SOUTH RUSSIAN JOURNAL OF CANCER
ЮЖНО-РОССИЙСКИЙ ОНКОЛОГИЧЕСКИЙ ЖУРНАЛ
VOL. 1
No 3, 2020

Южно-российский онкологический журнал 2020, т.1, №3, с. 50-59
https://doi.org/10.37748/2687-0533-2020-1-3-5

КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

РЕДКИЕ ФОРМЫ НЕХОДЖКИНСКИХ ЛИМФОМ: ОПЫТ ТЕРАПИИ ПЕРВИЧНЫХ ЛИМФОМ КОСТЕЙ

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РЕЗЮМЕ

К редким локализациям неходжкинских лимфом относят первичную лимфому костей. Эта форма составляет не более 1–2% всех неходжкинских лимфом взрослых. Диагноз первичной лимфомы костей устанавливают в случаях очагового поражения одной или нескольких костей. Кроме того, допускается вовлечение мягких тканей и регионарных лимфоузлов. Критерием исключения служит только поражение костного мозга и вовлечение отдаленных лимфоузлов. Первыми симптомами болезни являются некупируемые боли в костях, нередко сопровождающиеся локальным отеком, формированием опухолевой массы в зоне поражения, изредка присоединяются В-симптомы. Чаще встречается локальное (80%) и реже многофокусное (20%) поражение длинных трубчатых костей в области диафиза и метадиафиза. Диагностика поражения костной ткани при первичном и вторичном ее вовлечении основана на применении всех доступных методов исследования (рентгенография, компьютерная, магнитно-резонансная и позитронно-эмиссионная томография). Дифференциальная диагностика возможна только на основании иммуногистохимического исследования с определением экспрессии общего лейкоцитарного антигена, маркеров В-клеток, Т-клеток, а также клональности по одной из легких цепей иммуноглобулинов к или λ, bcl 2 и bcl 6, ALK, степени пролиферативной активности Ki-67. Оценка эффективности различных методов лечения первичной костной лимфомы осложняется небольшим числом наблюдений и отсутствием единой тактики лечения. В качестве терапии первой линии чаще применяют CHOP-подобные курсы. Персонифицированная терапия включает иммуно-химиотерапию, лучевую терапию и применение хирургических методов лечения — эндопротезирования.

Ключевые слова:
неходжкинская лимфома, кости, диагностика, химиотерапия, эндопротезирование, длительность наблюдения

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Информация о финансировании: финансирование данной работы не проводилось.
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования:
Лысенко И.Б., Барашев А.А., Лаптева Т.О., Николаева Н.В., Капуза Е.А., Шатохина О.Н., Пушкарева Т.Ф. Редкие формы неходжкинских лимфом: опыт терапии первичных лимфом костей. Южно-российский онкологический журнал. 2020; 1(3): 50-59.
https://doi. org/10.37748/2687-0533-2020-1-3-5

Получено 04.06.2020, Рецензия (1) 07.07.2020, Рецензия (2) 15.07.2020, Принята к печати 01.09.2020

South Russian Journal of Cancer 2020, v.1, №3, p. 50-59
https://doi.org/10.37748/2687-0533-2020-1-3-5
CLINICAL CASE REPORTS

RARE FORMS OF NON-HODGKIN LYMPHOMAS: EXPERIENCE IN TREATMENT FOR PRIMARY BONE LYMPHOMAS

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ABSTRACT

Primary bone lymphoma is a rare presentation of non-Hodgkin lymphoma. It accounts for a maximum of 1–2% of all non-Hodgkin lymphomas in adults. Primary bone lymphoma is diagnosed in focal lesions of one or more bones; soft tissue and regional lymph nodes may be involved too. The exclusion criteria are only bone marrow damage and involvement of distant lymph nodes. The first symptoms include intractable bone pain often accompanied by local edema, the formation of a tumor mass in the affected area; B symptoms occasionally join. Local lesions of long tubular bones in the diaphysis and metadiaphysis regions are more common (80%), while multifocal lesions are less frequent (20%). Diagnosis of lesions of the bone tissue in its primary and secondary involvement is based on the use of all available research methods (radiography; computed, magnetic resonance and positron emission tomography). Differential diagnosis requires an immunohistochemical study with determination of the expression of total leukocyte antigen, B-cell and T-cell markers, and clonality in one of immunoglobulin light chains κ or λ, bcl 2 and bcl 6, ALK, proliferative activity of Ki-67. Evaluation of the effectiveness of various treatments for primary bone lymphoma is complicated by a small number of observations and the absence of a uniform treatment strategy. CHOP-like chemotherapy cycles are often used as first-line therapy. Personalized therapy involves immunochemotherapy, radiation therapy and surgical treatment — endoprosthetics.

