Uncommon presentations of non-Hodgkin's lymphoma

In this issue of *Hospital Medicine*, a case of a primary adrenal lymphoma (PAL) and a primary cutaneous B cell lymphoma (PCBCL) are presented (p. 759). These extranodal lymphomas are uncommon presentations of B cell non-Hodgkin's lymphoma.

Malignancies of the lymphoproliferative system can broadly be classified into Hodgkin's disease and all other lymphomas, which are termed the non-Hodgkin's lymphomas. For the purposes of brevity, the term lymphoma will be used in this article to indicate non-Hodgkin's lymphoma.

'Extranodal lymphomas, as their name implies arise in components of the lymphoreticular system other than lymph nodes, either in lymphoid organs such as the spleen, thymus or tonsils, in organs that have a lymphoid component, such as the gut, or, less frequently in sites where no native lymphoid tissue is recognized, such as the brain' (Isaacson, 1995).

In fact they can arise from any site in the body. Up to 40% of all lymphomas are truly extranodal, as compared to the primary nodal lymphomas extending to involve extranodal sites (Freeman et al, 1972). A higher incidence of extranodal lymphoma is seen in diseases of immunity such as AIDS and autoimmune and chronic inflammatory diseases (e.g. rheumatoid arthritis and coeliac disease).

There follows a summary of the main features of the most common extranodal lymphomas.

GASTROINTESTINAL LYMPHOMAS

The gastrointestinal tract is the most common primary site of extranodal lymphoma. Primary gastrointestinal lymphoma accounts for at least 15% of all lymphomas, and the incidence, mainly of gastric lymphoma (Severson and Scott, 1990), is rapidly increasing. The primary lesion is in the stomach in 60% of cases, in the small bowel in 30% and in the large bowel in the remaining 10%. The high incidence of lymphoma in the gastrointestinal tract is not surprising as it contains more lymphoid tissue than the lymph nodes and spleen combined. This lymphoid tissue, known as gut-associated lymphoid tissue (GALT), has different morphological and functional characteristics than peripheral lymph nodes.

LYMPHOMAS OF MUCOSA-ASSOCIATED LYMPHOID TISSUE

Similar lymphoid tissue is found at other mucosal sites and, together with GALT, this is collectively known as mucosa-associated lymphoid tissue (MALT). Lymphomas arising from MALT are described in multiple extranodal sites, most frequently the gastrointestinal tract (stomach) but also the respiratory tract, salivary glands, thyroid, thymus, breast, skin, liver, pancreas, conjunctiva, lacrimal gland and orbital soft tissue. Lymphomas arising from MALT share many clinicopathological features (Isaacson and Spencer, 1987) and differ significantly from nodal lymphomas. They share a long history, associated autoimmune disease or chronic inflammatory conditions, good response to surgical excision and a favourable prognosis.

LOW-GRADE B CELL MALT LYMPHOMA OF THE STOMACH

A significant proportion of gastric lymphomas is of low-grade histology and arises from MALT. Such MALT lymphomas may be associated with *Helicobacter pylori* infection. Initial management of MALTomas in the stomach is *H. pylori* eradication. Responses are seen in over 90% of patients but of interest are reports of complete regression of low-grade gastric lymphoma after eradication of *H. pylori* (Bayerdorffer et al, 1995). In tumours that do not respond, surgery and/or chemotherapy may be used.

Lymphomas in the small bowel, colon and rectum are less common, but more diverse than those found in the stomach. They include both T cell and B cell lymphomas, and distinct clinicopathological entities, such as primary intestinal T cell lymphoma, immunoproliferative small intestinal disease, and multiple lymphomatous polyposis.

CUTANEOUS LYMPHOMA

The skin is the second most common site of extranodal lymphoma. Skin lymphomas are often low-grade and slow growing, with the majority being of T cell lineage (80%). Mycosis fungoides is a characteristic T cell skin lymphoma, which has a long pretumour phase before developing into the characteristic skin infiltration, which may be widespread.

PCBCLs, as in the first case report, comprise about 20% of all cutaneous lymphomas. They characteristically remain localized to the skin, and although they tend to recur, extracutaneous spread is very rare. They respond favourably to radiotherapy and share an excellent prognosis (Santucci et al, 1991).

