

Extranodal lymphoma: a reappraisal

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primary extranodal presentations of non-Hodgkin lymphoma

Approximately one-third of non-Hodgkin lymphomas (NHLs) arise primarily from sites other than lymph nodes, spleen or the bone marrow and even from sites which normally contain no native lymphoid tissue [1, 2]. Indeed, extranodal lymphomas can arise in almost every organ [1, 2]. However most of the presentations appears to be clustered in a few sites: skin, stomach, brain, small intestine and—when included in the reports—the Waldeyer's ring [3, 4].

The extranodal lymphomas represent a challenge in routine lymphoma diagnosis, due to the variety of histological types, molecular abnormalities and clinical pictures that can be present. Correct diagnosis and appropriate treatment of extranodal lymphoma are also complicated by the relative rarity of many of these tumours. Moreover, in comparison with nodal presentation, B- and T-cell lymphomas diagnosed at extranodal sites may have quite different outcomes and may frequently require different therapeutic approaches due to specific organ-related problems.

The definition of primary extranodal lymphoma is controversial, particularly in the presence of both nodal and extranodal disease. Strict criteria were first proposed in 1961 by Dawson, who defined primary gastric lymphoma as presentation with main disease manifestation in stomach, with or without involvement of regional lymph nodes. Later these criteria were extended to allow for contiguous involvement of other organs (e.g. liver, spleen) and for distant nodal disease providing that the extranodal lesion was the presenting site and, after routine staging procedures, constituted the predominant disease bulk, to which primary treatment must be directed [3].

The inclusion among primary extranodal lymphomas of cases presenting with stage III and IV is also questionable and several authors consider only stage I and II presentation as primary extranodal disease. Since many extranodal lymphomas have the potential to disseminate, this approach may, however, lead to an imperfect representation. On the other hand, extranodal involvement in a disseminated disease may represent a secondary spread. Any chosen definition inevitably introduces a selection bias; in a recent Dutch study the frequency of extranodal NHL fluctuated from 20% to 34% depending on the definition criteria adopted [5].

The incidence of extranodal NHL in Western countries has increased substantially in the last 40 years [4, 6]. This may in part be due to improved diagnostic procedures (particularly in brain and gastrointestinal lymphomas) and changes in classification systems, but much of the change is real and the AIDS epidemic in the 1980s does not completely explain this rise [4]. The aetiology of extranodal lymphomas appears to be multifactorial and includes immune suppression, infections, both viral and bacterial, and exposure to pesticides and other environmental agents. Nevertheless, despite the considerable progress made in the understanding of MALT lymphoma and its relationship to bacterial infections [7], the precise cause of most lymphoid neoplasms remains unknown [1–3].

The proportion of NHL presenting at extranodal sites comprises 25–50% of new lymphoma cases with important geographic variations that may be explained by the variability of the reporting criteria (variable definitions of primary extranodal disease) as well as by different types of data source (referral cancer centres versus tumour registry). True geographic differences are, however, present, for example, the incidence of Epstein–Barr virus and human T-cell lymphotropic virus 1-associated T-cell lymphomas is higher in Asia than in Europe and North America.

The histological spectrum of extranodal lymphomas somehow differs from that of nodal lymphomas. Nearly half of the extranodal cases are of diffuse large cell histology. Aggressive subtypes, mainly diffuse large B-cell lymphomas (DLBCLs) are predominant in NHL of central nervous system (CNS), testis, bone and liver while in the gastrointestinal tract a large spectrum of histological disease entities can be seen, comprising DLBCL, MALT lymphoma (including the immunoproliferative small intestinal disease), Burkitt's lymphoma, enteropathy-associated T-cell lymphoma, mantle cell lymphoma and follicular lymphoma.

Although extranodal lymphomas are not rare, the frequency of involvement of any particular site is not high enough for a single institution to answer the major question about their natural history and proper therapy. Attempting to overcome these difficulties, in the late 1990s, the International Extranodal Lymphoma Study Group (IELSG) was created to provide an adequate network to study the extranodal lymphomas. This international collaboration has originated a number of retrospective and prospective trials aimed to clarify the management issues distinct to extranodal presentations (<http://www.ielsg.org>).

Whether or not extranodal lymphomas as a whole have a worse overall survival in comparison with that of nodal cases

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Table 1. Outcome of primary extranodal lymphomas in studies of the IELSG: overall survival by histologic subtype and presentation

NHL site, histology	No. of patients stage I–II/total	Survival (95% CI)	Reference
Stomach, MALT type	100/100	5-year OS: 91% (83–98%)	Hancock et al. 2005 [8]
Intestine, MALT type	21/35	5-year OS: 65% (43–81%)	Cortelazzo et al. 2002 [10]
Non-gastrointestinal, MALT type	131/180	5-year OS: 90% (82–94%)	Zucca et al. 2003 [9]
Stomach, DLBCL	219/312	5-year OS: 75% (n.r.)	Cortelazzo et al. 1999 [11]
Intestine, DLBCL	40/87	5-year OS: 68% (55–78%)	Cortelazzo et al. 2002 [10]
Breast, DLBCL	193/204	5-year OS: 63% (55–70%); 10-year OS: 47% (38–56%)	Ryan et al. 2008 [13]
Testis, DLBCL	294/373	5-year OS: 48% (42–53%); 10-year OS: 27% (21–33%)	Zucca et al. 2003 [14]
Central nervous system, DLBCL	370/370	2-year OS: 37% (nr); 10-year OS: 10% (nr)	Ferreri et al. 2003 [15]

