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Supplement Article

X. Extra-nodal lymphoma in rare localisations: bone, breast and testes

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Introduction

There are many reasons why the study of extra-nodal lymphomas is a priority. They can be present with specific clinical syndromes and concomitant disease associations where familiarity aids prompt diagnosis of both the lymphoma and the associated diseases, the epidemiology and pathogenesis are often specific or even unique for that disease site—histological and molecular disease characteristics, and disease behaviour, natural history and prognosis are site-specific—and ultimately optimal treatment needs to be individualised by the organ of origin. Historically, many of the entities now classified under the broad label of 'primary extra-nodal lymphomas' had other labels. However, these are now all considered within the current World Health Organization (WHO) framework, and WHO terminology should be used for clarity and precision.

General principles in the aetiopathogenesis of extra-nodal lymphomas

A reproducible aetiologic association of many forms of extra-nodal lymphoma is that of an underlying state of chronic immunologic activation. Although recent years have seen clarification of a number of novel associations [e.g. *Campylobacter jejuni* and immunoproliferative small intestinal disease, *Chlamydia psittaci* and ocular adnexal lymphoma and hepatitis C and splenic marginal zone lymphoma (MZL)], the putative initiating antigenic stimulus remains undefined for many of the more common extra-nodal lymphomas, including those of the breast, testis and bone. It could be postulated that the immune activation frequently associated with extra-nodal lymphomas may lead to a skewing of the proportion of 'activated B-cell' (ABC) to 'germinal-centre' B-cell types among cases of diffuse large B-cell lymphoma (DLBCL); although there are individual organ instances of such [e.g. primary central nervous system (CNS) lymphoma], there are insufficient data to yet state that this is a generalisable phenomenon.

As mentioned, a reproducible feature of many forms of extra-nodal lymphoma is the propensity for involvement of the contralateral paired organ, as well as a strong predisposition for relapses to involve the tissue type or organ of origin. As well as being an important factor to consider in treatment choice [i.e. loco-regional irradiation proportionately plays a greater role than in other non-Hodgkin lymphoma (NHL) types], this should also inform surveillance procedures of patients in remission. There are a number of potential explanations for this phenomenon, including the persistence of the driving trophic stimulus or initiating causative organism (e.g. poor dietary control in celiac disease or failure of *Helicobacter pylori* eradication), organ-restricted chemokine expression or the expression of tissue-specific homing receptors. The best studied example of the latter concept is that of cutaneous T-cell lymphomas, but it is not known which such mechanisms underlie the tissue-specific propensity of most extra-nodal B-cell lymphomas.

Primary testicular lymphoma (PTL):

Primary testicular lymphoma comprises 1–2% of all cases of NHL and <5% of all testicular malignancies but with this proportion rising steeply with increasing age, such that it is the most frequent form of testicular tumour in men over 50 years of age. The typical presentation of PTL is of a unilateral sub-acute progressive painless scrotal swelling, often accompanied by a hydrocoele in an older man (median age at diagnosis is 67 years). The presence of systemic symptoms almost always signifies disseminated disease. Regional (para-aortic) nodal involvement is present in 20–30%, and bilateral testicular involvement (usually subclinical) is present in ~10% but should be specifically sought during imaging and staging. Inguinal orchiectomy is the preferred diagnostic (and

therapeutic) procedure with the consideration of blind biopsy of the contralateral testis. Staging procedures should include routine CNS imaging, and cerebrospinal fluid (CSF) cytology and flow cytometry, given a propensity for CNS involvement, even when apparently clinically localised and low volume, as well as HIV serology [1–3].

More than 90% of PTLs are DLBCL, with the remainder comprising Burkitt lymphoma, often in HIV + patients, rare T-cell lymphomas and the rare but distinct syndrome of primary follicular lymphoma (FL), typically histological Grade 3 lacking Bcl-2 expression and the *t*(14;18), in paediatric patients. This entity of 'paediatric FL' is important to recognise as despite the histological appearance, such cases tend to follow a more indolent clinical course and if localised, appropriate initial management is usually excision and abbreviated chemotherapy or observation [4]. Histologically, the typical PTL of DLBCL often lacks HLA-DR and HLA-DQ expression, suggesting that immune evasion plays a role in their development and is of ABC-type by immunohistochemical profiling in >90% of cases. Some DLBCL may arise from the transformation of a clinically occult MZL, but MZL as the sole histology at presentation is very rare [5,6].

