Summary

Introduction. The work highlights the problematic issues of diagnosis and treatment of toxocariasis infection in people in Ukraine, which become even more acute and urgent due to the migration of the population and animals, and the destruction of the country’s infrastructure as a result of the war unleashed by Russia.

The aim of the study. Improvement of aspects of clinical, laboratory and instrumental diagnostics, as well as treatment of VML in humans

Materials and methods. A literature research of the state of the problem of primary and differential diagnosis of the migrating larva in Ukraine and the world has been conducted. 2 clinical cases of diagnosis and treatment of migrating larva in are described.

Results. The article describes two clinical cases of visceral migrating larva. The differences of these cases, in addition to the migrating formations in the lungs, were the asymptomatic course, the absence of eosinophilia, and the simultaneous determination of blood class G antibodies by ELISA to Toxocar and human roundworm (A. lumbricoide), which persisted even after treatment. Patients at the stage of diagnosis were examined in an oncology hospital, were consulted by thoracic surgeons and oncologists to exclude lung cancer. Both women were immunocompetent, one patient had a history of cervical cancer. From the epidemiological anamnesis, both women kept cats, and one of them, during chemotherapy for the treatment of a tumor, had a propensity for carnivorous raw-eating. Before prescribing systemic antiparasitic chemotherapy, the patients were examined by an ophthalmologist to exclude parasitic chorioretinitis. The patients were prescribed a 20-day course of albendazal 800 mg/day in two doses. Support therapy consisted of a 5-day course of prednisolone at a dose of 30 mg/day orally in two doses, which started one day before the appointment of albendazole. A control CT scan of the lungs after therapy did not reveal any formations, fibrosis, or calcifications.

Discussion. This case proves that tocoscarosis in humans is a multidisciplinary medical and social problem. Conclusions were made on the need to restore the national registration of the disease, adopt national consensuses on treatment and diagnosis, and implement into clinical practice modern methods of verification of specific antibodies to nematodes based on immunoblotting.

Conclusions. The registration of cases of VML and T. in the system of control and prevention of infectious diseases in Ukraine should be resumed. It is expedient to introduce specific studies on nematodes in clinical laboratory practice.

Key words: toxocariasis in humans, clinic, serological diagnosis, instrumental diagnosis, differential diagnosis in oncology, therapy

INTRODUCTION

The war waged by the Moscow Empire on the territory of Ukraine led to the catastrophic destruction of the biogeocenosis of the country, a large migration of people and animals, which is a potential threat of an increase in the number of cases and geographical spread of anthropozoon infections, primarily parasitic diseases [2, 3, 4]. One of these diseases is VML, which is associated with infection with geohelminths from the group of animal roundworms —
toxocaris (T) and beilisascaris (B). In Ukraine, first of all, this concerns T., which is associated with an increase in the number of homeless dogs and cats, with the lack of measures to deivnaze their excrement, which in turn leads to the spread of the pathogen T. circulation, both among animals and eggs on the soil in settlements and cities. Considering that VML has a polymorphic clinical picture and doctors of various specialties are involved in the process of diagnosis and treatment (radiation diagnostics, oncologists, infectious disease specialists, ophthalmologists, general family practice doctors, pediatricians, etc), in our opinion, the presentation of cases of this disease has scientific and practical value.

THE AIM: Improvement of aspects of clinical, laboratory and instrumental diagnostics, as well as treatment of VML in humans.

MATERIALS AND METHODS

A literature research of the state of the problem of primary and differential diagnosis of the migrating larva in Ukraine and the world was conducted. 2 clinical cases of diagnosis and treatment of migrating larva are described.

The «visceral migrating larva» syndrome (VML) occurs as a result of human ingestion of eggs of Toxocara canis (dog roundworm), Toxocara cati (cat roundworm), or Baylisascaris procyonis (raccoon roundworm), which belong to the group of animal nematodes (roundworms) [1].