Abbreviations: CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue; NHL, non-Hodgkin lymphoma; OS, overall survival; nr, not reported.

is controversial [1]. However, it is questionable whether such a general distinction has any clinical relevance. As shown in Table 1, which reports the survival rates of extranodal lymphomas in some large series of the IELSG [8–15], the clinical outcome varies among all the specific sites of primary extranodal lymphomas. In fact, the histological subtype is undoubtedly the main predictor of prognosis in either nodal or extranodal lymphomas but the primary location represents the most significant discriminatory factor among aggressive extranodal lymphomas. This is partially due to differences in natural history, but mainly to differences in management strategy which are related to organ-specific problems (e.g. the blood–brain barrier). Furthermore, some specific disease localizations require specific staging procedures (such as an ophthalmologic examination with slit-lamp in brain lymphoma).

The influence of the localization site on the outcome is less clear in MALT lymphoma, where multifocal lesions are present in 20–40% of patients [9, 16–18] but—at least when limited to mucosal sites—do not seem to be necessarily associated with a poorer outcome [9, 18].

In conclusion, the pronounced heterogeneity in the pathogenesis, clinicopathological features and outcome of the various primary extranodal presentations are important reasons for a detailed consideration of the different sites of origin of these lymphomas. The aim of the present review (which will focus largely on some rare presentations) is to provide an updated summary of some recent advances, mainly provided by IELSG studies, concerning extranodal lymphomas arising at certain extranodal sites.

Intravascular large B-cell lymphoma

Intravascular large B-cell lymphoma (IVL) is a rare form of DLBCL characterized by preferential intravascular growth of malignant lymphocytes, aggressive behaviour and, often, fatal course. It usually affects elderly patients with poor performance status (PS), elevated lactate dehydrogenase (LDH) serum levels, anaemia and B-symptoms; it displays some differences in clinical presentation among diverse geographical areas, mostly

between cases diagnosed in Western Countries and those diagnosed in Japan. Only recently included in lymphoma classifications, IVL is currently defined by WHO classification as an extra-nodal lymphoma characterized by the presence of neoplastic lymphocytes within the lumina of small vessels. A few different histological patterns can be identified in IVL: free-floating neoplastic lymphocytes are often found in the vessel lumen; alternatively these cells may form aggregates completely filling the lumen or may adhere to endothelia, without forming neoplastic thrombus.

Etiologic factors in IVL are unknown and it is virtually impossible to draw incidence figures: the published information is almost exclusively represented by case reports with only a few relatively large series. Nevertheless, some clinical features of IVL diagnosed in Western Countries seem different from those reported in patients from Asia [19–21].

Despite being scanty, the literature data suggest that pathologic diagnostic criteria as well as clinical features of this disease may be broader than described in the current classification schemes. Under the sponsorship of the IELSG, clinicians and pathologists with an interest in IVL, coming from Western and Eastern countries, joined to reach a consensus on defining features as well as to focus on the most urgent unresolved issues in IVL [22]. Some anatomical sites show a peculiar pattern of involvement. First, renal involvement, other than classical intravascular location, may preferentially disclose neoplastic cells in glomeruli. In the liver, along with the classic intrasinusoidal distribution, focal, extravascular intraparenchymal spread could be noted. The definition of spleen (especially when IVL is confined within the red pulp) and bone marrow involvement, as well as the classification of the reported cases of ‘solid’ large cell lymphoma with an intravascular component is sometimes problematic [22].

Some clinical features appear not to be randomly distributed worldwide; cases diagnosed in Western countries display a relative high frequency of central nervous system and skin involvement, while patients from Asian countries preferentially show haemophagocytic syndrome, bone marrow involvement,

fever, hepatosplenomegaly and thrombocytopenia.

Interestingly, most patients presenting with skin involvement (the so-called 'cutaneous variant' of IVL) are young females with good PS, and normal leukocyte and platelet counts.

Despite its intravascular growth pattern, IVL is associated with peripheral blood involvement in <10% of cases. At relapse the disease often involves the CNS. The patients with 'cutaneous variant' have a significantly longer survival, independently of the International Prognostic Index (IPI) [22].

