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ABSTRACT

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CLINICAL CASE OF LYMPHEDEMA AS A COMPLICATION OF CAT SCRATCH DISEASE

Introduction. Cat scratch disease (CSD) is zoonotic infectious disease caused by the bacterium *Bartonella henselae*. Domestic cats, which are infected by fleas are the primary source of this infection. In humans, the disease occurs through contact with an infected animal, as a result of a bite or scratch. Difficulties in diagnosis are associated with the variety of clinical symptoms and lack of doctors' alertness, especially in cases of atypical disease forms. Lymphadenopathy is the basis for differential diagnosis of CSD with neoplastic processes.

The aim of the study: to focus doctors' attention on the possibility of an atypical subclinical course of CSD by analyzing a clinical case of the disease in the patient with lymphedema of the lower extremity.

Materials and methods. The clinical examination results, laboratory and instrumental tests of a 35-year-old woman were analyzed.

Case presentation. A 35-year-old woman consulted her family doctor with complaints of severe swelling of the left lower extremity, which had been bothering her for several months. Edema appeared in perfect health and gradually spread from the foot to the thigh. On examination, the left lower limb is swollen throughout. The diameter of the left lower leg is 4 cm larger than the right one, and the left thigh is 2.5 cm larger than the right one. In the left inguinal region, lymph nodes are visible and palpable, sensitive to palpation - 1.5-2 cm in size, dense, in the right inguinal region - up to 1 cm, not dense and not sensitive to palpation. The family doctor referred the patient to a vascular surgeon. After an ultrasound examination of the veins of the lower extremities, a complete blood count, no pathology of the veins of the lower extremities, and no other disorders were detected. The diagnosis was made: "Lymphedema of the left lower limb of unknown etiology". The patient was referred to the regional oncology center to exclude oncological pathology. Based on the results of MRI and CT of the chest,

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abdominal cavity, and pelvic organs oncological pathology was excluded. Excision of the left inguinal lymph node with histopathological examination was performed, the results of which meet the histological criteria of benign lymphoreticulosis with fibrosis.

When the patient was examined by an infectious diseases specialist, the doctor found out the details of the medical history: in July 2023, a domestic cat bit her foot under the left ankle joint. An enzyme-linked immunosorbent assay of blood for *Bartonella henselae* was prescribed and positive IgM and IgG antibodies were detected. Considering the presence of adenopathy, a cat's bite in the anamnesis, a positive serological test, and the exclusion of other causes, the diagnosis was established: Cat scratch disease, subclinical form. Lymphedema of the left lower limb, stage II-III. In addition to the vascular surgeon's recommendations – compression stockings, lymphatic drainage massage, the patient was prescribed: bicillin-5 (benzathine penicillin with procaine penicillin sterile salt) 1,500,000 units IM once every 4 weeks, for 6 months.

Conclusion. *Bartonella henselae* infection should be considered in all cases of lymphadenitis and lymphedema of unknown etiology for timely diagnosis and antibiotic treatment at the initial stage of the cat scratch disease.

Keywords: bartonellosis, cat scratch disease, benign lymphoreticulosis, lymphedema, oncological search.

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КЛІНІЧНИЙ ВИПАДОК ЛІМФЕДЕМИ ЯК УСКЛАДНЕННЯ ХВОРОБИ КОТЯЧОЇ ПОДРЯПИНИ

Актуальність: Хвороба котячих подряпин (ХКП) – це зоонозне інфекційне захворювання, що викликається бактерією *Bartonella henselae*. Домашні коти, заражені блохами, є першоджерелом цієї інфекції. У людини захворювання виникає при контакті з інфікованою твариною, в результаті укусу або подряпини. Труднощі діагностики пов'язані з різноманітністю клінічних симптомів і недостатньою уважністю лікарів, особливо при атипичних формах захворювання. Лімфаденопатія є основою для диференціальної діагностики ХКП з неопластичними процесами.

