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Tumour Review

Primary and secondary bone lymphomas

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ABSTRACT

Recent studies have contributed to the enhancement of clinical and molecular knowledge on bone lymphomas, a group of rare malignancies with particular characteristics. Nevertheless, several questions remain unanswered and the level of evidence supporting some diagnostic and therapeutic decisions remains low. Currently, three different forms of bone lymphomas can be distinguished: the primary bone lymphoma, consisting of a single bone lesion with or without regional lymphadenopathies; the polyostotic lymphoma, consisting of multifocal disease exclusively involving the skeleton; and the disseminated lymphoma with secondary infiltration of the skeleton. The first two forms exhibit a good prognosis, requiring treatments similar to those commonly used for nodal lymphomas of the same category, but several issues regarding the role of surgery and local control of the disease, the sequence of treatment, radiation volumes and doses, management of pathological fractures and prevention of late sequelae deserve particular attention. Due to its rarity, prospective trials exclusively focused on bone lymphomas appear unrealistic, thus, critical revision of our own experience and analyses of large cumulative series as well as molecular studies on archival cases remain valid alternatives to improve our knowledge on this obscure lymphoproliferative malignancy.

The present review is based on the analysis of the largest available database of bone lymphomas established under the sponsorship of the International Extranodal Lymphoma Study Group (IELSG) as well as on the critical revision of related literature. We provide recommendations for diagnosis, staging, treatment, and response assessment of these patients in everyday practice as well as for the management of special conditions like pathological fractures, indolent forms and central nervous system prophylaxis.

Introduction

Every lymphoma category can involve the skeleton, as an exclusive lesion or as a part of a disseminated disease. Although skeletal involvement is relatively common in non-Hodgkin lymphomas, the available literature on diagnostic and therapeutic management of primary bone lymphomas, that is lymphomas exclusively involving the skeleton, is sparse and fragmentary, mostly reported before worldwide use of rituximab and positron emission tomography (PET). The level of evidence supporting therapeutic decisions in primary bone lymphomas is very low as no prospective trials have been published. The relevant literature is almost exclusively constituted by small, retrospective series often furnishing conclusions on unreliable subgroup analyses, and with important interpretation biases due to stage migration and use of obsolete histopathological classifications. An additional bias regards the use of radiotherapy as exclusive treatment in unfit patients, whereas recent advances in supportive care have extended the number of patients treated with curative intent. As a consequence of these methodological caveats and the impossibility of conducting large prospective trials, several therapeutic questions remain open: the role of surgery and radiotherapy, the best radiation volumes and doses, the most effective chemoimmunotherapy combination, and prognostic factors, among others. In this complicated context, large, retrospective studies of cumulative, unselected series remain a valid tool to improve our knowledge on primary bone lymphomas.

This review is based on the analysis of the largest available database of bone lymphomas, established under the sponsorship of the International Extranodal Lymphoma Study Group (IELSG),

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as well as on the critical analysis of related literature. It provides recommendations for the diagnosis, staging, treatment, and response assessment of these patients, and addresses the management of special conditions like pathological fractures, indolent bone lymphomas and CNS dissemination risk in everyday practice.

Definition, incidence and epidemiology

Criteria used to define and classify primary bone lymphomas changed several times in the last decades. While there is general agreement that cases with a solitary lesion arising in a bone should be considered as a primary bone lymphomas, there is no consensus over the best categorization of cases with multifocal osseous disease or cases with concomitant soft tissue, visceral and/or lymph nodal infiltration [1–5]. In the previous version of the World Health Organization (WHO) classification of tumours of soft tissue and bone, primary bone lymphoma was defined by (1) a single skeletal tumour without regional lymph node involvement, or by (2) multiple bone lesions without visceral or lymph node involvement [6,7]. Conversely, the last versions of the WHO Classification does not provide definition criteria for these disorders [8]. The opinion of the authors is that only cases with a clear bone origin should be considered as primary bone lymphomas, that is, primary bone lymphomas should include cases with a single bony lesion, with or without involvement of regional lymph nodes as well as cases with multiple bony lesions, but without lymph nodal or visceral disease. The latter subgroup is usually called "multifocal osseous lymphoma" or "polyostotic lymphoma", and represents an entity with particular clinical and prognostic characteristics [9]. Disseminated lymphomas with concomitant involvement of the skeleton should be defined as "secondary bone lymphoma". In these cases, bone involvement counts as a systemic extra-nodal site and the disease should be considered to be stage IV [10]. A lymphoma that has arisen in soft tissues, lymph nodes or other organs and infiltrates an adjacent bone secondarily should not be considered to be a primary bone lymphomas. However, this is a common issue in many types of extranodal lymphomas and, similarly, in bone lymphomas the differences are not so clear cut in practice and it may be very difficult to separate these two situations. Special difficulties arise in specific anatomical locations; for instance, it is difficult to distinguish lymphomas primarily arising in nasal-paranasal bones from lymphomas arising in the mucosal surfaces of paranasal sinuses. Similarly, it is often difficult to distinguish the primary site of disease in lymphomas of the spine (i.e., bone or nearby soft tissues) [7]. In many cases, a subjective judgement will be required about whether a case should be categorised as primary bone lymphomas or lymphoma secondarily affecting the bone.