Keywords:
non-Hodgkin lymphoma, bones, diagnosis, chemotherapy, endoprosthesis, observation period

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Information about funding: no funding of this work has been held.
Conflict of interest: authors report no conflict of interest.

For citation:
Lysenko I.B., Barashev A.A., Lapteva T.O., Nikolaeva N.V., Kapuza E.A., Shatokhina O.N., Pushkareva T.F. Rare forms of non-Hodgkin lymphomas: experience in treatment for primary bone lymphomas. South Russian Journal of Cancer. 2020; 1(3): 50-59. https://doi.org/10.37748/2687-0533-2020-1-3-5

Received 04.06.2020, Review (1) 07.07.2020, Review (2) 15.07.2020, Accepted 01.09.2020

RELEVANCE

Rare localities of non-Hodgkin's lymphomas include primary bone lymphoma. This nosological form makes up no more than 2–5% of all primary bone tumors 4–5% of all extranodal lymphoproliferative diseases, and 1–2% of all non-Hodgkin's lymphomas of adults. Until the middle of the last century, bone lymphomas were considered only cases with a local lesion of one bone without involving soft tissues and regional lymph nodes. In modern conditions, the diagnosis of primary bone lymphoma is also established in cases of focal lesions of several bones. In addition, the involvement of soft tissues and regional lymph nodes is allowed. The exclusion criterion is only the bone marrow lesion and involvement of distant lymph nodes. The first symptoms of the disease are non-stop pain in the bones, often accompanied by local edema, the formation of a tumor mass in the affected area, and occasionally b-symptoms are added. Very often, patients are concerned about restriction of limb movement, and pathological fractures are possible. More often, this is a local (80%) and less often multi-focal (20%) lesion of long tubular bones in the area of the diaphysis and metadiaphysis. Bone localization of lymphoma is more common in patients 60–70 years old, it is extremely rare in children younger than 10 years, the ratio of men: women are 1.5:1 [1–5].

Diagnosis of bone tissue damage with primary and secondary involvement is based on the use of all available imaging methods. The data of radiological methods of investigation (radiography, computer — CT, magnetic resonance-MRI and positron emission — PET tomography) for bone lymphomas are variable and non-specific, the initial changes may not go beyond the normal variants of the structure of bone tissue. During radiographic examination, changes can be represented by local lytic foci with uneven edges with areas of sclerotic lesions in the form of small multiple foci along the entire length of the bone, or by a diffusely distributed process with the destruction of cortical tissue and the involvement of adjacent soft tissues. The periosteal reaction occurs in 60% of patients and is characterized by the presence of lamellar or layered areas located along the long axis of the bone, alternating with normal periosteum and serving as an indicator of a poor prognosis. Changes close to different variants of the norm make it difficult to diagnose bone lesions based on review radiographs. In these cases, MRI is a more informative study. In T1-WI mode (WI-weighted image) MRI is better able to detect heterogeneous low-intensity signals that are characteristic of intraosseous changes, fibrosis, and soft tissue lesions, since it can detect areas with a low-intensity signal.T2-WI mode is more informative in the presence of Homo-and heterogeneous changes of high intensity, peritumoral edema, periosteal reaction and reactive changes in the bone marrow. MRI with contrast allows you to detect areas of bone damage with increased accumulation of contrast agent. CT is not the method of choice in PLC diagnostics and can only be used in combination with MRI or PET. However, CT scans can diagnose sequestration and cortical erosion at earlier stages of the disease and in a larger percentage of cases [2, 3, 5–9].