Patients with IVL should be considered as DLBCL patients with a disseminated disease, and, accordingly, treated with anthracycline-containing chemotherapy regimens in association with rituximab. Local therapy (including radiotherapy) alone can be recommended only in elderly patients with 'cutaneous variant' carrying a single lesion. In general, anthracycline-based chemotherapy results in near 60% response rate and a 3-year overall survival (OS) rate of >30% [23]. The use of high-dose chemotherapy supported by autologous stem cell transplantation, may improve the currently disappointing outcomes. However, this strategy appears feasible only in a small proportion of patients with IVL, considering that their median age is 70 years and their PS is usually poor [22].

testis lymphoma

Primary malignant lymphoma of the testis is a rare disease that represents ~5% of all testicular tumours and only 1–2% of all NHL, with an estimated incidence of 0.26/100 000 per year. Lymphoma, however, is still the most common testis tumour in men >60 years of age, and the large majority of patients with testis lymphoma are >60 years of age [1, 14].

Most cases (80–90%) are of diffuse large B-cell histology, but isolated cases of other histological subtypes have been described. Orchiectomy is both diagnostic and therapeutic providing local tumour control, but it is nearly always not curative. Indeed, primary testicular lymphoma has been recognized as a highly lethal disease, with overall 5-year survival rates ranging from 16% to 50%. The characteristic pattern of failure is mostly distant with a high proportion of relapses in the CNS (both meningeal and parenchymal) and other extranodal sites, including skin, lung, pleura, soft tissues, Waldeyer's ring and contralateral testis [3, 14].

The IELSG conducted a large retrospective survey of 373 patients with a diagnosis of primary testicular diffuse large cell lymphoma [14]. The median age at presentation in this study was 66 years. Approximately 80% of patients presented with Ann Arbor stage I–II and low or low–intermediate risk according to the IPI. Nevertheless, the 5-year survival was 48% and the 10-year survival was 27%, the survival curves showing no clear evidence of a substantial proportion of cured patients; even for patients with stage I disease and favourable IPI the outcome appears worse than that reported for DLBCL at other sites. At a median follow-up of 7.6 years, 195 patients had relapsed. Extranodal recurrence was reported in 140 cases. A continuous risk of recurrence in the contralateral testis was seen in patients not receiving prophylactic scrotal radiotherapy. Relapses/progressions in the CNS were detected in 15% of patients and appeared continuously up to 10 years following

the initial presentation. Prophylactic intrathecal chemotherapy was associated with an improved progression-free survival. High-dose intravenous methotrexate apparently did not improve the outcome but was given only to a very small subset of patients. The limited number of cases (9%) in this series who had received systemic CHOP-like chemotherapy together with prophylactic intrathecal chemotherapy and prophylactic scrotal irradiation appeared to have a better outcome with a 3-year OS of 88% [14].

The outcome data in the retrospective IELSG large series suggest that intrathecal chemotherapy may control microscopic meningeal disease but is unlikely to affect the risk of failure in brain parenchyma. There is very little published data regarding the benefit of prophylactic cranial irradiation in testis lymphoma. Based on the results of the retrospective series, the IELSG evaluated the feasibility and efficacy of a treatment programme comprising prophylactic radiotherapy to the contralateral testis and intrathecal methotrexate in addition to rituximab plus CHOP chemotherapy in a prospective single-arm trial.

The preliminary analysis of this study showed a complete remission rate of 98%, at a median follow-up of 28 months, 3-year OS and 3-year event-free survival were 86% and 77%, respectively. In spite of doxorubicin-based therapy plus rituximab, of 41 evaluated patients, 7 (17%) relapsed or progressed: 2 in nodal sites, 3 in extranodal sites with or without nodal disease and 2 in the CNS (1 isolated meningeal and 1 meningeal and nodal relapse). No contralateral testis relapses were observed, while prophylactic intrathecal methotrexate seems to have reduced, but not eliminated CNS relapses [24].

breast lymphoma

Breast is an uncommon primary site of lymphoma localization, comprising only 2% of localized extranodal NHL presentations. Only a few hundred cases have been reported, most in small retrospective series with only one small prospective study identified [13]. This sparse information prevents the definition of prognosis and patterns of failure of patients with primary breast NHL, and wide variations in outcomes and prognostic factors are reported. However, some common features have been described: predominant diffuse large B-cell histology (although follicular and MALT lymphomas and Burkitt's lymphoma have also been described), prognosis poorer than anticipated by stage, significant risk of contralateral breast involvement and tendency to CNS relapse. In a retrospective international IELSG survey of >200 cases of primary localized DLBCL of the breast, peculiar clinical features and characteristic patterns of relapse have been identified. The contralateral breast and other extranodal sites were major sites of relapse. The CNS relapse rate was lower than anticipated from literature series, despite the lack of CNS prophylaxis in the large majority of patients. In this patient population receiving chemotherapy in 80% of cases, mainly with anthracycline-containing regimens, and in a relevant proportion a combination strategy of both chemotherapy and radiotherapy, median OS was 8.0 years, with 5- and 10-year OS rates 63% and 47%, respectively; the median time to

progression was 5.5 years [13]. Based on these data, referring to a pre-rituximab era, the combination of anthracycline-containing chemotherapy and loco-regional radiotherapy seems adequate, following a diagnostic surgical biopsy. Addition of rituximab has never been studied but is very likely to be beneficial. The need for CNS prophylaxis remains controversial.

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