Historically, patients with PTL often received inadequate intensity systemic treatment because of the lack of understanding of the aggressive natural history, the lack of significant curative potential for loco-regional therapies used alone and the propensity for wide-spread systemic dissemination and very poor prognosis at relapse. Large historic series in the pre-rituximab era described a median survival of 12–24 months, and 5-year survival rates of 15–50% with a characteristic temporal pattern of frequent relapse within the first 2 years, but ongoing relapse risks out beyond 10 years with the contralateral testis involved in up to 40% of patients in the absence of prophylactic irradiation. Other distinctive patterns of relapse include the CNS, both leptomeningeal and parenchymal in equal proportions in 20–35% of cases in the absence of effective prophylaxis. Systemic sites of relapse are often extra-nodal and involve soft tissues such as skin and lung, and once manifest, relapsed disease has a very poor prognosis and is rarely curable [1–3].

In the absence of any randomised trials, these observations underlie the current treatment recommendations, derived from the IELSG10 prospective Phase-II study of 53 patients: six cycles of rituximab with chemotherapy (R-CHOP), contralateral testicular irradiation and CNS prophylaxis, ideally with both IT treatment as well as systemic delivery of high-dose antimetabolite, which has the ability to penetrate the CNS parenchyma, such as cytosine arabinoside or methotrexate. With IT treatment alone, CNS relapse still occurs in 10–25% of patients, mostly parenchymal, and is thus insufficient as a sole CNS-directed modality. The best agent, dose and schedule of systemic treatment for CNS prophylaxis are unclear. Some investigators have used high-dose cytosine arabinoside, but this is poorly tolerated in the elderly population, and there is also substantial encouraging experience for CNS prophylaxis in other forms of DLBCL by using methotrexate in renally adjusted doses 1.5–3 g/m^2. Regional irradiation to involved para-aortic nodes is effective in achieving local control at this site, but the impact on overall survival in the context of optimal systemic therapy is unclear. Its use is certainly warranted in patients with Stage II disease who are unable to tolerate optimal systemic therapy. With the delivery of such 'optimal' multimodality programmes, recent series have described 5-year progression-free survival (PFS) and overall survival (OS) rates of 75% and 85%, respectively [7].

Primary breast lymphoma (PBL):

Primary breast lymphoma is even more rare than PTL, comprising ~1% of all cases of NHL and <0.5% of breast malignancies. PBL includes a number of distinct clinicopathological syndromes:

1) Burkitt- or Myc-rearranged BLBCL, often bilateral occurring during pregnancy or lactation (<5% of PBL) [8],
2) Anaplastic lymphoma kinase-negative anaplastic large cell lymphoma of T-cell lineage associated with breast implants and chronic seromas, which have a favourable prognosis (<5% of PBL), [9,10]
3) 'Indolent' NHL presenting the breast, typically in older women (in aggregate ~25% of PBL, comprising 10–15% follicular NHL and 8–10% MZL) [11] and
4) DLBCL presenting a painless breast mass+/−axillary nodal enlargement (~70% of all PBLs of which ~80% are of ABC subtype) [12,13].

Beyond the obvious aetiologic links of the first two entities, there are no clear causative factors known for most cases of PBL, and imaging features are not sufficiently specific to reliably distinguish PBL from other pathologies, mandating diagnostic biopsy, ideally with an image-guided core, as fine-needle aspiration cytology is inadequate to allow robust subclassification. In all of the categories of PBL, there is a propensity for bilateral involvement, and initial staging must include careful imaging of the contralateral breast, ideally with at least two modalities as no one platform [mammography, ultrasound, MRI or positron-emission tomography (PET)] has perfect sensitivity. The 'low-grade' histological entities appear to have a favourable natural history equivalent to other localised indolent lymphomas, with the exception of a modest propensity for involvement or relapse in the contralateral breast in 5% and 10% of cases, respectively. The approach to management resembles that of other localised indolent NHL, with reliance on loco-regional irradiation as the primary treatment modality, which is highly efficacious, achieving durable local control in >90% of patients.

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Patients with PBL presenting as DLBCL are female in 98% of cases (median age 64 years) and typically present with a painless progressively enlarging unilateral breast mass (median 4 cm but can be occasionally massive, up to 20 cm in diameter) with clinically evident regional (usually axillary) nodal enlargement in ~10% of cases but nodal involvement on formal staging in ~30%. Performance status is typically well maintained and bilateral involvement evident in ~5%. CNS involvement at presentation is relatively common in Burkitt histology but present in <10% of cases with DLBCL but should be formally sought as part of initial disease staging. There is no therapeutic role for extensive surgical de-bulking beyond diagnostic biopsy. Optimal therapy includes at least three (and probably six to eight) cycles of R-CHOP chemotherapy and at least 'limited' loco-regional irradiation, encompassing the whole ipsilateral breast and axillary nodes. The optimal extent of irradiation is unclear, with some data supporting a role for more extensive irradiation including the supraclavicular nodes and contralateral breast in addition to the aforementioned 'limited' field.