CLINICAL CASE #1

Woman B-a Zhanna, 55 years old, ethnic Ukrainian, resident of the city of Kamianske, Dnipropetrovsk region, Ukraine, applied for a consultation at the regional center of thoracic surgery in the city of Dnipro on the referral of a family doctor. There are no health complaints.

Social status. The woman is socially adapted (she has a stable job and income), without chronic somatic and socially determined diseases. The patient is immunocompetent, HIV-negative, which was confirmed in the laboratory by the absence of specific antibodies.

According to the epidemiological history, the woman did not leave Ukraine during the years 2022-23. He keeps a cat at home, the laboratory examination of the animal for toxocariasis infection was not carried out. He works in a trade business that does not concern the spheres of animal husbandry, contact with the soil and the sale of raw meat.

According to the medical history: on March 14, 2023, during a preventive examination at the request of the employer, according to the results of X-ray examinations of the lungs, a coliform formation (solid nodule) was found in the right lung. The patient recalled that she suffered from myalgia for almost the entire year last year (since the spring of 2022), to overcome which she attended therapeutic massage.

On March 16, 2023, she was examined by a family doctor: there are no complaints, the general condition is satisfactory. Conclusion: Lung neoplasm.

03.17.23 consultation of a thoracic surgeon: no complaints, general condition satisfactory. Conclusion: Neoplasm of the right lung? Observation and repeated radiological examination of the lungs are recommended.

On May 3, 2023, a computer tomogram was performed (160 slice CT-scanner with intravenous contrast Tomogeksol) with contrast of the brain – without pathology; as well as a CT scan with contrast of the lungs (160 slice CT-scanner with intravenous contrast Tomogeksol) (Pic.1, 2). According to the results of the CT, the migration of formations from the upper part of the organ to the lower part of the right lung was determined (Pics. 1-3). Conclusion: Parasitic infection? Upon inspection: There are no complaints, the general condition is satisfactory.

05.09.23 examination by an infectious disease specialist. There are no complaints. The general condition is satisfactory. Conclusion: Migrant larva of the lungs, pulmonitis. Suspected case of toxocarose. A serological examination for the presence of specific antibodies to toxocariasis and human ascaris by the ELISA method, a general blood test, a coprocytogram and an ophthalmologist’s examination were prescribed.

05.09.23 Examination by an ophthalmologist: no pathology of the organs of vision and no chorioretinitis. The general condition is satisfactory, there are no complaints.

05.13.23 years old. After receiving the results of a serological examination, which revealed total antibodies to toxocariasis and human ascaris, anti-inflammatory and specific therapy was started. The treatment was carried out on an outpatient basis, communication with the patient was maintained throughout the duration of systemic anti-parasitic chemotherapy.

06.02.23 Albendazole was finished. Complaints of moderate pain in the stomach due to taking albendazole. The general condition is satisfactory.

June 7, 2023. CT with lung contrast: no formations. The general condition is satisfactory. There are no complaints. Conclusion: Healthy (Pic. 4).

CLINICAL CASE #2

A woman T-o Inna, 48 years old, ethnic Ukrainian, resident of the city of Kamianske, Dnipropetrovsk region, Ukraine, applied for a consultation at the regional center of thoracic surgery in the city of Dnipro on the referral of an oncologist-gynecologist in connection with a tumor found in the lungs according to the results of a CT scan. At the start of investigation woman had complaints for swelling of both lower limbs due to lymphostasis that occurred after treatment of uterine cancer.
Social status. The woman is socially adapted (she has a stable job and income). In 2020, the uterus was extirpated due to cervical cancer. She received chemotherapy. The patient is immunocompetent, HIV-negative, which was confirmed in the laboratory by the absence of specific antibodies.

According to the epidemiological anamnesis: a woman keeps a dog and a cat at home which move freely outside the house. According to culinary preferences, the patient likes to eat fresh raw meat, liver and fish, especially this increased during tumor chemotherapy. She works in the field of management, which does not concern the fields of animal husbandry, contact with the soil and the sale of raw meat.