Матеріали та методи. Проаналізовано результати клінічного обстеження, лабораторних та інструментальних досліджень жінки 35 років з лімфедемою нижньої кінцівки.

Результати: Жінка 35 років звернулася до сімейного лікаря зі скаргами на сильний набряк лівої нижньої кінцівки, який турбує її протягом кількох місяців. Набряк з'явився при повному здоров'ї і поступово поширився від стопи до стегна. При огляді ліва нижня кінцівка набрякла на всьому протязі. Діаметр лівої гомілки на 4 см більший від правої, а лівого стегна на 2,5 см більший від правого. У паховій ділянці зліва пальпуються лімфатичні вузли, чутливі при пальпації – розміром 1,5–2 см, щільні, в пахвинній ділянці справа – до 1 см, нещільні і нечутливі при пальпації. Сімейний лікар направив хвору до судинного хірурга. Після УЗД вен нижніх кінцівок, загального аналізу крові – патології вен нижніх кінцівок та

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інших порушень не виявлено. Встановлено діагноз: «Лімфедема лівої нижньої кінцівки нез'ясованої етіології». Для виключення онкологічної патології хвору направлено в обласний онкологічний диспансер. За результатами МРТ та КТ органів грудної клітки, черевної порожнини та органів малого таза онкологічну патологію виключено. Проведено висічення пахвинного лімфатичного вузла зліва для патогістологічного дослідження, результати якого відповідають доброякісному лімфоретикульозу з фіброзом.

При зборі анамнезу хвороби лікарю-інфекціоністу вдалося з'ясувати, що у липні 2023 року домашня кішка вкусила пацієнтку за стопу, нижче лівого гомілковоступневого суглоба. Призначено імуноферментний аналіз крові на *Bartonella henselae*, виявлено позитивні антитіла IgM та IgG. Враховуючи наявність аденопатії, укусу кішки в анамнезі, позитивну серологічну реакцію та виключення інших причин, встановлено діагноз: Хвороба котячої подряпини, субклінічна форма. Лімфедема лівої нижньої кінцівки II-III стадії. Крім рекомендацій судинного хірурга – компресійний трикотаж, лімфодренажний масаж, хворому призначено: біцилін-5 (бензатинпеніцилін з прокаїном пеніциліну стерильна сіль) по 1500000 ОД в/м 1 раз на 4 тижні протягом 6 місяців.

Висновки: У всіх випадках лімфаденіту та лімфедми невідомої етіології слід враховувати інфекцію викликану *Bartonella henselae* для своєчасної діагностики та лікування антибіотиками на початковій стадії хвороби.

Ключові слова: бартонельоз, хвороба котячих подряпин, доброякісний лімфоретикульоз, лімфедема, онкологічний пошук.

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INTRODUCTION

Bartonelloses are a group of infectious diseases of humans and animals caused by intracellular bacteria that are mainly transmitted by vector-borne and contact routes. Bartonelloses are characterized by an acute and chronic course, a polymorphic clinical presentation, and the involvement of different organs and systems. Cat scratch disease (CSD, benign lymphoreticulosis, felinosis) caused by *Bartonella henselae* is one of the most common clinical forms of bartonellosis [1]. There are no reliable statistics on the incidence of cat scratch disease in humans. The expected incidence is 10 cases per 100,000 population [2]. Around 13,000 cases are identified each year in the United States, with children under 14 years old representing 32.5% of the total cases, and the highest incidence is seen in those aged 5 to 9 years [3].

Intraerythrocytic parasitism allows bacteria to evade the host's immune system, which causes the infection process to become chronic. Prolonged bacteremia, as well as blood-sucking vectors (ticks, fleas, lice) contribute to the transmission of infection. Humans are

mostly secondary hosts who become infected during contact with the source of the pathogen. The incubation period lasts from 3 to 60 days (more often 2-3 weeks) [4].