A necessary condition for confirming the diagnosis of bone lymphoma is to perform an open biopsy of the affected area of the bone and/or soft tissue component of the tumor with histological and immunohistochemical examination of the material. Histological examination of surgical / biopsy material usually reveals diffuse proliferation of medium-and large-sized lymphoid cells located in the bone tissue between the trabeculae and fat cells of the bone marrow. Histological variants are different, but in most (60–80%) cases there is diffuse b-large cell lymphoma (DBLCL), of which 10% is the Central-cell variant of DBLCL and b-cell lymphoblastic lymphoma; other more rare variants include follicular lymphoma, lymphoma from the mantle zone cells, ALK+large-cell lymphoma, NK/T-cell lymphoma. Differential diagnosis is possible only on the basis of immunohistochemical studies with the determination of the expression of total leukocyte antigen (CD45 LCA), markers of B cells (CD 19, CD 20, CD 79a, RAX5, MuM1), T cells (CD 3, CD 4, CD 8, CD5), as well as clonality along

one of the light chains of immunoglobulins κ or λ, bcl 2 and bcl 6, ALK, and the degree of proliferative activity of tumor cells (Ki-67). Informative is the cytogenetic study of native material to identify chromosomal rearrangements characteristic of lymphomas — translocations t (8;14) (q24; q32), t(11;14) (q13; q32) and t(14;18) (q32; q21), rearrangements of the bcl 6 gene and detection of hyperexpression of cyclin D1 by polymerase chain reaction [3, 6, 10–12].

Evaluating the effectiveness of various treatment methods for primary bone lymphoma is difficult, because it is based on the analysis of retrospective data over a long period of time. The analysis is complicated to a large extent by a small number of observations and the lack of a unified treatment strategy. As a first-line therapy, SNOR-like courses are more often used. Treatment results depend on the presence of adverse prognosis factors: increased activity of lactate dehydrogenase (LDH) in serum, multiple bone lesions involving soft tissues, presence of B-symptoms, tumor size of 6 cm or more, localization in the spine and pelvic bones, involvement of regional lymph nodes, which reduce the effectiveness of therapy [11]. Data from various research groups agree that in local (IE) stages of bone lymphoma, the 5-year relapse-free survival after radiation or chemoradiation is 35–50 and 90–95%, respectively. In common stages (IIE and IV), only LT is not possible in principle, and with chemotherapy under the SNR program, the 5-year relapsed survival rate is 40–70%. The use of targeted drugs and primary intensification of PCT high dose chemotherapy followed by autologous hematopoietic stem cell transplantation can improve survival rates in patients with risk factors [1, 3, 5, 9, 11–14].

We present clinical cases of primary bone lymphomas.

Description of the clinical case

According to archived data from the FGBU NMRC of Oncology of the Ministry of health of Russia for the period 2009–2019, there were 4 patients with primary bone lymphoma, 3 men and 1 woman, with an average age of 43.5 years (table 1). All patients noted a direct link between the development of the tumor and the previous injury. the average time between the appearance of the first symptoms (in all patients it was local pain in the limb) and verification was 9.25 months (4–16).

In men, the tumor was localized in the left femur, in women, the right humerus was affected, in all patients, there was a multi-focal bone lesion and local involvement of the soft tissues of the limb. B-large-cell NCL was verified in three patients, and b-cell lymphoma from small lymphocytes was initially verified in one patient. later, during additional studies, this tumor was assigned to extranodal follicular lymphoma type 3A (table 1).

The prevalence of the process was determined using CT, MRI, and pet studies in two patients (the method has become widely available in routine practice since 2016), as well as standard clinical examination, including bone marrow trepanobiopsy, was performed in all patients.

R-CHOP/CHOEP schedule (rituximab, cyclophosphamide, vincristine, prednisone, doxorubicin, etoposide) was used as first-line therapy in all patients.after 6 cycles, partial remission was achieved in 3 patients, and these patients received consolidating radiation therapy at a total dose of 40 gray. In 1 patient with adverse prognostic factors B-large cell lymphoma after 6 cycles of R-CHOEP, the progression of the disease with PET-positive infiltration into the lung tissue was determined. The use of second-line therapy (R-GDP 2 cycles, R-MINE 3 cycles) did not bring any effect, the patient had primary refractoriness to chemo-immunotherapy, PET-positive (5 points according to Deauville) tumor infiltration of the bone, soft tissues of the left knee joint, including the patella, and infiltration in the lung regressed (table 1). The patient had a continuously progressive course, which led to a fatal outcome. The patient was followed up for 14 months.

