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Clinical features and management of localized extranodal lymphomas

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Introduction

Malignant lymphomas account for about 5% of human cancers with an age-standardized incidence of approximately 17 per 100 000 of the population. Non-Hodgkin's lymphomas are about four times more common than Hodgkin's disease and have an age-peak in the over-50 years age group. Both diseases share similar symptomatology in terms of characteristic symptoms (fever, night sweats, and weight loss) and with respect to nodal enlargement as the most common form of presentation. Both share a common staging classification which is based upon anatomical distribution of disease. A major difference occurs, however, in the frequency with which non-Hodgkin's lymphomas present with apparently localized disease in extranodal sites – primary extranodal lymphoma – a circumstance of extreme rarity in Hodgkin's disease.

Primary extranodal non-Hodgkin's lymphoma

The evolution of histological classifications of non-Hodgkin's lymphoma has followed from largely morphological observation stressing architecture and cytology to functional and biological measurements recognizing lineage and differentiation of lymphoma cells. Much of the controversy of lymphoma classification is illustrated in the histology of primary extranodal non-Hodgkin's lymphoma:

- extranodal sites rarely align themselves with lymph node structure, thus the majority of primary extranodal lymphomas manifest 'diffuse' effacement of tissue architecture.
- lymphoid aggregates within extranodal tissue may lack characteristic features of lymphoma in terms of invasion and mitotic activity. Such aggregates have been considered pseudotumors and have charac-

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teristically been recorded in orbital, pulmonary and gastrointestinal sites. Current functional characterization of the cells within such aggregates to define clonality should resolve the issue of 'benign' versus 'malignant' lymphoid infiltrates.

- certain extranodal sites clearly have a spectrum of lymphoma histology from low to high grade within the International Working Formulation e.g. orbit, head and neck, gastrointestinal tract, lung and skin. Other sites have a highly skewed representation of intermediate and high grade tumors e.g. extradural, brain, testis and bone lymphomas. The basis for this variable distribution of histology by geographic or anatomic site is unknown.
- certain extranodal sites have characteristic spectra of B- or T-cell disease. Cutaneous lymphoma clearly comprises a range of lymphomas of T-cell origin which demonstrate a preferential localization for the skin for long periods of the natural history of the disease. Similarly, the gastrointestinal tract favours a subset of lymphoma-mucosa associated lymphoid tissue lymphoma (MALT lymphoma) demonstrating preferential traffic patterns influencing localization and recurrence within the gastrointestinal tract. Similar analogies apply to thyroid and lung lymphoma.
- whereas the existing histological classifications apply satisfactorily to nodal and B-cell lymphoma, the histological classification of T-cell disease within nodes and in extranodal sites is less satisfactory. The diversity of T-cell disease is demonstrated in primary cutaneous lymphoma with a disease spectrum ranging from chronic, indolent lichenoid eruptions through to lymphoblastic disease with a fulminant natural history. Even within a single disease entity – lymphomatoid granulomatosis – a very wide pattern of clinical behaviour is contained within a seemingly uniform histology.

Thus, in terms of prognostic importance, histology is not only distinguished in its own right, but also in the context of histology in relation to primary extranodal site as a component of therapeutic management.

Despite the obvious clinical diversity of primary extranodal lymphoma, there are many common attributes to define prognosis and management strategy. Stage, in the context of localization, defines those who are potential candidates for radiation as opposed to those who require systemic therapy for more advanced disease. However within localized stage, additional factors – presence or absence of symptoms ('A' or 'B'), tumor bulk, and extent of local invasion – influence the success of local therapies (radiation and/or surgery) with respect to both local tumor control and distant relapse rate. Histology influences management of those with localized or advanced lymphoma. In

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