Cat scratch disease was first described in 1931, but the etiology remained unknown [1]. The etiological role of *Bartonella henselae* in CSD was first established by Regnery in 1992. A person becomes ill as a result of a bite, scratch, or lick by a cat. It is known that 25% of cat owners have antibodies to the pathogen, which indicates an asymptomatic course of the disease. After the disease, persistent immunity develops, and repeated cases are rare [2].

The disease is seasonal with an increase in incidence in the fall and a peak in October [5]. This pattern is due to the reproductive behavior of cats and the vital activity of fleas. Cases of the disease are often reported in Ukraine, but there are no statistical data on the incidence. Many cases of CSD remain unrecognized, especially if they have an atypical or subclinical course [4]. With the atypical form, patients often seek the help of specialists: ophthalmologist, otolaryngologist, neurologist, cardiologist, pulmonologist, dermatologist,

and others. A carefully obtained epidemiologic history and targeted laboratory tests play a leading role in the diagnosis of the disease. Only 57% of patients report contact with cats, 25% deny any contact, and 18% cannot recall the exact contact [6].

The disease is recognized at the stage of regional lymphadenopathy, which is the main clinical manifestation[4]. However, some patients do not have it despite positive serologic tests. At the peak of the disease, most patients experience fever, headache, and poor appetite. Lymphadenopathy appears much later than changes at the site of primary lesion, and the latter is often absent in the midst of the disease, which also complicates diagnosis [3].

In 85% of patients, one lymph node is affected: cervical or inguinal[7]. Sometimes the process is localized in unusual places – in front of the auricle, under or above the clavicle. The diameter of the affected lymph nodes can reach up to 6 cm. They are slightly mobile, and not painful to palpation. Lymphadenopathy spontaneously regresses within 2–5 months. The lymph nodes are painful, mobile, and of dense consistency. In 20–30% of patients, inflamed lymph nodes become suppurated.

The skin manifestations of CSD at the site of the pathogen's entry gate can be various and often cause misdiagnoses: papules, plaques, hyperkeratotic nodules, scarlet fever-like exanthema.

Sometimes the only manifestation of the disease may be a fever of “unknown origin”. The duration of the fever is usually 4–9 weeks [8].

Atypical manifestations are more common in adults (11–12% of patients): Parinaud's oculoglandular syndrome (conjunctivitis with concomitant palpable periauricular nodes – 50%), neurological manifestations (encephalopathy, seizures, unilateral neuroretinitis with visual loss, radiculitis, myelitis, paraplegia, central arteritis – 2%), hepatolienal granulomatosis – 1% [9].

Infection with regional lymphadenopathy can mimic neoplastic processes such as soft tissue or bone tumors, metastases, or lymphomas, leading to delayed diagnosis. Enlarged lymph nodes with preserved architecture and reactive changes in the surrounding adipose tissue and fascia are differential signs of CSD, which allow to distinguish it from neoplasms of soft tissues [9–11]. In difficult cases, biopsy is one of the most reliable methods for CSD diagnosing. Histological description of the preparation depends on the stage of the disease – lymphoid hyperplasia with the proliferation of arterioles, formation of granulomas with necrosis in the center, surrounded by lymphocytes, histiocytes and neutrophilic infiltrate. It differs from other granulomatosis by the presence of both microabscesses and granulomas [15].

Sonography is the initial imaging modality for the evaluation of superficial soft tissue tumors, and is also used in atypical CSD. It reveals enlarged, hypovascularized lymph nodes at the site of infection with varying degrees of liquefaction [9]. However, ultrasound examinations in 56% of cases do not detect lesions that are diagnosed by CT. At the same time, CT is inferior to MRI due to limited differentiation of soft tissue structures. On MRI in the early stages of the disease, the affected enlarged lymph node has a typical appearance with a thickened capsule and various stages of development of perinodal abscesses with gradual necrosis of the lymph node [10]. These imaging techniques make it possible to exclude other infections and a number of benign and malignant soft tissue tumors, such as peripheral nerve sheath tumors, synovial sarcoma, leiomyosarcoma, and distant metastases [4].

