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Bilateral Tibial Lesions as an Onset of the Diffuse B-Cellular Non-Hodgkin Lymphoma

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ABSTRACT

BACKGROUND: *Diffuse B-cellular non-Hodgkin lymphoma is the most widespread in this group of diseases, causing the highest number of lymphoma-related lethal outcomes worldwide. The clinical-pathological heterogeneity of the nosology negatively affects the possibilities of precise and timely diagnostics. The variety of extranodal locations of the disease requires the participation of a multidisciplinary team of high qualification specialists, the use of high-tech methods for diagnostics and the aggressive therapy. The article presents a discussion on the occurrence of the diffuse B-cellular non-Hodgkin lymphoma, on the rates of an onset with the lesions in the skeleton, on the specific features of the disease course that is mimicking the rheumatic disease, as well as on the difficulties of recognizing it due to the absence of specific symptoms at the beginning of the disease and to the necessity of using high-tech instrumental diagnostic methods.* ***CLINICAL CASE DESCRIPTION:*** *The article presents a clinical case of the patient aged 57 years, hospitalized to the Regional Tuberculosis Dispensary with the provisional diagnosis of tuberculosis-associated arthritis of the ankle joints. At the out-patient phase, the differential diagnostics was conducted between the inflammatory disease of the joints, the trauma, the bone tuberculosis and the orthopedic abnormalities. The radiology image of the chest cavity organs showed the presence of diffuse pneumosclerosis, according to the data from multispiral computed tomography, a cystic transformation was found along with the space-occupying mass lesions and osteolysis in the distal areas of both tibial bones. Based on the results of the histological examination of the lower third of the left tibia, a diagnosis of diffuse B-cellular non-Hodgkin lymphoma with high proliferative activity was set, confirmed at the specialized medical institution using the method for calculating the IPI prognostic index (International Prognostic Index).* ***CONCLUSION:*** *The presented case demonstrates the necessity for oncological alertness and for multidisciplinary approach for ruling out the primary and the secondary non-Hodgkin lymphomas of bone tissue location, mimicking the bilateral disease of the joints, for the purpose of early diagnostics and timely treatment, improving the prognosis for patients with this group of diseases.*

Keywords: *B-cell non-Hodgkin lymphoma; diagnosis; rheumatic diseases.*

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BACKGROUND

The diagnostics of lymphoid tissue tumors represents a complex task for the clinicist, which is due to the variety of nosologies in this group of diseases, many of which have a course mimicking other pathologies. Diffuse B-cellular large cell lymphoma differs by the aggressive clinical course with a tendency to rapid growth and early progression, as well as high sensitivity to chemotherapy. The occurrence rate reaches 40% of all the non-Hodgkin lymphomas. The incidence rate of diffuse B-cellular large cell lymphoma is 4–5 cases per 100 thous. of population. Every year worldwide, approximately 120 thous. of new cases are diagnosed. The diseases affect predominantly males with peak of incidence after 60 years of age [1, 2]. Currently, the clinical cases were described in which the course of lymphomas included the initial lesions in the liver, the heart, the mediastinum, the testicles or the central nervous system [1, 3, 4]. Non-Hodgkin lymphomas most commonly have a B-cellular origin [5].

Multiple research works have determined the interrelation between the autoimmune diseases and

Двустороннее поражение большеберцовых костей как дебют диффузной В-клеточной неходжкинской лимфомы

