Extranodal lymphomas

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Introduction

At least one quarter of non-Hodgkin’s lymphomas (NHL) arise from tissue other than lymph nodes and even from sites which normally contain no lymphoid tissue. These forms are referred to as primary extranodal lymphomas [1,2]. Since these tumours, numerous when considered together, are widely distributed throughout the body, it is difficult to find adequate series of any given site. Moreover, many historical series were published before the recognition of mucosa-associated lymphoid tissue as the origin of many extranodal lymphomas and in general, classification of primary extranodal lymphomas was similar to that of nodal lymphomas, without consideration that their origin could be different. Hence, the literature lacks uniformity in histopathological classification. The first attempt to eliminate this problem was made only very recently with the proposal of the Revised European–American Lymphoid Neoplasms (REAL) classification [3].

The definition of primary extranodal lymphoma, particularly in the presence of both nodal and extranodal disease, remains a controversial issue. Operationally, lymphomas can be considered as extranodal when, after routine staging procedures, there is either no or only ‘minor’ nodal involvement along with a clinically ‘dominant’ extranodal component, to which primary treatment must often be directed [1].

There are great differences in the incidence of extranodal lymphomas among countries: USA 24%, Canada 27%, Israel 36%, Lebanon 44%, Denmark 37%, the Netherlands 41%, Italy 48%, and Hong Kong 29%. Little is known about the actual incidence in developing countries, which, however, seem to have a high incidence of extranodal forms [1].

It has recently been demonstrated that NHLs on the whole are showing a rapid increase in incidence, and over the past 20 years extranodal disease increased more rapidly than nodal disease. The greatest increases have been observed for the lymphomas of the central nervous system, followed by lymphomas of the gastrointestinal tract and the skin. In addition to the AIDS epidemic, other predisposing factors, such as other viral infections, immunosuppressive treatments, or environmental factors, might explain the increased incidence of extranodal lymphomas.

Gastrointestinal localisations represent the most common form of extranodal lymphoma. Other frequent and clinically important sites include the CNS and the skin (and will be discussed with some details). However, extranodal lymphomas can arise in almost every organ.

Signs and symptoms at presentation depend largely on the localisation; generally, patients with extranodal lymphomas tend less often to present B symptoms than do patients suffering from lymphomas arising in the nodal regions.

The outcome can be different in the disparate specific sites of primary 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.

Testis and thyroid lymphomas are more often seen in elderly patients, while a significantly higher incidence of hepatic and intestinal lymphomas is related to younger age. Salivary gland and thyroid lymphomas are significantly more common in females, while intestinal and pulmonary lymphomas are more often found in males. NHL of the stomach, salivary glands and thyroid are more frequently localised, whereas extranodal lymphomas of the lungs, liver, bones and testes are often widespread. With respect to histological classification, aggressive subtypes (usually diffuse large B-cell lymphomas) are predominant in NHL of CNS, testes, bone, liver, and to some extent the stomach. Certain extranodal sites have characteristic patterns of either B-cell (e.g. gastric marginal zone lymphoma, MALT type) or T-cell disease (e.g., cutaneous lymphoma clearly comprises a wide range of lymphomas of T-cell origin, even though a subset of B-cell cutaneous lymphomas does exist).
Primary gastrointestinal lymphomas

The gastrointestinal (GI) tract is the most frequently involved extranodal localisation in NHL. In hospital-based and population-based series published thus far, GI-NHL accounts for 4–20% (on average 12–13%) of all NHL and 30–40% of all extranodal cases. In the Western world, the most common locations are the stomach (approximately 50–60%) and the small intestine (approximately 30%) [1].

Infection by Helicobacter pylori has been cited as an environmental factor of possible aetiological relevance in those cases of gastric NHL deriving from the so-called mucosa-associated lymphoid tissue (MALT) [4–8]. Less epidemiological information is available on intestinal localisations. Patients with coeliac disease have a highly increased risk of developing the so-called enteropathy-associated T-cell lymphoma (EATCL) and some authors even favour the hypothesis that adult-onset coeliac disease is itself a form of low-grade lymphoma [1].

Presenting symptoms are generally due to the local lesion (pain, obstruction, haemorrhage). Compared with nodal lymphomas, fewer patients with gastric lymphoma present with bone marrow involvement or elevated LDH levels. Fever and night sweats are uncommon. Weight loss, however, is common, although this is more often a consequence of the localisation of the primary lymphoma rather than a constitutional symptom of the disease.