In addition to the clinical presentation, patient history and radiological imaging, histopathology along with PCR and serology are used for diagnosis [12].

Symptoms usually last from 10 to 240 days. The disease usually ends with complete recovery.

Lymphatic edema (lymphedema) is one of the rare consequences, it occurs as a result of impaired lymph outflow through the lymphatic vessels and its stagnation in the tissues, which is accompanied by thickening of the limb and swelling of the skin[13]. As it progresses, ulcers and other signs of trophic lesions appear, and "elephantiasis" develops. Filariasis is the main cause of lymphedema, it affects 120 million people in Asia and Latin America. Among them, 25% of people have edema of the external genitalia, 15% have lymphedema of the lower extremities. In Europe and North America, neoplasm, resulting from the removal of lymph nodes during surgery or radiation therapy is the leading cause of lymphedema [15]. In 90% of cases, lymphedema occurs in the lower extremities as a consequence of oncological diseases – neoplasms of the lymphatic system, pelvic organs, female genital organs. Secondary lymphedema can occur as a complication of cardiovascular failure, kidney disease, chronic venous insufficiency, recurrent streptococcal lymphangitis, myxedematous edema in hypothyroidism, damage to lymphatic vessels, scars after burns, hypoproteinemia. It can be post-inflammatory as a complication of dermatitis, vasculitis, lymphadenitis, as well as post-traumatic.

There are three stages of lymphedema. In the first stage, slight edema occurs in the area of the toes and ankle joint at the end of the day and disappears after rest. The second stage is characterized by enlargement of the limb volume up to 2 cm, the edema is irreversible, and spreads along the lower limb from the bottom up. In

the third stage, the edema is persistent and irreversible, the volume of the limb increases up to 5 cm, and there are expressed trophic disorders as a result of impaired nutrition of the skin and tissues [6].

Lymphedema leads to chronic inflammatory processes with keratinocyte proliferation, collagen deposition, and destruction of elastic fibers, resulting in enlargement and deformation of the limb, as well as fibrosis, and trophic disorders. Recurrences of soft tissue infection cause progressive damage to the limb.

Aim: to focus doctors' attention on the possibility of an atypical subclinical course of CSD by analyzing a clinical case of the disease in the patient with lymphedema of the lower extremity.

Materials and methods. The clinical examination results, laboratory and instrumental tests of a 35-year-old woman were analyzed. The study was performed in accordance with the principles of the Declaration of Helsinki. The informed patient's consent was obtained for the study. The study was approved by the Ethics Committee of the Ivano-Frankivsk National Medical University.

Case presentation. Patient K., 35 years old, for 6 months has been suffering from swelling of the left lower limb, a feeling of heaviness, distension, discomfort, and tightening of the skin. At first, the swelling in the area of the left ankle-foot joint and the back surface of the foot was not expressed, it increased towards the end of the day and significantly decreased in the morning after sleeping. Over time, edema became permanent, it increased after physical exertion and prolonged standing. After 4 months, a feeling of distension appeared in the limb, the swelling increased and did not decrease after rest.

The patient had no history of lymphedema of the lower extremities, including during two pregnancies.

The woman noticed constant fatigue and heaviness in the left leg. She consulted her family doctor in April 2024, who referred her to a vascular surgeon and rheumatologist. Examination and instrumental examination did not reveal any pathology of the vessels of the lower limb. The results of a complete blood count and a normal level of C-reactive protein allowed the rheumatologist to rule out rheumatological diseases and not prescribe further tests.

After the surgeon's conclusion, the patient was referred to the regional oncology center with a diagnosis of "Lymphedema of the left lower limb of unknown etiology" to exclude oncological pathology. An instrumental examination was performed: a CT scan of the chest, abdominal cavity, and pelvic organs, based on the results of which oncological pathology was

excluded. Despite this, the patient insisted on consulting at the National Cancer Institute (Kyiv), where she was referred. Based on the results of an MRI examination of the chest, abdomen, and pelvic organs, oncological pathology was also excluded.