Two patients after the completion of chemoradiation treatment had a successful endoprosthesis with restoration of the functions of the corresponding limb for objective indications. the follow-up period for these patients was 83 and 95 months (table 1).

Table 1. Characteristics of patients with primary bone non-Hodgkin's lymphoma

Patients	A.	Ye.	S.	Sh.
Sex	Male	Male	Male	Male
Age, y.o.	55	29	27	63
Trauma	+	+	+	+
Time from the first symptoms to diagnosis, months	9	8	16	4
Localisation	Left femur, patella	Left femur	Left femur	Right humerus
Type of damage	Multifocal	Multifocal	Multifocal	Multifocal
Soft tissues	+	+	+	+
Local l\n	Inguinal, iliac	Intra-pelvic, popliteal	-	-
B-symptoms	+	+	-	-
LDH	↑↑	↑	N	N
Stage	IVB	IVB	IVA	IVA
International Prognostic Index (IPI)	High intermediate (3)	Lower intermediate (2)	High risk (FLIPI -1)	Lower intermediate (2)
Histology type of tumor	B-large- cellular	Extranodal B-large-cellular	B-cell lymphoma from small lymphocytes. Revision of extranodal 3A type FL	Extranodal diffuse B-large cell
PET for setting the stage	+	+	Not performed	Not performed
First Line Therapy	R-CHOEP 6	R-CHOEP 6	R-CHOP 6	R-CHOP 6
First line therapy response	Progression + easy PET+	PET-full remission	Partial remission	Partial remission
DGT	-	40 Grey	40 Grey	40 Grey
Response time, months	6	10	13	95
Relapse/ refractoriness	refractoriness	-	Relapse +light	-
Second line therapy	R-GDP 2/ R-MINE 3	-	R-B 3 – PD R-GDP 2 - PD	-
Second line therapy response	PD PET+	-	PR	-
Surgical treatment	-	-	Endoprosthesis	Endoprosthesis
Examination duration, months	14	10	83	95
Outcome	Passed away	Alive	Alive	Alive

Note: PET – positron emission tomography; FL – follicular lymphoma; R – GDP-rituximab 375 mg/m^2, gemcitabine 100 mg/m^2, cisplatin 100 mg m^2, dexamethasone 40 mg; R – CHOP/snoer-rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2, doxorubicin 50 mg/m^2, prednisone 100 mg/m^2, etoposide 100 mg/m^2; R – mine-rituximab 375 mg/m^2, ifosfamide 1330 mg/m^2, mesna 1330 mg/m^2, etopozod 65 mg/m^2, mitoxantrone 8 mg/m^2; R – b-rituximab 375 mg/m^2, bendamustine 90 mg/m^2

Three patients with primary bone lymphomas are currently alive, with an average follow-up time of 49 months (4–95).

To show the modern possibilities of complex therapy of rare forms of non-Hodgkin's lymphomas using various methods, we present the following clinical case more detailed.

Clinical case 1

Patient Sh., a 63-year-old woman.

The patient noted an acute onset of the disease in December 2010, after a minor bruise, acute pain in the right upper limb appeared, edema, restriction of movement of the hand, "cyanosis of the hand". For a month at the place of residence, the patient was treated for" thrombophlebitis " without effect. In January 2011, radiography of the right upper limb was performed and diffuse changes in the right humerus were detected, and the patient was referred to the NMRC of Oncology with suspicion of "sarcoma". A comprehensive examination in NMRC Oncology revealed an osteodestructive lesion of the distal metaphysis of the right humerus (fig. 1).

