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– ORIGINAL PAPER –

# Etiological, Clinical, Diagnostic, and Treatment Particularities of Primary Aggressive Bone Lymphoma

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***Abstract***

*Primary bone lymphoma (PBL) is a neoplasm of malignant lymphoid cells that presents with one or more bone lesions without nodal or extranodal involvement. It accounts for approximately 7% of primary malignant bone tumors and can occur at any age, although it is most frequently diagnosed between 45 and 60 years, with a slight male predominance. The etiology of PBL remains unclear; however, several factors have been implicated in its development, including hereditary exostoses, AIDS, sarcoidosis, trauma, and bacterial or viral infections. The predominant histological subtype is diffuse large B-cell lymphoma. Most patients are diagnosed at stage IV, as the clinical presentation of PBL is generally nonspecific, often leading to delayed diagnosis. The most common symptom is localized bone pain in the affected area. Diagnosis requires a combination of histopathological and immunohistochemical examination. The treatment of PBL is based on systemic therapy, with current approaches including chemotherapy or immunochemotherapy with or without radiotherapy. Overall, PBL carries a generally favorable prognosis.*

***Keywords:*** *primary bone lymphoma, non-Hodgkin lymphoma, etiology, diagnosis.*

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## Introduction

Primary bone lymphoma (PBL) is a neoplasm of malignant lymphoid cells that presents with one or more bone lesions without nodal or extranodal involvement [1]. It accounts for approximately 7% of primary malignant bone tumors [2]. PBL must be distinguished from secondary bone involvement in systemic lymphomas, which occurs in 16–20% of lymphoma patients and carries a poor prognosis, whereas PBL is considered to have the most favorable prognosis among all primary malignant bone tumors [3]. PBL can occur at any age but is most commonly diagnosed between 45 and 60 years, with a slight male predominance. This form of extranodal lymphoma may develop in any part of the skeleton, although it most frequently involves the femur, humerus,

tibia, spine, and pelvis [4]. According to the literature, diffuse large B-cell lymphoma (DLBCL) accounts for the majority of PBL cases [5]. In many patients, diagnosis is delayed due to nonspecific clinical manifestations and equivocal radiographic findings. PBL generally has an excellent prognosis with multimodal therapy, primarily based on chemotherapy and radiotherapy. Surgery is reserved only for cases with skeletal complications [6].

## Objectives

To examine the incidence of aggressive primary bone lymphoma and to assess its etiological, clinical, diagnostic, and treatment characteristics, with the aim of identifying patients in the early stages of the disease, improving their quality of life, and increasing survival rates.

## Material and Methods

An analytical, qualitative study was conducted, including 140 patients with aggressive extranodal non-Hodgkin lymphoma at the Department of Hematology of the Oncology Institute in Chișinău, Republic of Moldova. The article involved both a review of the scientific literature and the processing of information obtained from the group of patients included in the research.

Patients were selected according to the inclusion criteria: age over 18 years, informed consent, and a histologically and immunohistochemically confirmed diagnosis. The collected data were subsequently processed using electronic computer-based evaluation techniques. Simultaneously, relevant literature was reviewed to compare and analyze the findings with those reported in international studies.

## Outcomes

In the studied group, PBL accounted for 7.1% (10 patients) of aggressive extranodal non-Hodgkin lymphomas (NHL). The mean age at diagnosis was 55 years, with the youngest patient being 39 years old and the oldest 83 years old. Contrary to the literature, which reports a male predominance [7], our study revealed a slight female predominance, with a male-to-female ratio of 2:3.