At the National Cancer Institute the patient underwent excision of the left inguinal lymph node with histopathological examination. The results of histopathological examination: fragments of fibrous tissue with angiomatosis and areas of lymph node tissue with proliferation of cellular elements. This result meets the histological criteria of benign lymphoreticulosis with fibrosis.

The patient followed the recommendations of the vascular surgeon - moderate physical activity, dosed walking, and elastic compression of the limb. During the period of examinations (2 months) in the oncology centers, the patient lost 6 kg of body weight, which alarmed the doctors.

The woman got an appointment with an infectious disease doctor by accident in June 2024 because she was with her husband, who is being observed for chronic hepatitis C. The woman informed the infectious disease specialist about the presence of lymphedema of the lower extremity of unknown etiology and told about all the previous tests, according to the results of which it was not possible to establish the cause of the disease. When talking to the patient, the doctor found out the details of the medical history: in July 2023, a domestic cat bit her foot under the left ankle joint. There was minor bleeding, the woman treated the wound herself at home. The wound healed completely within a week. No visual changes were observed in the bite area. The general condition was satisfactory. However, in November, she noticed pastiness (slight swelling) of the left ankle joint without visible changes on the skin.

On examination, the left lower limb (Fig. 1A) was swollen throughout, with the most expressed swelling in the ankle joint and lower leg. The diameter of the left lower leg was 4 cm larger than the right one, and the left thigh was 2.5 cm larger than the right one. The swelling was doughy (Fig. 1B), the skin was "shiny", thickened, the soft tissues were dense when pressed, deep pits were formed, and it was impossible to fold the skin on the dorsum of the foot (Stemmer's sign). There were no cracks with lymphorrhea or trophic disorders.

On examination: in the left inguinal region, lymph nodes are visible and palpable, sensitive to palpation - 1.5–2 cm in size, dense, in the right inguinal region - up to 1 cm, not dense and not sensitive to palpation. In both areas, the lymph nodes are mobile, not fused with the surrounding tissues. The skin over them is not changed.



A



B

Figure 1 – The lower lower limbs of the patient on examination

There are no signs of other organs and systems disorders according to the results of an objective examination.

In June 2024, an enzyme-linked immunosorbent assay (ELISA) of blood for *Bartonella henselae* (qualitative determination) was prescribed and positive IgM and IgG antibodies were detected (14.06.24); repeated ELISA from 13.11.24 - the result of IgM antibodies was weakly positive. Considering the presence of adenopathy, contact with a cat in the anamnesis, which was accompanied by a bite, a positive serological test, and the exclusion of other causes, the diagnosis was established: Cat scratch disease, subclinical form. Lymphedema of the left lower limb, stage II-III. In addition to the vascular surgeon's recommendations – compression stockings, lymphatic drainage massage, the patient was prescribed: bicillin-5 (benzathine penicillin with procaine penicillin sterile salt) 1,500,000 units IM once every 4 weeks, for 6 months.

Tests results:

Complete blood count (June 14, 2024): Hemoglobin 138 g/L, erythrocytes $4,2 \times 10^{12}/L$, leukocytes $4,8 \times 10^9/L$, eosinophils 3%, band neutrophils 6%, segmented neutrophils 47%, lymphocytes 39%, monocytes 5%, thrombocytes $220 \times 10^9/L$, ESR 12 mm/hour.

Indexes of complete blood count for the entire period of the disease are within normal limits.

Anti-HIV antibodies – not detected.

Ultrasound examination of veins on February 14, 2024

Right lower limb: great saphenous vein main trunk is patent, diameter up to 0.6 cm. Valves are functional. The small saphenous vein: patent. Valves are functional. The function of lower limb perforator veins is preserved.

Left lower limb: great saphenous vein is patent, diameter up to 0.65 cm. Valves are functional. The small saphenous vein is patent. Valves are functional.

