory changes in the lungs have been described in the scientific literature, both in typhoid fever and leptospirosis. In the presented clinical case, the etiology of bilateral pneumonia could not be clarified because bronchoscopy, bronchoalveolar lavage examination, and sputum examination were not performed. From our point of view, this complication may be associated with the addition of a secondary bacterial infection in the presence of a severe course of a combined infectious disease. In the presented clinical case, the change in antibacterial therapy and correction of pathogenetic and symptomatic treatment contributed to a favorable disease outcome. The patient was discharged in a satisfactory condition under the supervision of a polyclinic doctor at the hospital. An untimely late appointment for etiotropic therapy for leptospirosis can increase mortality up to 50% [11].

Thus, the detailed analysis of the clinical and laboratory picture of the disease and anamnestic and epidemiological

Table 1. Laboratory parameters of the patient during inpatient treatment

Indicators	Date						
	January 29	February 3	February 5	February 7	February 8	February 12	February 20
Hemoglobin (120–160 g/L)	132	105	103	93	98	97	96
Red blood cells (3.9–5.6×10^{12}/L)	4.33	3.43	3.34	3.12	3.28	3.12	3.04
Trombocytes (150–50×10^{9}/L)	163	23	19	40	58	220	257
Leukocytes (4.0–10.0×10^{9}/L)	10.9	3.4	4.3	7.9	4.4	4.4	4.9
• Band neutrophils (1–6%)	40	–	–	–	16	4	–
• Segmented neutrophils (45–72%)	45	–	–	–	73	–	–
• Lymphocytes (21–45%)	10	14	27.4	–	10	23	–
• Monocytes (3–9%)	4	25.4	23.0	1	1	19	54
Total protein (65–85 g/L)	61.3	47.8	48.3	56.7	60.9	62.6	73.5
Albumin (35–50%)	–	–	21.4	–	21.2	–	–
Urea 3.2–8.2 mmol/L	4.7	12.3	8.5	3.9	4.5	1.6	3.9
Creatinine (53–115 mmol/L)	75	125.5	114	45.1	46.6	76	67
Total bilirubin (8–20.5 mmol/L)	6.4	24.9	38.1	16.4	12.8	8.4	10
Alanine aminotransferase (10–45 U/L)	74.6	104.6	97.8	84.4	84.4	55	30
Aspartate aminotransferase (10–45 U/L)	75.2	226.1	187.1	145.6	146.8	47	30
Alkaline phosphatase (40–150 U/L)	66	–	811.2	647	571	–	198
α-Amylase (28–100 U/L)	45	71.9	56.5	62.7	94	–	119
C-reactive protein (0–5 mg/L)	–	–	69.6	–	14.9	–	–

data made it possible to timely diagnose the combination of typhoid fever and leptospirosis and subsequently correct and prevent the development of irreversible complications. Simultaneous infection of a person with these pathogens can lead to significant damage to the liver, kidneys, lungs, and intestines with the development of multiple organ dysfunction and severe surgical complications (intestinal perforation, intestinal bleeding, and perforation of the gallbladder) [12, 13].

The clinical manifestation of blastocystosis and the severity of its course largely depend on the state of the patient's digestive and immune system. The detection of blastocysts in immunocompromised patients may indicate deep dysbiotic changes in the gastrointestinal tract, which was considered for treating the patient [14].

CONCLUSION

The presented clinical case illustrates the complexity of diagnosing and managing patients with combined infectious diseases. An in-depth analysis of clinical and epidemiological data, considering the results of laboratory and instrumental examinations, allows for the timely diagnosis of the disease, prescribing the correct etiotropic treatment, and preventing the development of possible complications. Examination of patients with symptoms of acute gastroenteritis should include a complex of various laboratory methods, such as polymerase chain reaction, coprovoscopy, and bacteriological and serological studies.

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AUTHORS' INFO

*** Tatiana V. Kharlamova**, MD, Cand. Sci. (Med.);
address: 6 Miklukho-Maklay street, 117198 Moscow, Russia;
ORCID: 0000-0003-4261-3000;
eLibrary SPIN: 2102-1234;
e-mail: kharlamova_tv@pfur.ru

Irina V. Barysheva, MD;
ORCID: 0000-0002-3543-9086;
eLibrary SPIN: 7381-8660;
e-mail: barysheva-iv@pfur.ru

Nadezhda A. Polovinkina, MD, Cand. Sci. (Med.), Associate Professor;
ORCID: 0000-0003-3183-852X;
eLibrary SPIN: 1377-8985;
e-mail: polovinkina-na@pfur.ru

Elena Yu. Burdova, MD;
ORCID: 0000-0003-0521-4502;
eLibrary SPIN: 8451-5845;
e-mail: burdova_eyu@pfur.ru

Mariya V. Bogdanova, MD;
ORCID: 0009-0000-7421-6398;
e-mail: Maria.v.bogdanova@gmail.com

ОБ АВТОРАХ

*** Харламова Татьяна Владимировна**, к.м.н.;
адрес: Россия, 117198, Москва, ул. Миклухо-Маклая, д. 6;
ORCID: 0000-0003-4261-3000;
eLibrary SPIN: 2102-1234;
e-mail: kharlamova_tv@pfur.ru

Барышева Ирина Владимировна;
ORCID: 0000-0002-3543-9086;
eLibrary SPIN: 7381-8660;
e-mail: barysheva-iv@pfur.ru

Половинкина Надежда Александровна, к.м.н., доцент;
ORCID: 0000-0003-3183-852X;
eLibrary SPIN: 1377-8985;
e-mail: polovinkina-na@pfur.ru

Бурдова Елена Юрьевна;
ORCID: 0000-0003-0521-4502;
eLibrary SPIN: 8451-5845;
e-mail: burdova_eyu@pfur.ru

Богданова Мария Владимировна;
ORCID: 0009-0000-7421-6398;
e-mail: Maria.v.bogdanova@gmail.com

* Corresponding author / Автор, ответственный за переписку