Belated Diagnosis of a Primary Bone Lymphoma of the Elbow: A Rare Case and Review of the Literature

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Keywords
Primary bone lymphoma · Elbow · Pseudoarthrosis · Bone biopsy · Chemotherapy

Abstract
Primary non-Hodgkin bone lymphoma (PBL) is a rare disease that accounts for <2\% of all lymphomas in adults. PBL can be monostotic or polyostotic, mainly causing destructive and lytic bone lesions frequently located in the femur, humerus, and pelvis. PBL is rarely considered a differential diagnosis of the osteolytic tumor. In addition, PBL is not uncommonly diagnosed with delay because patients do not experience symptoms nor show objective abnormalities in the early stage of disease. Here, we reported a 60-year-old woman with a PBL of the elbow.
Introduction

Primary non-Hodgkin bone lymphoma (PBL) is a rare disease that accounts for <2% of all lymphomas in adults [1]. Most primary bone marrow lymphomas are B-cell non-Hodgkin lymphomas, among which the diffuse large B-cell lymphomas predominate [2]. The definition of PBL varies within the literature. Generally, PBL is regarded as a malignant lymphoma arising within the medullary cavity of a single bone without nodal or visceral involvement. Accurate early diagnosis is crucial for treatment. However, it is not uncommon to diagnose PBL with delay because patients do not experience relevant symptoms frequently, nor do they show abnormal clinical signs in the early stage. These lymphomas are known to have a poor prognosis with a median survival of 14.9 months, and approximately 70% of patients die within 2 years despite receiving chemotherapy [3]. Here, we reported a 60-year-old woman with a PBL of the elbow initially misinterpreted as a fracture nonunion. The elbow itself is a very rare site for tumors, accounting for <1% of all bone and soft tissue neoplasms [4].

Case Report

A 60-year-old woman with no comorbidities was admitted to the Emergency Department of our institution due to persistent elbow pain after a direct trauma which had occurred 3 months before. The patient reported a direct fall onto the flexed left elbow but decided not to consult any physician at that time. Radiographs showed a possible nonunion of a previous untreated fracture of the olecranon (Fig. 1a, b). Since the actual presence of an osteolytic area could not be ascertained with radiographs, further radiological investigations were mandatory. MRI showed an area of altered signal with irregular margins in the olecranon. The lesion appeared hypointense both in spin echo T1 and T2 sequences and hyperintense in high-contrast sequences (Fig. 2a). After gadolinium administration there was a homogeneous enhancement of the signal (Fig. 2b), and MRI finally revealed an intraosseous tumor mass that caused a pathological fracture of the olecranon. Thus, a trocar biopsy was performed, and the final histologic diagnosis was a diffuse, large B-cell non-Hodgkin lymphoma with a high presence of surrounding T cells. The tumor cells stained positively for CD45, CD20, and CD79a but were negative for CD5 and CD30. CD3 was positive only in typical small lymphocytes near the lesion. The proliferation index (Ki-67) was about 25–30% in higher activity regions. The patient was therefore referred to the Oncology–Hematology Department. PET-CT showed the pathological lesion in the ulna and a suspicious lesion at the left inferior nasal concha. A biopsy confirmed the same histology in the skull. The disease was only skeletal and extranodal (stage IVA) and the patient started a chemotherapy protocol (R-CHEOP) with complete response. Four years later she still suffered from persistent pain; resection of the affected bone and reconstruction of the elbow was proposed, but the patient refused. One month later an axillary lymph node was biopsied, showing relapse of disease. PET-CT showed multiple nodal involvement and tumor recurrence of the olecranon. Due to religious conviction, the patient refused autologous (self) stem cell transplantation and started a second line of chemotherapy with R-Bendamustine. External radiotherapy was performed at the elbow and the axillary region. After therapies, PET-CT showed no sign of disease. At the time of manuscript submission, the patient had reached 7 years of follow-up. There was no evidence of disease and the patient
complained of only slight elbow pain (VAS score 2/10) with good residual function. She demonstrated a lag of 5° in elbow extension, while flexion and pronosupination showed full range of motion. Daily consumption of pain killers was not needed.