From the anamnesis of the disease: during the next examination by the CT method from 04.13.23, several formations were found in the liver, lungs and an enlargement in the subclavian lymph node, which was considered as metastases. During a repeat CT scan on May 12, 2023, changes are described that are more typical of an inflammatory process, but «migration of formations» to other segments of the lungs was noted, and formations in the liver were not confirmed by MRI with contrast. Due to it, an examination by an infectious disease specialist was scheduled.

Examination by an infectious disease specialist on June 24, 2023: a serological blood test was performed for the presence of total antibodies by the ELISA method to toxocariasis and roundworms, the results of which determined specific immunoglobulins to both helminths. Conclusion: Migrating larva. Toxocarosis. After an ophthalmologist’s examination of the fundus on 06.25.23, as a result of which no signs of damage to the eye were detected, anti-inflammatory therapy with prednisolone 30 mg/day was started, and the next day, a. 400 mg twice a day. The course has lasted 20 days. The treatment was carried out on an outpatient basis, communication with the patient was maintained during all course of systemic anti-parasitic chemotherapy.

**DISCUSSION**

As defined, VML occurs as a result of infection with T. or B., and the list of etiology of this syndrome does not include other nematodes, for example, ascariasis, hookworm (cutaneous form of the migrating larva syndrome), strongyloidosis, trichinellois, etc. [1]. This is fundamentally important, in our case, because it limits the range of potential pathogens that can cause VML in our patients. The last systematic epidemiological studies of the spread of T. in Ukraine among adults and animals were conducted by Ihor Bodnya (2019) in the territory of the Kharkiv region, bordering the Dnipropetrovsk region, where both our patients are from [5]. According to the data of the «Ukrainian Center for Disease Control and Monitoring of the Ministry of Health of Ukraine», referred to by the author of the work, the average rate of soil contamination with geohelminth eggs in Ukraine as a whole was 2.7 %, and in the Dnipropetrovsk region this rate was higher – 3.1 %. Yes, according to the researcher’s personal data, the blood examination for the presence of specific antibodies using the ELISA method showed that 43.5±4.2 % of people had immunoglobulins to T in their blood serum [5]. But according to Christina Strube et al. (2020), who performed a meta-analysis of European scientific publications devoted to T., the number of seropositive (the presence of specific antibodies to T.) persons in the general population of other European countries was several times smaller and amounted to 6.2 % (95 % CI: 4.7-8.3 %) [6]. Commenting on such a large difference in the levels of herd immunity, it should be noted the shortcomings that were in the Ukrainian study, first of all, it is limited (n=321) and «selectivity» — testing was performed in patients who had clinical signs of systemic non-specific diseases, as well as clinically healthy ones persons keeping domestic animals. But the authors of the European review themselves emphasize that people over 50 years old and professional groups in contact with soil and animals have a T. infection level higher than the European average [6]. Also there are data that the average seroprevalence rate of human toxocariasis from 19 published studies was 27.9 % and ranged from 1.4 % to 92.4 % [7, 8, 9]. There is no data on the prevalence of raccoon roundworm (B. procyonis) in Ukraine, but according to the CDC, about 25 cases of Baylisascaris among humans have been documented in the United States [10, 11]. Thus, from the point of view of the distribution of nematodes in animals, VML syndrome does not belong to «orphan diseases» and the probability of human infection, especially in Ukraine, with these geohelminths is very likely. However, it should be noted that according to the data of the Public Health Center of the Ministry of Health of Ukraine, no cases of T. or VML were registered for the period from June 2022 to June 2023 [12]. VML syndrome is a systemic pathology, in connection with which the semiotics of the disease is quite diverse — from asymptomatic forms to brain damage in the form of encephalitis with a fatal outcome, which is due to the peculiarities of the pathogenesis, where the main factors are the mechanical impact of the larva: the type of pathogen, the target organ (lungs, brain, eyes, liver), the number of larvae in the body, and the immune reaction of the immune system to the parasite, which is genetically determined [1]. Considering that the vast majority of people who are infected with T. do not have any symptoms (this is something unusual that a person feels) [13, 14, 15], the VML syndrome in our patients was caused by one of two types of T., because upon infection V. is expected to have a more severe course of the disease [11, 16, 17]. In our opinion, the main condition for the emergence of clinical manifestations in case of infection with T. is the number of larvae in the human body, so in our observations according to CT lung data, there was a single formation, that is, one larva in the lungs of female patients. The pathognomonic sign of the VML syndrome...
is «a neoplasm that can change [migrate] location in the target organ over time», which is determined exclusively by dynamic instrumental examination by radiological methods (X-ray, ultrasound, CT or MRI). In addition, VML is diagnosed based on the results of a biopsy of the formations, which is quite often an extremely complicated intervention. In our cases, VML was also discovered by chance according to the results of radiological diagnostics, which was carried out as a preventive examination. In connection with this, the first to make a responsible decision to treat/not to treat a neoplasm that has been diagnosed are an oncologist and a radiologist. Taking into account the small size of the neoplasm, the absence of signs of systemic and local inflammation, as well as the satisfactory clinical condition of the patient, the oncologist and radiologist made a decision to refrain from interventions, and to conduct a repeat radiological examination after a few months, which made it possible to determine the translocation of the tumor, thus ruling it out lung neoplasia. It should be emphasized that the larva of T. does not always migrate, and still often appears in the form of nodes, which do not change their location in the organ. [18]. In our cases, we observed the movement of formations in the lungs, which became possible due to the fact that the repeated CT scan was done with a relatively long interval of at least a month from the previous examination (Pic. 1-4).