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АННОТАЦИЯ

Обоснование. *Диффузная В-клеточная неходжкинская лимфома является наиболее распространённой в данной группе заболеваний, вызывающих самое высокое в мире число смертей, связанных с лимфомами. Клинико-патологическая гетерогенность нозологии отрицательно влияет на возможность точной и своевременной диагностики. Разнообразие экстранодальной локализации заболевания требует участия мультидисциплинарной бригады специалистов высокой квалификации, применения высокотехнологичных методов диагностики и агрессивной терапии. В статье обсуждается распространённость диффузной В-клеточной неходжкинской лимфомы, частота дебюта с поражения скелета, особенности течения под маской ревматического заболевания, а также трудности распознавания ввиду отсутствия специфических симптомов в начале болезни и необходимости использования высокотехнологичных инструментальных методов диагностики.* ***Описание клинического случая.*** *В статье представлен клинический случай пациента в возрасте 57 лет, госпитализированного в областной противотуберкулёзный диспансер с предварительным диагнозом туберкулёзного артрита голеностопных суставов. На амбулаторном этапе дифференциальный диагноз проводился между воспалительным заболеванием суставов, травмой, туберкулёзом костей и ортопедической патологией. По рентгенограмме органов грудной клетки выявлен диффузный пневмосклероз, по данным мультиспиральной компьютерной томографии — кистозная перестройка, объёмные образования и остеолиз дистальных отделов обеих большеберцовых костей. По результатам гистологического исследования нижней трети левой большеберцовой кости выставлен диагноз диффузной В-клеточной неходжкинской лимфомы с высокой пролиферативной активностью, подтверждённый в профильном медицинском учреждении методом расчёта прогностического индекса IPI (International Prognostic Index).* ***Заключение.*** *Представленный случай демонстрирует необходимость онкологической настороженности и мультидисциплинарного подхода для исключения первичных и вторичных неходжкинских лимфом костной локализации, имитирующих двустороннее заболевание суставов, с целью ранней диагностики и своевременного лечения, улучшающего прогноз для пациентов с этой группой заболеваний.*

Ключевые слова: *В-клеточная неходжкинская лимфома; диагностика; ревматические заболевания.*

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the high rate of developing B-cellular lymphomas. The highest risk of non-Hodgkin lymphoma was observed in cases of Sjogren disease, systemic lupus erythematosus, rheumatoid arthritis, scleroderma, dermatomyositis, polymyositis and Still syndrome [4–6]. The process of differential diagnostics for such conditions sometimes takes up to two years, which determines a significant delay of adequate therapy [7]. The most frequent locations of primary non-Hodgkin lymphomas are the femoral and tibial bones, the pelvic bones, the vertebrae and the ribs. The predominant findings are the osteolysis foci or a combination of lytic and sclerotic changes [8]. The tumor tissue often contains foci of necroses and of accumulating atypical cells. The process is accompanied by thinning of the spongy and of the compact bone tissue [8–11].

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Here we present a clinical case of the B-cellular non-Hodgkin lymphoma patient with bilateral lesions in the distal areas of the tibial bones, by its onset mimicking the rheumatic disease.

CLINICAL CASE DESCRIPTION

Patient info

Patient S., aged 57 years.

Case history. In autumn of 2018 he started feeling pain in the area of the ankle joints, increasing with movements, and swelling in the ankle joints. He was repeatedly consulted by the surgeon with such manifestations being estimated as the complications of chronic ischemia in the lower limbs. Taking into consideration the past medical history of the patient (in 2017 — thrombosis of the aneurism in the popliteal artery with the development of acute ischemia, femoropopliteal autovenous prosthetic replacement), this version was considered the top-priority one. The patient was referred to the vascular surgery specialist, underwent ultrasound duplex scanning, as a result of which, a conclusion was drawn that the circulation in the arteries of the lower limbs was compensated. At the out-patient phase, the differential diagnostics also was carried out between the inflammatory disease of the joints, the trauma, the bone tuberculosis and the orthopedic abnormalities. The vascular surgery specialist, the rheumatologist and the orthopaedist have ruled out the presence of specific abnormalities.

For several months, the severity of symptoms was progressing, the patient was not able to move without assistance because of pain. He was then consulted by the phthisio-orthopaedist and hospitalized to the Regional Tuberculosis Dispensary with the following provisional diagnosis: “Tuberculosis-associated arthritis of the ankle joints, congestive peri-articular abscesses, severe pain syndrome”.