The MRI study showed a multi-node formation of inhomogeneous proton density with intra-and extraossal growth with destruction of the cortical layer of the right humerus in the distal metaphysis region and a circular extraossal component with dimensions of 70x40x43 mm. vessels of the main neurovascular bundle of the shoulder without convincing evidence of involvement in the tumor process. Osteoscintigraphy determined a focus of 63 mm, the percentage of pathological hyperfixation of RPF at the level of 70%. Complex examination did not reveal any other pathological foci, lesions of internal organs and bone marrow.

An open tumor biopsy was performed. In the finished histological preparation, a fragment of muscle-fibrous tissue with diffuse infiltration by lymphoid elements. The tumor cells were large with large polymorphic nuclei with uneven angular contours, with coarse chromatin and large centrally or eccentrically located nuclei, the presence of cells with multi-lobed nuclei (fig. 2). immunohistochemical study was performed with antibodies to panCK AE1/AE3, S-100, CD20, CD79a, CD3, CD45LCA, VCL-6, BCL-2, MuM1, Ki — 67–70% (fig.3). Expression of CD20 (membrane reaction) (fig. 4), CD79a (cytoplasmic reaction), MuM1 (nuclear reaction), BCL-6 (nuclear reaction in part of cells) (fig. 5), BCL-2 (cytoplasmic reaction in most cells) was observed in tumor cells. Conclusion of the immunohistochemical study-extranodal diffuse b-large cell lymphoma (CD20+, MuM1+, BCL6+, BCL2+).

The patient had a pathological fracture of the lower third of the right humerus with dislocation of bone fragments and impaired function of the upper limb before starting therapy in March 2011 (fig. 6). on the basis of NMRC Oncology, 6 cycles of R-CHOP polychemotherapy were performed in the Department of oncogematalogy, partial remission was achieved (areas of destruction in the lower third of the humerus were preserved), unfortunately, the function of the arm was not restored. For the purpose of consolidation in the Department of radiotherapy, the patient underwent a course of DGT 40 gy on the area of tumor lesion. There were no adverse events during therapy. An x-ray of the right humerus performed in June 2011 showed a consolidating pathological fracture of the lower third of the right humerus with a rough angular displacement against the background of the bone structure (fig. 7–8).

The callus was weak, the bone edges of the fragments showing signs of sclerosis. Conclusion of the orthopedist — atrophic pseudoarthritis (false joint) of the epimetaphysis of the right humerus. The patient continued to have impaired upper limb function, and in order to improve the quality of life, in November 2013, after confirming remission of the disease, the patient underwent resection of

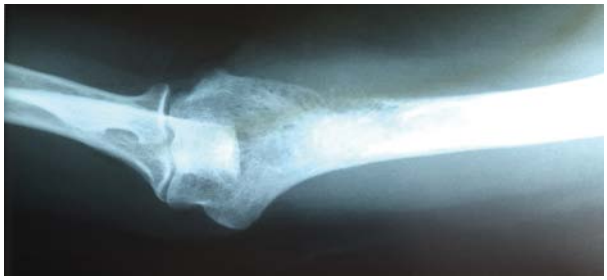

Fig. 1. Patient Sh. An X-ray of the right humerus before getting the treatment.

the lower third of the right humerus (fig. 9) and replacement of the defect with a prosthetic elbow joint PROSPON (fig.10–11).

Histological analysis of the removed bone: the bone marrow is represented by adipose tissue; there are small lymphocytic infiltrates between the bone beams. Healing took place within the standard time frame, and the function of the right upper limb was fully restored. In January 2019, after an injury (falling from the height of her own body with the support of her right arm), the patient again complained of pain in her right arm. Radiography of the right elbow joint in 2 projections showed radiological signs of instability of the leg of the

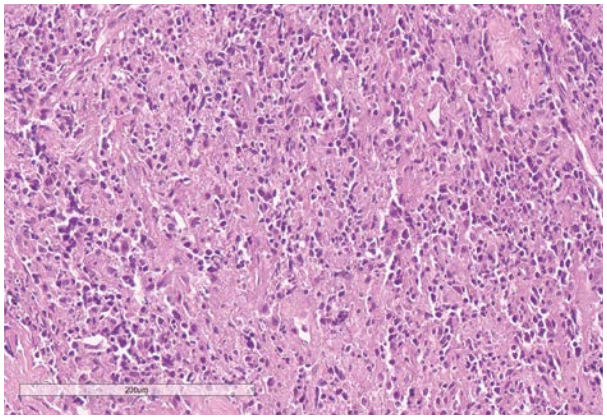

Fig. 2. Patient sh Historiarum bones, hematoxylin x200.