Fig. 1. CT-scan picture of the clinical case at the moment of diagnostics.
In the upper lobe of the right lung, paravasally (S3\S2, mostly S2), there is a partially solid nodule with total dimensions of up to 31x30mm / the size of the solid component is 10x5mm, the contours are clear, spicule-like.

Fig. 2. CT-scan picture of the clinical case after 6 weeks of follow-up.
In S6 and S10 of the lower lobe of the right lung (formerly in the upper lobe), there are partially solid nodules with total dimensions of up to 16.5x13.5mm and 18.5x16.5mm, respectively, are determined, solid components are centrally located up to 5-6mm in d, contours are unclear. Conclusion: CT signs of partially solid migrating nodules of the right lung (previously in the upper lobe \ in the current study - in the lower lobe of the lung), in comparison with CT data from 03.17.2023. - dynamics in the form of migration and greater spread of structural changes in the lungs - differentiate eosinophilic pneumonia \ atypical lesion (parasitic?).
The main diagnosis for the differential diagnosis of lung neoplasms is lung cancer. As is well known, morphological diagnosis is the basis of establishing an oncological diagnosis. However, in some clinical situations, observation tactics or differential diagnosis with infectious diseases may be chosen. First, according to international guidelines, lung neoplasms up to 8 mm in size can be observed, with a repeat CT scan after 3 months to assess clinical dynamics (Fig. 1-4). Secondly, there is a correlation with clinical data. Patients with suspected pulmonary tuberculosis, for example, have characteristic clinical manifestations of the disease (intoxication syndrome, medical history, etc.). Malignant neoplasms are characterized by the growth of foci over time, as well as the appearance of new ones. The disappearance, or partial regression, of foci may indicate the non-malignant nature of the neoplasm, and, for example, an infectious or helminthic process [26, 27, 28].