The exact incidence of primary bone lymphomas is difficult to define, but it seems to account for about 5% of extranodal lymphomas, <1% of all non-Hodgkin lymphomas (NHL), and 3–7% of all malignant bone tumours [2,6,11]. Most reports suggest a slight male prevalence (male/female ratio: 1.5), with a median age at diagnosis ranging between 45 and 60 years old, and a wide range (15–99 years); paediatric cases have been also reported [12–14]. No racial or geographic predominance has been demonstrated.

Primary bone lymphomas have been reported in association with some specific conditions including HIV infection [15,16], sarcoidosis [17], Gaucher disease [18,19], hereditary exostoses [20], Paget's disease [21], osteomyelitis [4], and following some specific treatments including hip replacements [22,23], renal transplants [24], and cladribine therapy [25]. However, none of these putative associations are consistent enough to suggest a true relationship or predisposition towards the development of primary bone lymphomas.

Clinical presentation

Table 1 summarizes the main patient characteristics at presentation reported in the largest available series of bone lymphomas [9,26]. Although the tumour itself can affect fitness, particularly if it occurs in weight-bearing bones, most patients have ECOG performance status of 0–1. Pain is the most common presenting symptom (80–95%), tumour mass is present in 30–40% of cases and pathological fracture in 15–20%, with a mean duration of the period between symptoms and diagnosis of 8 months [11]. Most patients have an early-stage disease at presentation [27]. Every bone is a potential site for lymphoma development, but the femur is the most commonly affected [4]. Lymphomatous lesions occur most often in the diaphysis, whereas metaphysis and epiphysis involvement often reflects progressive disease [28]. Small bones of the hands and feet are rarely involved. Spinal cord compression is the first presenting complication in 16% of cases [29]. Pelvic bones seem to be more commonly involved in Japanese studies, but these series were mostly constituted by patients with disseminated lymphoma [30]. Osteolysis and hypercalcemia are observed in 5–15%, of patients, mostly related to progressive disease. Symptoms related to hypercalcemia, such as constipation, lethargy and somnolence are uncommon.

Radiographic findings

Radiographic findings of primary bone lymphomas are usually non-specific, with important limitations to distinguish lymphomas from other primary bone tumours like Ewing's sarcoma, osteogenic sarcoma and chondrosarcoma. On plain films, lesions are mostly lytic, but half of the patients have also osteoblastic lesions, and both patterns can coexist, even in the same bone [28]. The bone cortex shows a mixture of permeative, moth-eaten or destructive patterns. The periosteum often shows reactive changes, and features usually occurring in osteosarcoma, like onionskin layering, breach of the periosteum or sunburst appearance, can be occasionally recorded in primary bone lymphomas.

Table 1
Patient's characteristics at presentation in the IELSG-14 series.

	Limited stage DLBCL (n = 161)	MB-DLBCL (n = 37)	Stage IV DLBCL (n = 63)
Males	51%	59%	40%
Median age; years (range)	55 (18–99)	53 (17–75)	62 (28–83)
Clinical presentation (%)			
ECOG-PS > 1	15%	38%	62%
High LDH serum level	34%	30%	65%
B symptoms	9%	24%	30%
Pain	82%	92%	90%
Swelling	40%	45%	34%
Bulky disease	23%	15%	32%
Fracture	15%	25%	29%
Sites of involvement (%)			
Skull	15%	32%	19%
Spinal cord	17%	65%	51%
Pelvis	17%	32%	33%
Humerus	7%	13%	17%
Forearm	7%	16%	8%
Femur	20%	38%	24%
Forefoot	13%	19%	14%
Lymph nodes	–	–	28%
Cerebrospinal fluid	–	3%	1%
Bone marrow	–	–	35%
Other	4%	–	–

DLBCL = diffuse large B-cell lymphoma; MB-DLBCL = multifocal bone diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group Performance Status; LDH lactate dehydrogenase.