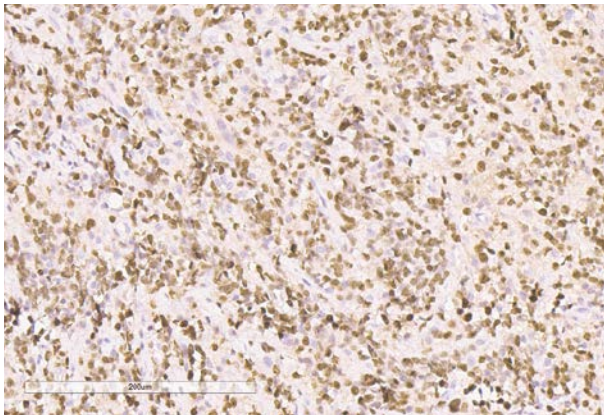

Fig. 3. Patient Sh. The histology slide of bones, Ki67x200 expression.

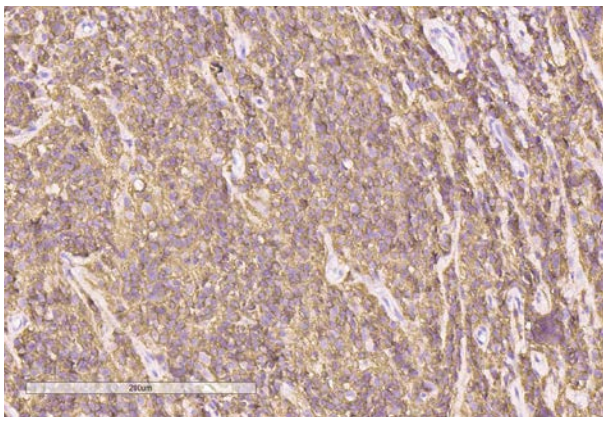

Fig. 4. Patient Sh. The histology slide of bones, CD20x200 expression.

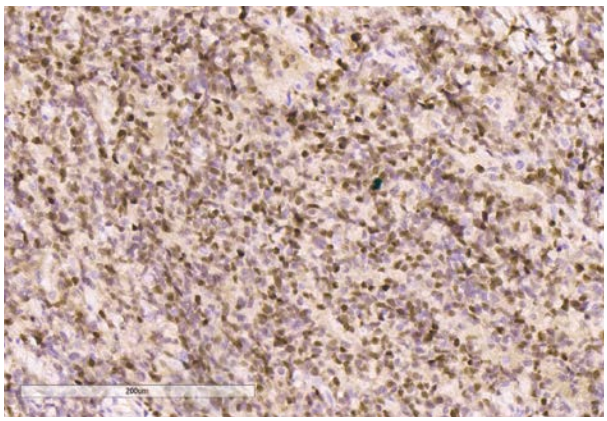

Fig. 5 Patient Sh., The histology slide of bones, BCL6x200 expression.

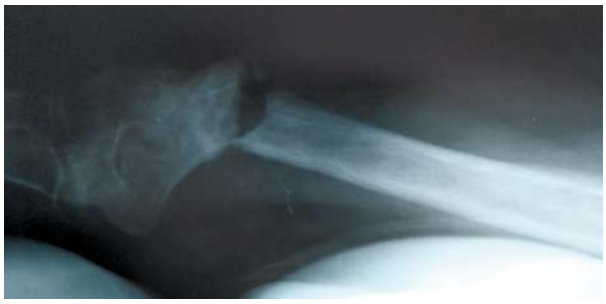

Fig. 6. Patient Sh. An X-ray of the right humerus. Pathological fracture.