Past medical history. Growth and development according to the age. Living at a well-furnished apartment, the living conditions are satisfactory. Contact with tuberculosis patients — negative (verbal information provided by the patient). Smoking approximately one pack a day for many years. In 2015 — pacemaker implantation (ischemic heart disease, sick sinus node syndrome, atrial fibrillations, paroxysmal form, normosystole). Suffers from the obliterating atherosclerosis in the arteries of the lower limbs, chronic ischemia of the left lower limb stage IIb, in 2017 — surgery operated — femoropopliteal autovenous by-pass grafting on the right side. Group III disability according to the general disease.

Laboratory and instrumental diagnosis

On admission the state of the patient has moderate degree of severity. Body position — sitting on his bed. The skin and the visible areas of mucosal membranes are pale-pink and moistened. At the internal surface from the middle third of the right thigh to the middle third of the right shin, there is a postoperative scar. The subcutaneous-fatty tissue and the muscular system are satisfactorily developed. The occipital, the parotid, the submandibular, the submental, the cervical, the supraclavicular, the subclavian, the subpectoral, the axillary, the cubital, the inguinal, the femoral and the popliteal lymph nodes are not palpable, the skin above them is unremarkable. The chest has a correct shape, being symmetrical and painless, with both halves participating in the respiratory movements, the percussion of the lungs reveals a clear pulmonary percussion sound. The auscultation reveals vesicular breathing without any abnormal respiratory sounds. The respiratory rate is 16/minute. The heart projection area visually has no abnormalities, the cardiac rhythm is correct, the heart tones are clear and the heart rate is 76 bpm. Blood pressure — 120/80 mm.Hg. in both arms. The tongue is clear and moistened. The abdomen is participating in respiratory movements, soft and moderately painful in the right hypochondrium; the liver on palpation is located near the margin of the right costal arch. The kidneys and the spleen are not palpable; the costovertebral tenderness test in the lumbar area is negative on both sides. The urination and stools show no abnormalities.

Local status: the skin in both feet is hyperemic, densified and swollen (more on the left side), the swelling is spreading to the middle third of the shin. The active and passive motions in the ankle joints are significantly limited due to the sensation of pain. The axial load is sharply painful. The peripheral pulsation in the foot arteries is weakened, more on the left side. Smoothened contours of the medial malleolus on the left side, the palpation reveals a non-dislocatable tumor lesion with doubtful deviation of its dimensions from the normal ranges, the skin above it has a dark-crimson shade, being warm.

Laboratory examination. The clinical tests of blood and urine samples dated 17.05.2019 were normal. Sputum microscopy in search of Mycobacteria tuberculosis: the result was negative. The microprecipitation reaction was also negative. No antibodies were detected to human immunodeficiency virus, as well as the markers of hepatitis B or C. The blood biochemistry panel values (parameters: glucose,

transaminases, bilirubin, total protein, creatinine, urea) were also within the normal ranges.

Instrumental examination. Multispiral computed tomography on 12.05.2019: cystic transformation, volume-occupying mass lesions and osteolysis in the distal areas of both tibial bones (Fig. 1). Chest cavity X-ray dated 16.05.2019: diffuse pneumosclerosis. Ultrasound examination of the abdominal cavity organs dated 20.05.2019: no signs of structural abnormalities.

Diagnosis

On 28.05.2019, in the settings of the Regional Tuberculosis Dispensary, the patient underwent an open-access biopsy of the lower third of the left tibial bone. The conclusion from the protocol of intra-vitam pathology examination was the following: "The examined sample contains a fragment of the bone tissue, in which the findings include a hypercellular infiltrate of large lymphocyte-like cells with light-colored nuclei. Upon the immunophenotyping with using the CD20 marker (×100) — significant expression was found in all the tumor cells, Ki-67 (×100) — nuclear expression in 60–70% of the tumor cells, high proliferative activity. Small fragments of grey-brown tissue, the histological examination reveals a diffuse hypercellular infiltrate of large lymphoid cells with light-colored nuclei, with the presence of nucleoli and of small lymphoid cells. Diffuse B-cellular large cell non-Hodgkin lymphoma with high proliferative activity".