CEREBRAL LYMPHOMAS

The incidence of primary cerebral lymphoma is increasing and accounts for approximately 2% of all lymphomas. At least half the cases are associated with immunodeficiency, either post-transplantation or HIV-related. Historically, the main treatment modality has been whole-brain radiotherapy. However, there is some evidence that

patients under the age of 60 years benefit from the use of chemotherapy (Maher and Fine, 1999).

LYMPHOMAS OF WALDEYER'S RING, NASOPHARYNX AND NOSE

Waldeyer's ring lymphomas arise in the lymphoid tissue of the oropharynx and nasopharynx. They present with local symptoms similar to those of a carcinoma in these regions, as a localized enlarging mass, with local pain, epistaxis, nasal dicharge or congestion, and difficulty in swallowing. For disease localized to Waldeyer's ring, treatment may comprise radiotherapy alone, while more advanced disease requires the addition of chemotherapy.

PULMONARY LYMPHOMA

A variety of histological subtypes may manifest as primary pulmonary lymphoma; the most common being low-grade B cell lymphoma of the MALT type accounting for 69–78% in different series (Haberman et al, 1999). MALT is present in the lung as lymphoid nodules in the bronchi (BALT).

Low-grade B cell pulmonary lymphoma usually presents as an incidental finding of radiographic opacity, and is particularly slow growing. Observation is the initial treatment of choice in asymptomatic patients, reflecting the characteristic indolent clinical behaviour of the underlying disease. Local progression or transformation into high-grade can occur, requiring chemotherapy.

SALIVARY GLAND LYMPHOMA

Almost all cases of primary lymphoma of the salivary glands are B cell lymphomas of the MALT type. The majority arise with Sjögren's syndrome, as a consequence of chronic autoimmune inflammation; the so-called myoepithelial sialadenitis (MESA). The tumour again conforms to MALToma rules, is slow growing, and may remain localized to the parotid for many years before dissemination or transformation to a high-grade occurs. Treatment is with a combination of surgical excision and radiotherapy.

THYROID GLAND LYMPHOMA

This is a rare tumour, of low grade B cell lymphoma and of the MALT type. It almost invariably occurs in the setting of Hashimoto's thyroiditis. There is no native MALT in the thyroid; however, as in MESA, the lymphoid infiltrate of Hashimoto's thyroiditis closely resembles MALT. The low grade lymphoma has similar clinical behaviour to other MALT lymphomas.

PRIMARY ADRENAL LYMPHOMA

This is the second case presented in this issue. In contrast to the PCBCL and the other extranodal lymphomas presented so far, PAL is indeed extremely rare, with 65 cases reported worldwide (Wang et al, 1998), and underlies the fact that extranodal lymphomas have been reported to arise in nearly every conceivable anatomical location.

Contrary again to the PCBCL, prognosis is generally poor, while treatment comprises a combination of surgery and chemotherapy as opposed to mainly radiotherapy for PCBCL. This is indicative of the marked heterogeneity in clinical behaviour of extranodal lymphomas, this being dependent upon the histological type, staging and primary site of organ involved.

PRINCIPLES OF MANAGEMENT

Where previously thought that the clinicopathological characteristics of the well-studied nodal lymphomas could simply be extended to extranodal disease, this is clearly no longer the case, especially regarding the MALT lymphomas. Primary extranodal lymphomas must therefore be strictly distinguished from primary nodal lymphomas.

TREATMENT

Therapeutic options for extranodal lymphomas include surgery, radiotherapy, single and combination chemotherapy, antibacterial and antiviral agents, immune modulation, monoclonal antibodies, discontinuation of immunosuppressive drugs, bone marrow transplantation, and antisense oligonucleotides. Therapy should be tailored to the individual patient, taking into account the primary site of origin, the histological subtype of lymphoma and the natural history of the disease. HM

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KEY POINTS

- Extranodal lymphomas comprise up to 40% of non-Hodgkin's lymphomas and their incidence has been increasing during the past two decades.
- They can arise in nearly every organ and are associated with altered immunity.
- Their clinical course is highly variable, and differs from that of their nodal counterparts.
- Therapeutic options include surgery, radiotherapy, chemotherapy, antibacterial and antiviral agents, immune modulation, monoclonal antibodies and bone marrow transplantation.
- Treatment should take into account the histological type, the primary site of origin and the natural history of the disease.

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