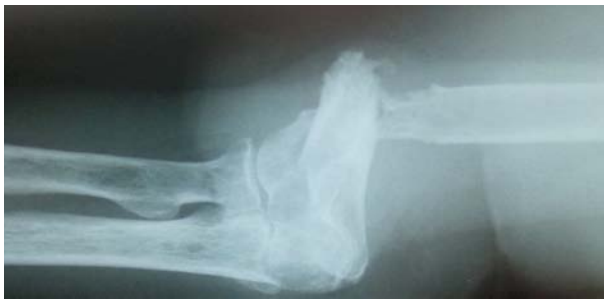

Fig. 7. Patient Sh. An X-ray of the right humerus, after PCT.

endoprosthesis in the ulna. A comprehensive examination confirmed remission of the disease. And in April 2019, the patient underwent a successful re-endoprosthesis of the right elbow joint. Currently, the patient is alive, and the limb function has been fully restored. The total follow-up time for the patient is 95 months.

DISCUSSION

The examined literature data and our own clinical experience confirm that primary bone lymphomas are an extremely rare form of lymphoproliferative diseases. many studies are based on a retrospective analysis of clinical material. We

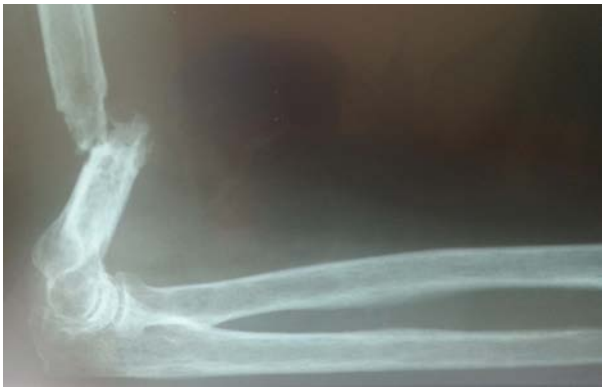

Fig. 8. Patient Sh. An X-ray of the right humerus, after PCT.

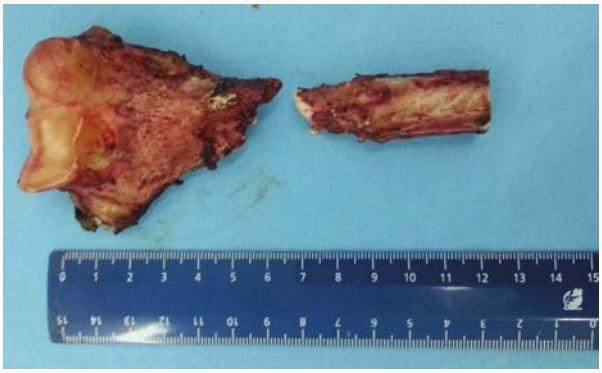

Fig. 9. Patient Sh. Removed gross sample of the right humerus.

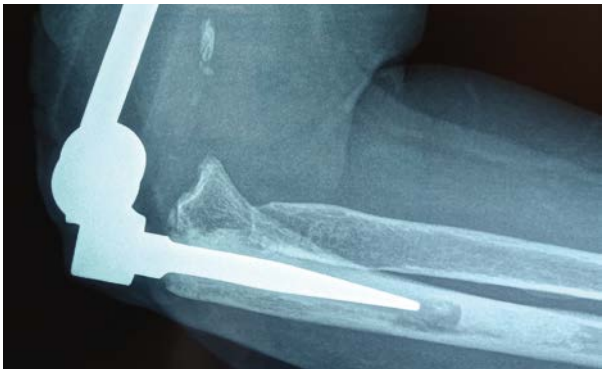

Fig. 10. Patient Sh. An X-ray of the right elbow joint after endoprosthesis (side projection).