The optimal treatment of gastrointestinal lymphomas is still a controversial issue and depends on the histological type and stage of the disease [1,9,10].

Increasing evidence indicates that eradication of H. pylori with antibiotics can be effectively employed as the sole initial treatment in low-grade gastric MALT lymphoma provided that strict oncological and endoscopic follow-up is carried out [4–6,8]. However, it is still unknown whether H. pylori eradication will definitely cure the lymphoma. No treatment guidelines exist for the management of patients after failure of antibiotics and for the subset of cases in which no evidence of H. pylori can be found [4,6]. It has been shown that the chance of a response to antibiotics is dramatically reduced in this latter group [4]. A choice can be made between conventional oncological modalities including chemotherapy, radiotherapy, surgery, alone or in combination. There are data suggesting that both chemotherapy and radiotherapy are effective but, unfortunately, there are no published randomised studies to help the decision [4].

Combination chemotherapy is the treatment of choice for patients with locally advanced or disseminated aggressive (high grade) lymphomas. In a prospective study from the GELA French group including more than 700 patients with aggressive lymphomas treated with intensive chemotherapy, no difference in therapy outcome was observed between patients with an advanced aggressive nodal lymphoma and the subset of patients in which the lymphoma was deemed to have arisen in the gastrointestinal tract [11].

The effectiveness of combination chemotherapy in advanced cases of gastrointestinal lymphomas has led to a reconsideration of the role of primary surgery in less advanced cases and new approaches have been advocated. It has been suggested by the results of some recent gastric lymphoma series (including the interim results of an ongoing large German trial with more than 250 GI-NHL patients) that chemotherapy, sometimes combined with radiotherapy, can be curative and that gastrectomy must be critically reconsidered [12,13]. For primary intestinal lymphoma, however, there are as yet no studies which clearly demonstrate that surgery is unnecessary and combined modality treatment is widely considered the procedure of choice [1].

Primary cutaneous lymphomas

Primary cutaneous lymphomas can be defined as the presence of cutaneous localisations alone, with no nodal or systemic disease. They represent a very numerous group of extranodal lymphomas, accounting for approximately 10% of cases. Moreover, the skin is a relatively common site of dissemination of many nodal NHLs, especially those of T-cell phenotype. However, the clinical behaviour of primary cutaneous lymphomas is usually different from that of primary nodal lymphomas of similar histology involving the skin secondarily.

It is difficult to define properly the primary cutaneous lymphoma on morphologic grounds alone: several types of primary lymphoma of the skin classified as high grade according to the Kiel classification or the Working Formulation very often show an indolent clinical behaviour. Therefore, only a combination of histologic, immunologic and clinical data can adequately define the primary cutaneous lymphoma entities. On this basis, a new classification scheme has recently been proposed by the EORTC cutaneous lymphoma study group [14].

Lymphomas of the skin are more often of T-cell type, with mycosis fungoides and Sezary syndrome constituting around 65% of the cases. The other types of primary cutaneous T-cell lymphomas (CTCL) are
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less frequent and may be further characterised according to the specific expression of cell surface antigens such as CD30. They differ from mycosis fungoides in that the epidermotropism is usually absent (i.e. the neoplastic T-cells usually infiltrate the dermis and subcutaneous tissue but not the epidermis) [14].

Classification of primary cutaneous B-cell lymphomas is particularly controversial [1]. The subtypes, follicle-centre lymphoma of the head and trunk and immunocytoma of the EORTC classification, constitute over 90% of primary cutaneous B-cell lymphomas [14]. This group includes a large percentage of diffuse large-cell lymphomas which, in the scalp and in the trunk, despite their cytologically and histologically aggressive features, spread only very rarely beyond the skin and have a clinically indolent course. More aggressive is the clinical course of primary cutaneous large B-cell lymphoma of the leg. Moreover, cutaneous follicle-centre lymphoma appears to be distinctly different from the nodal counterpart both immunophenotypically and genotypically, lacking the chromosomal translocation t(14;18) and the expression of the common leukocyte antigen (CD10). Extranodal marginal zone lymphomas (MALT type) of the skin have been described and the cutaneous immunocytoma may also be interpreted as a low-grade B-cell lymphoma of MALT type [1,14]. Since skin-associated lymphoid tissue (SALT) is usually devoid of B-cells, in analogy to the MALT concept in the stomach, an acquired SALT could represent the background for the development of the lymphoma [15]. Furthermore, the association of cutaneous B-cell lymphoma with acrodermatitis chronica atrophicans suggests that Borrelia burgdorferi might have a role similar to that of H. pylori in the stomach [16].