Although the etiology of PBL remains unclear, several factors have been implicated in its development. In our department, the following were identified: hereditary exostoses—5%, AIDS—5%, sarcoidosis—7%, and trauma—35%. According to the literature, additional factors that may contribute to the development of this lymphoma include bacterial and viral infections, particularly Epstein–Barr virus, previous bone implants, joint prostheses, Paget's disease of bone, environmental factors, and post-transplant immunosuppression [8]. The predominant histological subtype was diffuse large B-cell lymphoma (DLBCL), representing 70% (7 patients), followed by B-cell lymphoblastic lymphoma—20% (2 patients) and T-cell lymphoblastic lymphoma—10% (1 patient). The average time from symptom onset to presentation to a specialist was 5 months. Disease staging was established according to the Ann Arbor classification [Fig. 1] and the International Extranodal Lymphoma Study Group staging system for osseous DLBCL [Fig. 2]. Thus, 80% of patients (8 cases) were diagnosed with primary stage IV, while 20% (2 cases) were diagnosed in stage I. The clinical features of PBL are generally nonspecific, often leading to delayed diagnosis [9]. The most common symptom is localized bone pain in the affected area, observed in 100% of cases, which was not relieved by rest and was described as insidious, intermittent, and progressively worsening. Less frequent manifestations included soft tissue swelling—32%, palpable mass—18%, pathological fracture—12%, and restricted range of motion in the involved joint—11%. "B" symptoms, namely fever, night sweats, and unintentional weight loss, were observed in 2 patients (20%), while the remaining patients did not exhibit signs of systemic intoxication. Diagnosis of PBL is often delayed and requires combined histopathological and immunohistochemical examination. Although CT is the primary imaging modality for radiologically guided biopsy, MRI is the standard method for early detection [10]. Treatment of PBL is based on systemic therapy, with current approaches including chemotherapy or immunochemotherapy with or without radiotherapy [11]. In 90% of cases (9 patients) in the study, Rituximab was administered. The preferred regimen in the study group was R-CHOP in 80% of cases (8 patients), while the remaining patients received EPOCH or R-DHAP protocols. Radiotherapy was once the standard treatment for PBL, providing adequate local disease control, but it resulted in disappointing relapse rates, leading to the introduction of chemotherapy for better management of this neoplasm [12]. Accordingly, radiotherapy was indicated in 50% of patients (5 cases), administered in combination with chemotherapy. PBL generally has a favorable prognosis. In fact, it is considered to have the best prognosis among all primary malignant bone tumors and a better prognosis than secondary bone lymphoma [13]. Complete remission was achieved in 84.1% of cases.

**Stage:**

**I** – Involvement of a single lymph node region (I) or localized involvement of a single extralymphatic organ or site (IE)
**II** – Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single extralymphatic organ or site plus one or more lymph node regions on the same side of the diaphragm (IIE)
**III** – Involvement of lymph node regions on both sides of the diaphragm
**IV** – Diffuse or disseminated involvement of one or more extralymphatic organs, with or without lymph node involvement

***Fig. 1*** *Ann Arbor Classification*

**IE** – Single bone lesion
**IIE** – Single bone lesion with involvement of regional lymph nodes
**IVE** – Multifocal disease in a single bone or multiple bone lesions in disease confined exclusively to the skeleton (without lymph node or visceral involvement)
**IV** – Disseminated lymphoma with at least one bone lesion

***Fig. 2*** *Staging System for Osseous DLBCL by the International Extranodal Lymphoma Study Group (IELSG)*

## Conclusions

PBL affects the working-age population and can develop in any part of the skeleton. In most cases, the etiology remains unclear. The majority of patients are diagnosed at the advanced stage of the disease due to the nonspecific clinical presentation, which often leads to diagnostic confusion. PBL has a favorable prognosis, with complete remission achieved in 84.1% of cases.

**Ethics Statement and Conflict of Interest Disclosures**

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**Ethics Consideration:** The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws. Written informed consent was provided by all participants in this study.

**Conflict of interest:** No known conflict of interest correlated with this publication.

**Availability of data and materials:** The data used and/or analyzed throughout this study are available from the corresponding authors upon reasonable request.

**Competing interests:** The authors declared that they have no competing interests.

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