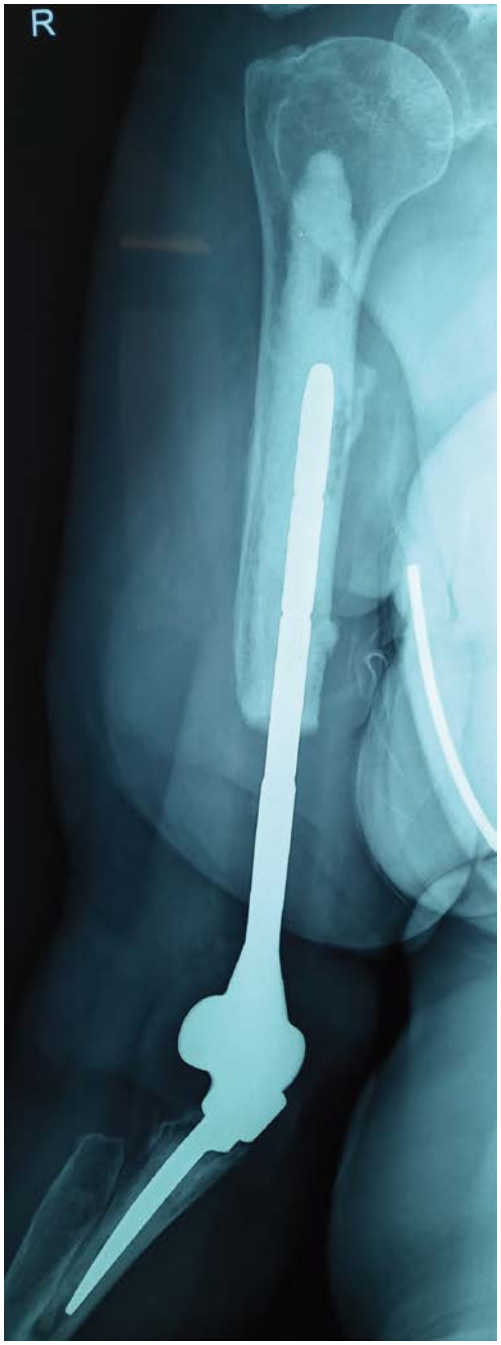

Fig. 11. Patient Sh. X-ray of the right elbow joint after endoprosthesis (front projection).

have seen only 4 cases of primary bone lymphoma in ten years. The General principles of diagnosis of this form of lymphoma are based on the principles of examination of all patients with oncohematological diseases. In determining the treatment tactics for primary bone lymphoma, the prevalence of the process and the immunohistochemical variant of the tumor undoubtedly play a dominant role. A number of researchers performed initial resection of the bone and soft tissue involved in the process, but faced the problem of rapid relapse. We can agree with other researchers that at this stage of disease development, surgical aggression is unnecessary and intervention should be limited to biopsy [2, 11].

Since all lymphomas, including primary bone lymphomas, are still highly sensitive to chemotherapy neoplasms, primary remission can be achieved in more than 80–95% of patients. Many researchers use CHOP-like regimens as basic therapy and achieve a 5-year event-free survival rate of 40–95%, depending on the prevalence of the initial process. This choice may be the main one in groups of patients with local bone damage, without risk factors. Colleagues from FGBU GNC of the Ministry of health of Russia widely use advanced stage lymphoma therapy using the intensive mNHL-BFM-90 program and achieve a 5-year relapse-free survival rate of 92% [5, 12, 13].

In our observation, a patient with an unfavorable subspecies of DBKL and a large spread of the process had a refractory course of the disease. Perhaps in patients with an initially unfavorable prognosis, more aggressive polychemotherapy tactics should be used. Patients with more favorable lymph immunotypes showed a better response to treatment and are still alive with a good quality of life. In our routine practice, we share the position of researchers who use consolidating radiotherapy in patients with primary bone lymphoma [3, 5].

Among the patients we observed, two patients underwent successful endoprosthesis due to existing pathological fractures and impaired function of the corresponding limb, which significantly worsens the quality of life. Our clinical experience allows us to recommend the use of this method of surgical treatment in patients in remission of primary bone lymphoma, as an option that restores the patient's vital needs.

CONCLUSION

Thus, if there is a suspicion of bone lymphoma, the patient should be examined using all available modern research methods to determine the extent of the tumor process, including PET research. Mandatory tumor biopsy with immunohistochemical examination. It should be noted that local bone damage often proceeds relatively favorably. If the limb function is impaired, the quality of life is unsatisfactory and there are clinical indications in the complex of treatment measures, and our experience confirms this, during the period of remission of the disease, surgical methods of therapy are used, in particular endoprosthesis to restore the quality of life of patients. The main method of therapy is polychemotherapy with targeted drugs for patients with advanced stages of bone lymphoma.

Authors contribution:
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