To verify the etiology of the parasitic infection, taking into account the epidemiological history, clinical condition, laboratory data and CT lung results, in addition to T., an examination for human ascaris (A. lumbricoide) was also included, despite the absence of hypereosinophilia in the blood. In the conditions of war-limited resources, laboratory diagnostics was based on the detection of specific antibodies to parasite antigens by the ELISA method, and direct microscopy of stools for the presence of helminth eggs. We considered the determination of specific antibodies to T. and A. lumbricoide at the same time, and the patient’s serological studies were conducted in different commercial laboratories, as false positive results. The possibility of cross-immune reactions between T. and A. lumbricoide and other nematodes is reported by all manufacturers of test systems for serological diagnosis of these helminthic infestations [19]. In connection with this, a question arose before us, which has remained unsolved — in relation to which of the helminths the antibody results are incorrect, or the results are generally incorrect and antibodies to these parasites are completely absent. Considering the life cycle of A. lumbricoide, where the «migratory phase»
is two weeks, while the formations lasted much longer in our patients, it is possible to rule out current human ascariis infection with confidence. In addition, it should be added that an adult female is able to lay her first egg 60 days after infection, but direct microscopy of feces did not reveal any parasite eggs in our patients. The lifespan of an adult A. lumbricoides in human bodies can reach two years [20]. Regarding the validity of the results of serological tests for T., resources are even more limited because, for this pathogen, a person is a «paratenic host» — an intermediate one, where the complete life cycle of the parasite does not take place (it does not delay or accelerate its development) [21]. In connection with this, T. does not release eggs from the human body into the external environment, there is no parasitaemia, and the determination of the current infection is possible, exclusively, through the intervention of the lungs for the purpose of biopsy, which was not possible (technically, dangerous, etc.) in our cases. Solving the problem of the validity of serological tests for helminthiasis is possible exclusively through the use of confirmatory methods, which are based on the determination of antibodies to specific antigens based on immunoblotting, which, unfortunately, are currently unavailable in Ukraine [22, 23]. In addition, the use of serological tests in clinical practice to determine the avidity index of IgG to T. may allow distinguishing current infection (low index) from past infection (high avidity index). The presence of a migrating formation in the lungs and the determination of antibodies to T. allowed us to formulate a clinical diagnosis of VML, which substantiated the strategy of therapy. It should be noted that there are several aspects to the problem of VML therapy associated with T. First, it is an indication for the appointment of systemic antiparasitic chemotherapy, where in the arsenal of drugs. The drug of first choice is albendazole (A). According to all recommendations, patients, adults and children with VML, should receive systemic antiparasitic chemotherapy (SAC) A. [1, 24], which was prescribed in our cases. It should be emphasized that before appointing A., it is necessary to conduct an examination by an ophthalmologist to rule out damage to T.’s eye (granulomatous chorioretinitis). Damage to the eye of T. carries great risks of increased inflammation of the retina due to the destruction of A. the larva. The second aspect of VML therapy is the duration and purpose of therapy, and the criteria for recovery. In our patients, except for formations in the lungs, which then disappeared without the formation of calcifications or sclerotic consequences, there was nothing. Serological studies demonstrated the presence of specific antibodies even after treatment, which was expected, and therefore cannot serve as the goal of therapy. It is interesting that one of the main arguments in the appointment of A.’s three-week therapy was the desire of the patients themselves to accept the longest possible course of treatment, which they learned about during self-education on T.’s issues. This example is a vivid fact of the loss of the «sacredness of medical professional competence» in modern civilization. And the last aspect in the discussion of VML therapy is the use of adjuvant drugs — glucocorticosteroids (GCs). The use of targeted systemic chemotherapy has a potential risk of causing a systemic inflammatory response syndrome due to the destruction of the larva T., this fact is of particular importance during the treatment of ophthalmotoxocarosis, where the appointment of GCs is a mandatory component of therapy [25]. Taking into account the non-trivial nature of the results of serological studies, which did not allow us to be completely sure of the etiology of VML, it was decided to use GCs — prednisone at a dose of 30 mg/day in one dose after meals for a course of 5 days. Moreover, the intake of GCS started a day earlier for targeted therapy and continued together for another four days. One of the patients required proton pump inhibitors for the entire duration of adjuvant and systemic antiparasitic chemotherapy due to the occurrence of iatrogenic gastropathy. Thanks to the diagnosis of VML with the help of a dynamic examination of the lungs by the CT method, their qualified interpretation and serological verification of T. infection, it was possible to prevent interventional diagnostics and aggressive treatment, and to prescribe a rational systemic antiparasitic chemotherapy, which led to the recovery of the patient.