Discussion and Conclusion

Non-Hodgkin lymphoma presenting as primary isolated bone marrow involvement is extremely rare, although it has been described in the literature since the 1970s [2]. The criteria for diagnosing lymphoid neoplasia in the bone marrow as PBL are well described in the literature [5] and reported in Table 1. PBL is defined as an intramedullary tumor without evidence of nodal disease for at least 6 months after initial presentation in the bone [6, 7] and can affect a broad range of patients, with a peak of prevalence at the 6th and 7th decades [8]. Clinically it manifests with insidious and intermittent bone pain that can persist for months. Other signs and symptoms include local swelling or tenderness, a palpable mass, and presence or absence of systemic symptoms such as weight loss and fever. The epiphyses of long bones are seldom affected, and the ulna is indeed very rarely involved [6, 7]. In plain radiographs three different patterns are described: a lytic-destructive pattern is the most frequent, followed by a blastic-sclerotic pattern and a subtle pattern with "near-normal" findings [6]. As reported in the clinical case described above, the pathological fracture, based on clinical and radiographic characteristics, was initially misinterpreted as a pseudoarthrosis of the ulna in a previously untreated trauma. Suspicion of a subjacent oncologic disease is crucial and brought to the execution of MRI, which is essential to obtain a correct diagnosis and to drive the correct treatment. MRI demonstrates bone marrow changes revealing hypointense areas in T1-weighted sequences and hyperintense in T2-weighted sequences compatible with a neoplastic lesion. STIR sequences confirm an abnormal signal within the marrow. The low intensity of the signal in spin echo T2 sequence is related to the entity of intralesional fibrosis [8–12]. Peritumoral edema, cortical erosion, as well as soft tissue and joint involvement are frequently associated, mostly with most aggressive pattern lesions. Almost all of them, but specifically this last pattern, benefit from MRI study to demonstrate the extension of the lesion [8–12]. The standard CT protocol (including the use of a low pitch setting, a high tube current, and high peak kilovoltage during acquisition and the use of wide and narrow window setting for bone and soft tissue study) allows for a more precise assessment of the osteolysis involving the medullary bone. It also may reveal mild periosteal reaction and intralesional calcifications. CT is useful to evaluate the lesion before chemotherapy or radiotherapy and it can even guide a biotic procedure [12]. The usual appearance of primary bone lymphoma on FDG-PET scanning is that of a focal hypermetabolic lesion [9], even if there are few reports on the initial diagnosis of PBL using FDG-PET or PET-CT scanning [10]. However, several studies have demonstrated PET-CT scanning to be an effective modality for evaluation after therapy, particularly in documenting treatment response. PET-MRI has shown encouraging results in early studies [11]. MRI sequences can help characterize changes in the cellular content of lesions, particularly using diffusion-weighted imaging sequences and MRI spectroscopy.
Differential Diagnosis

Regarding diagnosis, it is crucial to remember that various radiographic findings can mimic bone and soft tissue tumors and vice versa. Whenever approaching diagnosis, it is critical to consider other malignant lesions (such as osteosarcoma, fibrosarcoma, metastatic disease, secondary osseous lymphoma, multiple myeloma, and Ewing sarcoma) [12], and also to prescribe more advanced radiological examinations and refer the patient to the reference center for eventual biopsy and multidisciplinary treatment. Osteosarcoma usually affects younger people, but in metaphyseal localizations the imaging characteristics can be misinterpreted. Solitary metastatic disease generally presents as a more aggressive osteolytic lesion than primary bone lymphoma. Fibrosarcoma determines an osteolysis with moth-eaten margins and is seldom associated with periosteal reaction. Myeloma can be similar to primary bone lymphoma as to radiological aspects, but serological examination can be diagnostic in most cases. Clinical and biological data help in the diagnosis of chronic osteomyelitis.