Treatment and outcome

The patient was hospitalized to the specialized medical institution, where, using the calculated IPI prognostic index (International Prognostic Index), developed for predicting the outcome in patients with aggressive non-Hodgkin lymphoma, he was confirmed as having a high risk of lymphoma and polychemotherapy cycles were prescribed.

Sadly, but, despite the conducted therapy, the status of the patient has progressively worsened, and in several months the patient has deceased. Such an outcome, probably, was resulting from the presence of several risk factors for unfavorable prognosis, including the age, the extranodal (i.e. localizing in the internal organs) location of the lymphoma, its aggressive clinical course with a tendency to rapid growth and early progression, high IPI risk, high proliferative activity index in the tumor cells (Ki-67). There is an opinion stating that the increase of the Ki-67 specific protein concentration by more than 20% leads to the worsening of the prognosis and to the increases probability of developing a recurrence [10, 11].

DISCUSSION

The bony skeleton in cases of non-Hodgkin lymphoma gets involved in more than 25% of the cases of metastatic spreading or even less frequently in cases of primary bone lymphoma.

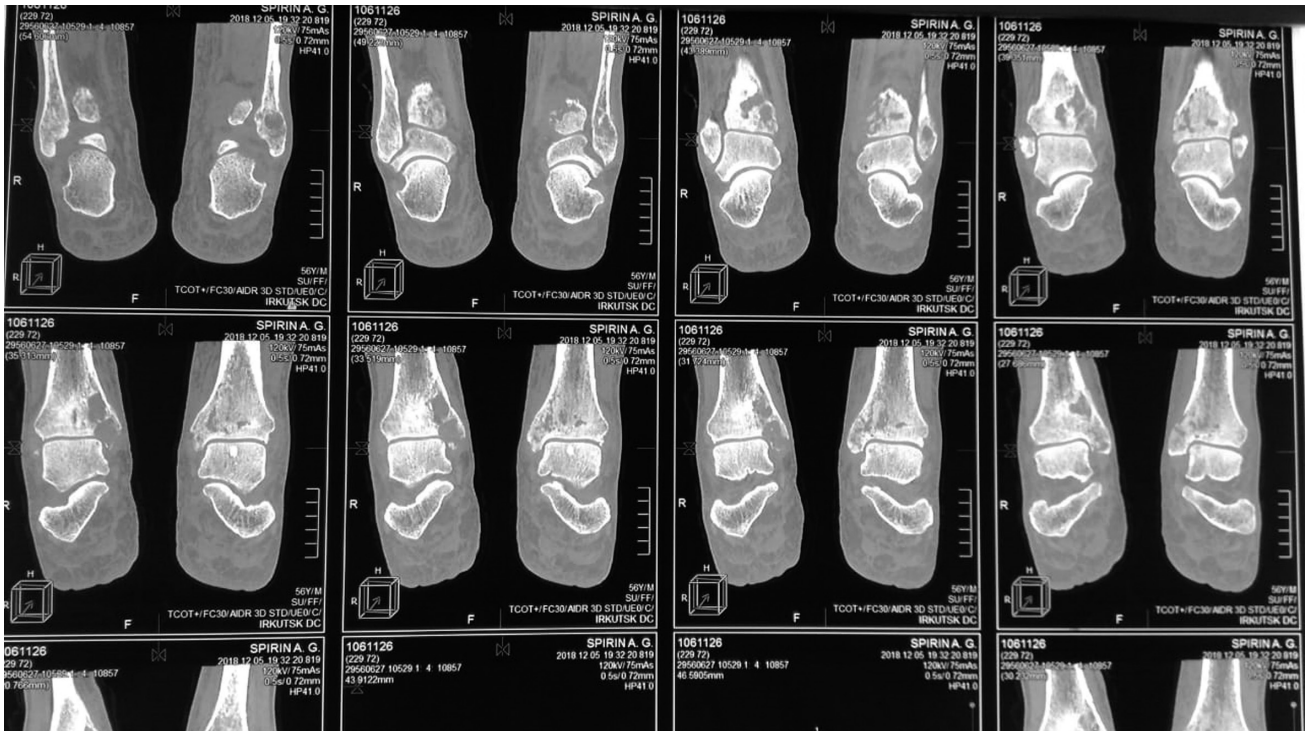

Fig. 1. Multispiral computed tomography: osteolytic destructive changes in the distal areas of the tibial bones.

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Primary non-Hodgkin lymphoma in the bone tissue may cause multiple osteolytic lesions in the skeleton, in particular, in the lower limbs, the pelvis and the vertebral column [9, 11–15]. The cases were described that involve the cranial bones, the orbit, the upper or lower jaws [16–19]. Non-Hodgkin lymphoma occurs infrequently, which is why it is rarely included into the differential-diagnostic search in cases of osteolytic tumors, besides, the primary non-Hodgkin lymphoma can be misdiagnosed due to the absence of symptoms or objective changes in the patients at early stages, being detected, for example, in cases of pathological fractures developing as a result of falling in elderly patients [19]. In the absence of peripheral lymphadenopathy and lesions in the internal organs, the diagnosis of non-Hodgkin lymphoma can be set only as a result of histological examination. During its onset, the non-Hodgkin lymphoma can mimic a rheumatic disease, which is confirmed by the clinical case described above. The foreign literature describes 17 cases of non-Hodgkin lymphoma with the course mimicking the mono- or polyarthritis [9, 12, 19]. Most frequently, lesions were located in the elbow or the knee joints, and only 