CONCLUSIONS

1. The registration of cases of VML and T. in the system of control and prevention of infectious diseases in Ukraine should be resumed.

2. It is expedient to introduce into clinical laboratory practice serological studies on B. procyonis, as well as confirmatory tests for the validation of specific antibodies to nematodes (T. canis, T. cati and A. lumbricoide) based on the immunoblotting method.

3. It is necessary to develop a national consensus (clinical protocol) on the topic of VML, which will allow to unify the quality criteria of diagnosis and treatment of this syndrome (disease).

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COMPLIANCE WITH ETHICAL REQUIREMENTS

The ethical approval was obtained from Bioethics Committee of the Dnipro State Medical University. All patients provided written consent to participate in research in accordance with the recommendations of the Ethics Committees for Biomedical Research, Ukrainian Health Legislation and the Declaration of Helsinki of 2000.
CONTRIBUTION OF THE AUTHORS OF THE WORK

Viktor V. Mavrutenkov – the idea of the work, the diagnostic and therapy of patients, writing of the text, searching of the literature.

Anna V. Prochach the idea of the work, work on the English-language text of the article, literature search.

Dmytro G. Shkarupa – counseling the patients.

Olena Н. Kovalchuk – counseling the patients.

LITERATURE


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Резюме

ВІСЦЕРАЛЬНА МІГРУЮЧА ЛИЧИНКА. КЛІНІЧНІ ВИПАДКИ. УКРАЇНСЬКИЙ ТЯГАР
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Вступ. В роботі висвітлюються проблемні питання діагностики та лікування токсокарозної інфекції людей в Україні, які стають ще більш гострими та актуальними за рахунок міграції населення і тварин, та руйнування інфраструктури країни внаслідок війни, яку розв'язала Росія.

Мета дослідження. Удосконалення аспектів клініко-лабораторної та інструментальної діагностики, а також лікування ВМЛ у людей.

Матеріали та методи. Проведено літературний огляд стану проблеми первинної та диференційної діагностики мігруючої личинки в Україні та світі. Описано два клінічних випадки діагностики та лікування мігруючої личинки

Результати. В статті надано опис двох клінічних випадків вісцеральної мігруючої личинки. Відмінностями цих випадків, крім мігруючих утворень в легенях, були: асимтомний перебіг, відсутність еозинофілії та визначення водночас антитіл класу G до токсокар і до аскариди людини (A. lumbricoide) у крові методом ІФА, які зберігались і після лікування. Пацієнтки на етапі діагностики були обстежені в лікарні онкологічного профілю, їм була надана консультація торакальними хірургами та онкологами для виключення раку легенів. Обидві жінки були імунокомпетентними, одна пацієнта в анамнезі мала рак шийки матки. З епідеміологічного анамнезу обидві жінки утримували котів, також одна з них під час хіміотерапії з приводу лікування пухлини мала схильність до м'ясоїдного сироїдіння. Перед призначеним антипаразитарним курсом пацієнтки були обстежені офтальмологом для виключення паразитарного хоріоретиніту. Пацієнкам було призначено 20-ти добовий курс альбендазалу 800 мг/добу в два прийоми. Терапія супроводжувалась виключенням токсокарозу.

Обговорення. Даний випадок доводить, що токсокароз у людини це мультидисциплінарна медико-соціальна проблема. Зроблено висновки в потрібності відновлення національної реєстрації захворювань, прийняття національних консенсусів щодо лікування та діагностики, та втілення в клінічну практику сучасних методів верифікації антитіл до нематод.

Висновки. Необхідно відновити естрадіо дослідів ВМЛ та токсокарозу в системі контролю та профілактики інфекційних захворювань в Україні. Слід продовжити проведення специфічних досліджень в Україні.

Ключові слова: токсокароз у людей, клініка, серологічна діагностика, інструментальна діагностика, диференційна діагностика в онкології, терапія