Primary central nervous system lymphoma

Primary central nervous system lymphoma (PCNSL) is a disease distinct from other extranodal lymphomas in its biology, clinical features and response to treatment. PCNSL can be defined as lymphoma arising in and confined to the cranial–spinal axis (brain, eye, leptomeninges and spinal cord). Formerly a rare tumour, PCNSL is showing increased incidence both in immunocompromised (congenital, acquired or iatrogenic) high-risk groups and in the general population. Clinical and radiological characteristics of the disease in immunocompetent patients are very different from those observed in the AIDS-associated patients in whom the PCNSL often presents with an encephalopathic picture. PCNSL accounts for 1–2% of malignant brain tumours and 2–4% of all extranodal lymphomas. Secondary involvement of the central nervous system occurs in 5–30% of systemic non-Hodgkin’s lymphoma [2].

PCNSL is usually disseminated within the nervous system at diagnosis, in approximately 40–50% of immunocompetent and in nearly 100% of AIDS patients. About 40% of patients have a demonstrable involvement of the spinal fluid and 20% of the eyes. In addition to the usual procedures staging requires contrast-enhanced computerised tomography scan and magnetic resonance imaging (MRI) with gadolinium of the brain and orbits, before steroids are started because of the rapid radiographic disappearance of tumour following the administration of steroids (‘ghost tumour’), a peculiar feature of PCNSL, not shared by any other intracranial malignant tumour. Histologically, the vast majority of lymphomas are of diffuse large B-cell type in the immunocompetent patients.

A surgical procedure more extensive than stereotactic biopsy is rarely indicated. Aggressive surgical decompression with partial or gross total removal of the tumour is of no benefit. Historically whole brain radiation has been the treatment of choice, but, despite different radiation schedules with good initial responses, over 90% of patients recur in the brain, often in sites remote from the initial ones. Systemic dissemination occurs in only 10% of the cases, and many of these have single localisations. The prognosis for unselected patients with immunocompetent PCNSL treated with radical irradiation alone is very poor, the 5-year survival rate is 5–10% with a median survival between 12 and 18 months. Several single institutions have reported encouraging results with systemic chemotherapy alone or combined with radiotherapy, with 5-years projected overall survival of 30–50% and median survival of 2–3 years. In general, the most recent studies seem to point out that radiation therapy alone is unable to provide significant long-term survival, may interfere with later chemotherapy and may increase the risk of treatment-induced dementia. There is mounting evidence that initial chemotherapy should be the treatment of choice, reserving irradiation for resistant or relapsing disease [2,17–21].

A particular PCNSL is the primary ocular lymphoma. It should be pointed out that primary orbital and ocular adnexa lymphomas represents a different entity, most often of extranodal marginal zone histotype, and must not be confused with lymphoma of the eye. Primary ocular lymphoma — i.e. restricted to the globe, usually the vitreous body, retina, and
chorioid — is exceedingly rare. Ocular involvement is often bilateral and more than half of the patients will later develop brain lesions. Radiotherapy to both eyes has been the standard treatment, and, like in the other PCNSL, the combination with systemic chemotherapy is being investigated [2,21].

In rare instances, PCNSL presents as a localised leptomeningeal disease in the absence of parenchymal brain involvement. Diagnosis is commonly obtained by positive CSF cytology or on meningeal biopsy. The therapeutic approach is similar to primary brain lymphomas. Prognosis is usually poor [2].

Primary extradural lymphoma represents approximately 1% of all localised NHLs, it most often presents with spinal-cord compression at thoracic level. The diagnosis is generally obtained at the time of decompressive surgery with diffuse large-cell lymphoma being the most common histology. Its inclusion among the PCSNL is controversial. CNS involvement is very uncommon and the good results obtained with radiotherapy and systemic chemotherapy seem to indicate that the natural history of primary extradural lymphoma is different from that of PCNSL.

References