Prognosis

The diagnosis of PBL is often delayed, leading to a poor prognosis and a median overall survival of <18 months [1–3, 5]. Therefore, it is essential that hematologists recognize patients with underlying primary bone marrow lymphoma at an early stage [5]. A biopsy of the lesion should be performed in any doubtful case [8, 12].

Treatment

Little is reported about surgical procedures, even if surgery does, in some cases, become necessary for fractures or impending fractures. An incidence of orthopedic surgical procedures other than biopsy ranging from 13.8 to 26% [13, 14] or even 47% [15] is reported, but most papers either do not mention incidence or type of surgery [16–22] or report incomplete data about the surgery performed [23, 24]. Marshall et al. [25] stated that surgery in patients with PBL is indicated for biopsy, prophylactic fixation of impending fractures, treatment of fractures before or after radiotherapy and systemic therapy, and theoretically in patients with disease unresponsive to conventional therapy. Scoccianti et al. [26] reached the same conclusions. In their opinion surgery should be limited to a very select subset of patients; also, lesions at fracture risk can often successfully heal with chemotherapy and radiotherapy, without surgical treatment, with rest and no weight bearing. In the upper limb, considering the minor disability achievable with the use of a brace, delayed surgical treatment can be adopted, allowing immediate chemotherapy and radiotherapy treatment. Resection and reconstruction with an allograft or a modular prosthesis may have a role in bigger and solitary lesions in long-surviving patients. Timing of surgery is another controversial issue. Many authors believe that surgery should be postponed as long as possible in order to prevent delaying medical treatment. In this concept, treating pathological fractures can also be delayed after chemotherapy and radiotherapy if fracture location and patient conditions make it possible, as when dealing with fractures of the upper limb, where immobilization with a sling or bandage does not cause a major impairment in quality of daily living. Some authors report an increased incidence of fractures after radiotherapy [27, 28], and this could lead to a preference for early stabilization of the affected bones.
Conclusion

Surgical treatment in primary bone lymphomas should aim to restore function and eliminate pain while minimizing potential delays in chemotherapy initiation. Even though this is a disease with a poor prognosis, it is possible to deal with long-surviving patients. Hence, it is crucial to suspect this kind of lesions when clinical and radiographic examinations are not sufficient for diagnosis. An immediate indication for more advanced imaging and histology could lead to prompt diagnosis, and the patient could benefit from therapy sooner.

Acknowledgment

The authors would like to thank the Fondazione per la ricerca sui tumori dell’apparato muscoloscheletrico e rari Onlus, which provided support for all phases of this study.

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The subject gave her written informed consent to publish her case (including publication of radiological images). All information was anonymized.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors received no funding to sponsor this study.

Author Contributions

All authors have made substantive contributions to the research and the preparation and revision of the manuscript.

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**Fig. 1.** a, b Plain radiographs of the left elbow showing a fracture of the olecranon with signs of nonhealing with normal density of the peripheral soft tissue. Also, a subtle osteolytic area could be suspected in the proximal aspect of the ulna in both planes.
Fig. 2. a Sagittal spin echo T1-weighted MRI. b Sagittal spin echo T1-weighted MRI after gadolinium contrast injection. A diffuse, moderately heterogenous contrast enhancement providing a good differentiation between bone and lesion can be appreciated.

Table 1. Diagnostic criteria for primary non-Hodgkin bone lymphoma (adapted from [5])

| Pathologically confirmed bone marrow infiltration with NHL ± peripheral blood involvement | No evidence of lymph node involvement (>1 cm on imaging studies) |
| --- | --- |
| Absence of tumor formation | Exclusion of leukemia cases with primarily bone marrow involvement |
| Exclusion of lymphoma cases with primarily bone marrow involvement | NHL, non-Hodgkin lymphoma. |