Conclusion: on the left lower limb in the area of the ankle joint there is moderate lymphostasis. The deep veins of both lower extremities are passable during the examination.

Duplex ultrasonography of the veins of the lower extremities on March 2, 2024: the vessels of both extremities are patent, unchanged, no pathological changes in blood flow were detected.

Ultrasonography of inguinal lymph nodes – multiple lymph nodes of reduced homogeneous echostructure are visualized in the left inguinal area with dimensions of 16-24 mm, in the right - 8 by 11 mm, with clear smooth contours.

Magnetic resonance imaging (MRI) (June 6, 2024): Expressed edema of the subcutaneous tissue of the foot without pathological lesions in the scanning area. No evidence of damage to the ligamentous apparatus was found at the time of the examination. The pathological amount of free fluid in the ankle joint cavity is not determined.

MRI of the lower extremities (October 18, 2024) - the configuration of the bones of both lower extremities is normal, the ratio in the joints is preserved, the MR signal from the bone tissue is not changed, the integrity of the cortical layer is not impaired. The muscles bilaterally are of sufficient volume, their differentiation is traced. There is edema in the subcutaneous adipose tissue of the left inguinal area, thigh, the lower leg along the anterior-medial contour, and no pathological changes on the right. The vascular and nervous structures are without visible changes. No additional formations or inclusions were

found at the levels examined. Conclusion: edema of adipose tissue of the left inguinal region, lower extremity.

Vascular surgeon examination (October 21, 2024). Diagnosis: Secondary lymphedema of the left lower limb. Severe inguinal lymphadenitis. Angiotrophoneurosis of both lower extremities. Recommended: moderate physical activity, dosed walking; ceftriaxone 1g BID 7 days, metronidazole 100ml infusion 5 days; furosemide 2.0q.d. /three days. Elastic compression of the limb (compression stocking - to increase tissue pressure, which increases lymphatic drainage), decompression exercises, diosmin, hesperidin – 1000mg q.d. 3 months.

After 3 months of antibacterial therapy, the patient noted a decrease in the feeling of heaviness and pastiness of the left lower limb at the end of the day and significant relief when walking. On examination, the volume of the left ankle joint decreased by 1.5 cm (4 cm), and the left hip by 1.2 cm (2.5 cm). The left inguinal lymph node decreased in diameter – 1 cm (1.5–2 cm), not dense and not sensitive to palpation. When repeated ELISA from 09.01.25 – the result of IgM antibodies was negative. Therefore, the prescribed treatment is effective, positive dynamics are observed, so it is recommended to carry it out for up to 6 months duration of such pathological process.

DISCUSSION

The incidence of CSD in the population is studied in many countries of the world; clinical cases of atypical manifestations have been reported [4, 14].

AUTHOR CONTRIBUTIONS

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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In the described clinical case, it is interesting to note that the patient's visit to the infectious disease specialist was accidental and not directly related to her problem. At that time, the patient was under the supervision of a surgeon and received treatment for lymphedema recommended by him. The peculiarity of the case is that the disease was subclinical without the formation of primary affect and the absence of clinical manifestations in the first 3 months. Regional lymphadenitis, lymphangitis with the development of lymphedema occurred in the fourth month after the cat bite. Its spread to the lower leg and thigh and the detection of regional lymphadenopathy became the basis for an oncologic search eight months after the cat bite.

There was no clinical reaction at the site of Bartonella penetration. From the primary focus, the pathogen by lymphatic route reached the regional lymph nodes, where it multiplied with the development of granulomatous lymphadenitis with fibrosis without any systemic disorders or changes in the general condition. Thus, in this case, we can conclude that the disease is atypical, subclinical, which can be due to patient's immune system peculiarities.

CONCLUSION

Bartonella henselae infection should be considered in all cases of lymphadenitis and lymphedema of unknown etiology for timely diagnosis and antibiotic treatment at the initial stage of the cat scratch disease.

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