The pattern of relapses reported in retrospective series is useful to consider, informing primary management decisions. In most series, relapses predominate in the ipsilateral breast (if not irradiated), contralateral breast in 10–12% and the CNS (both leptomeningeal and parenchymal) in 8–10% of cases, more commonly in those with bilateral disease at presentation (who also have a worse overall prognosis, and 3-year PFS and OS rates of 36% and 46%, respectively). This risk of CNS relapse is intermediate between an unselected population and true 'high-risk' subsets such as those with PTL but probably warrants specific prophylaxis in younger patients treated with curative intent, given the lack of curative options for patients who relapse (median survival <12 months), especially for those with CNS involvement at relapse. Patients treated with such an 'optimal' multimodality treatment approach appear to have a relatively favourable outlook that is not markedly different from prognostically matched patients with limited stage nodal DLBCL, 5-year PFS rate of ~80% and median OS of ~15 years.

Primary lymphoma of bone (PLoB)

Primary lymphoma of bone is a more heterogeneous and less well described entity than the other forms of extra-nodal lymphoma discussed. It comprises ~5% of all primary bone malignancies and also ~5% of extra-nodal lymphomas. The distribution of primary lesions within the skeleton appears to reflect the distribution of hemato-poietic marrow, suggesting that this may be the true tissue of origin. However, there is clearly a tissue trophism for osseous tissue as there are many cases, which present as multiple anatomically separate bone lesions, and there is a clear propensity for osseous involvement at relapse, which must be considered if any surveillance imaging is planned. Frequent fibrosis and crush artefact are common in diagnostic biopsies and as large a core as are felt safe, given that the risk of structural compromise of the involved bone is indicated to establish the diagnosis. The majority of cases of PLoB is DLBCL histologically, but infrequent cases of indolent histologies (FL and MZL) are well documented. The rare but distinct entity of B-cell lymphoblastic lymphoma presenting as an isolated primary bone lesion needs to be remembered, as such patients require more intensive systemic and CNS-directed therapy appropriate for their histology. In contrast to the other entities discussed, GC type disease comprises at least 50% of cases of PLoB [14].

A typical presentation is that of a progressive painful radiologically destructive and expansile bone lesion, at times with associated pathological fracture in 10–20% (which appears to be associated with a somewhat adverse prognosis). The median age is in the mid-60s but with a wide distribution and slight male predominance; both of these features reflect the epidemiology of DLBCL generally. Preservation of the mobility and maintenance of the performance status of the patient are high priorities during the initial evaluation, and urgent structural fixation may be required, which also facilitates the acquisition of appropriate diagnostic specimens. Imaging features can suggest lymphoma but are not specific. MRI will usually demonstrate more extensive infiltration than what is evident on other structural imaging modalities, and PET scanning relatively frequently demonstrates other anatomically disparate osseous lesions [15].

Historical series have consistently demonstrated that radiation therapy (RT), typically delivered to the whole of the involved bone, can achieve local control in >80% of cases, but systemic relapse occurs in >50% of such patients treated with RT alone, and thus, single-modality RT is no longer considered an optimal therapy. Systemic R-CHOP chemotherapy is recommended, and if it can be delivered with acceptable short-term and long-term morbidities, local RT probably improves 5-year PFS by ~10% and is recommended. This is especially so for those patients who present with pathological fracture where local control is inferior and in those cases where local recurrence would pose specific risk to structural integrity or threaten critical organ function. There is no particular indication of CNS prophylaxis in PLoB unless the involved site is anatomically proximate to the meninges, for example, base of the skull or the vertebrae with substantial soft tissue extension.

A specific issue in PLoB is the difficulty in assessing the adequacy of treatment response. CT scans can show regression of soft-tissue masses and restoration of cortical bone but are insensitive to residual disease. Conversely, MRI, gallium and PET scans all typically demonstrate persisting abnormalities post-treatment. The residual PET uptake appears to reflect bone healing and does not carry the adverse prognostic impact of such findings post-treatment at other sites [16]. Re-biopsy is fraught with sampling issues, and if there is doubt, I prefer serial imaging at a 6–8-week interval.

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The overall prognosis for a patient with PLoB is favourable, and at least comparable with prognostically matched cases of primary nodal DLBCL. A large series from Memorial Sloan Kettering Cancer Center (MSKCC) described 5-year PFS and OS rates of 81% and 88%, with a 5-year cause-specific survival of 96%, illustrating that with contemporary treatment approaches, few patients die of their disease, and many of those who do relapse can be effectively salvaged [17]. Given this favourable outlook, it has proven difficult to identify reproducible and meaningful prognostic factors for PLoB. Of the ~20% of patients who do manifest recurrent disease, there is a predisposition, albeit difficult to quantify, for osseous involvement. Thus, if any surveillance imaging is planned, a modality that is sensitive to such bone lesions, such as PET, should be used.

Conflict of interest

The author has no conflicts of interest to declare.

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