3 patients had the presence of general symptoms (loss of body weight, weakness, nighttime sweating, fever with chills). In the majority of cases, the involvement of joints was the early manifestation of the disease, and the data from magnetic resonance tomography were showing signs of a non-specific inflammatory process in the joints [20]. The clinical observation presented above is interesting by its symmetrical location of the pathological process. The literature has the descriptions of cases of bilateral lesions in the bones of the lower limbs with their “disappearance”, i.e. osteolysis. Also known is the possibility of bilateral location of the pathological process in the adrenal glands, the urinary ducts and the testicles with a rapid development of severe functional disorders. It is recognized that in case of diffuse B-cellular large cell lymphoma, bilateral symmetrical location of the process, both in the bones and extranodally, occurs rarely [20, 21]. Primary bone lymphoma represents not more than 2% of all the non-Hodgkin lymphomas in adult patients [20–22]. The detected findings are the defects in one or more bones, with the possible involvement of the regional lymph nodes and of the soft tissues. The disease starts with pain syndrome with local swelling and developing tumor masses in the affected area. Most commonly, the diaphyses of the long tubular bones get involved [22–24].

The difficulties of diagnostics in this case are related not only to the low incidence of non-Hodgkin lymphoma, but also to the absence of symptoms usually associated with the oncological disease [25].

CONCLUSION

The presented case demonstrates the necessity of oncological alertness and of the multidisciplinary approach for the purpose of ruling out the primary or secondary non-Hodgkin lymphomas with bone tissue location, imitating the bilateral disease of the joints, for the purpose of early diagnostics and timely treatment, for improving the prognosis in patients with this group of diseases.

ADDITIONAL INFORMATION

Author contributions: *M.V. Karnakova*, creation of a research concept, preparation of a draft article; *I.V. Andryushchenko*, *D.V. Belykh*, conducting research; *A.N. Kalyagin*, revision and editing of the article. Thereby, all authors provided approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Consent for publication: The authors received written informed voluntary consent from the patient to publish personal data, including photographs (with the face covered), in a scientific journal, including its electronic version (signed on 2019 May 16). The volume of published data was agreed upon with the patient.

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