Extranodal lymphoma: clinical presentation and diagnostic pitfalls

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Non-Hodgkin's lymphomas (NHL) are known to present extranodally in 25% of cases, in contrast to Hodgkin's disease which rarely involves extranodal sites. In this article, the authors will to review the presentation of extranodal head and neck NHL and the difficulties that can be encountered in making the diagnosis in these cases.

Lymphomas are the second most frequent non-cutaneous malignancies in the head and neck. Historically, they have been categorized as either Hodgkin's or non-Hodgkin's lymphomas (NHLs). NHLs are a diverse group of malignant lymphoproliferative disorders with varying cell origin, biologic behaviour, sites of predilection, response to treatment and prognosis (Conley et al, 1987).

Extranodal disease is seen in 25% of patients with NHL. The head and neck accounts for between 10% and 30% of these cases (Wulfrank et al, 1987), over half of which present to an otolaryngologist. Overall, men and women appear to be equally affected by extranodal lymphoma of the head and neck, although this may not be true for all NHL subtypes or anatomical sites within the head and neck (Hart et al, 2004).

The incidence of extranodal NHL, as with its nodal equivalent, increases with age, with a peak incidence in the sixth decade (Hanna et al, 1997). There is a well documented risk of NHL with a variety of clinical conditions and immunosuppressed states, including human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), rheumatoid arthritis, coeliac disease, Sjögren's syndrome, radiation exposure and immunosuppression.

The incidence of NHL in Western populations has greatly increased over the last 30 years (Liu et al, 2003). This may be related in part to improved diagnosis, immunosuppressive therapy, HIV and AIDS, but even considering these factors, the magnitude of the increase is greater than anticipated. This remains unexplained but it suggests that extranodal head and neck lymphoma will be encountered by the otolaryngologist with increasing frequency.

Given their heterogeneity, a comprehensive satisfactory classification system for NHL remains elusive. They may be classified in terms of their clinical behaviour related to histopathological patterns as low-, intermediate- and high-grade lymphomas (Working Formulation) (National Cancer Institute, 1982). Most NHLs in the head and neck are intermediate grade. They may also be described in relation to the cells of origin, B-cell, T-cell or natural killer(NK)/T-cell, histopathologic appearance (Revised European American Lymphoma (REAL) classification (Harris et al, 1994) or the immunophenotypic and molecular genetic characteristics of the constituent cells according to the World Health Organization classification (Jaffe et al, 1999; Garcia-Cosio et al, 2003).

B-cell subtypes are most often observed, but Asian people are more liable to have NK/T-cell, particularly in the sinonasal tract (Cheung et al, 1998). The Ann Arbor staging system is widely used for NHL. The majority of patients are stage one or two, and the presence of B symptoms, defined as fever, sweats or unintentional weight loss of >10% body weight, occurs in only 10% of cases of extranodal NHL of the head and neck (Hart et al, 2003).

Extranodal NHL of the head and neck has been reported in many sites. Waldeyer's ring (WR), the nose and paranasal sinuses, the salivary glands and thyroid gland are the most common sites of involvement, in descending order of frequency, but anywhere in the head and neck can be affected.

The presentation of extranodal NHL in the head and neck will vary with different anatomical

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sites, but most have presenting features similar to carcinomas and other solid tumours which occur in these areas. It is imperative to distinguish lymphoma from other malignant lesions because lymphomas are chemosensitive and radiosensitive tumours and surgery offers no curative potential (Hanna et al, 1997). In general, radiation treatment alone is used for localized low-grade disease, while chemotherapy, in the form of doxorubicin-based combinations such as CHOP, alone or in combination with radiation treatment is utilized in the higher grade disease or more advanced stage.

WALDEYER'S RING

WR is a band of lymphoid tissue incorporating the nasopharynx, palatine tonsils, oropharyngeal wall and the base of tongue. There is debate as to whether it is truly an extranodal site but most consider it to be so (Gurkaynak et al, 2003). It accounts for between 36% and 50% of extranodal NHL in the head and neck and is the primary site of disease in 5–10% of all patients with NHL (Saul and Kapadia, 1985).

In the WR subregion, the tonsil is most frequently affected, followed by the nasopharynx. Bilateral tonsillar involvement is said to occur in 10% of patients and multiple sites of involvement within WR are reported in 4–26% of cases (Banfi et al, 1970). A possible male predominance has been reported (Ezzat et al, 2001).

The presenting signs and symptoms of WR lymphoma include unilateral tonsillar enlargement, odynophagia and dysphagia. With nasopharyngeal involvement, a conductive hearing loss secondary to eustachian tube dysfunction and middle ear effusion is possible. Extension to adjacent soft tissue sites occurs frequently, especially with tonsillar lymphoma, which also can involve locoregional nodes (*Figure 1*). Ulceration may also be noted. These features are similar to the squamous cell carcinoma from which, WR lymphoma must be distinguished. Approximately 20% of tonsillar lymphomas have gastrointestinal tract involvement (Hanna et al, 1997), therefore all cases should have a full gastrointestinal tract work up.

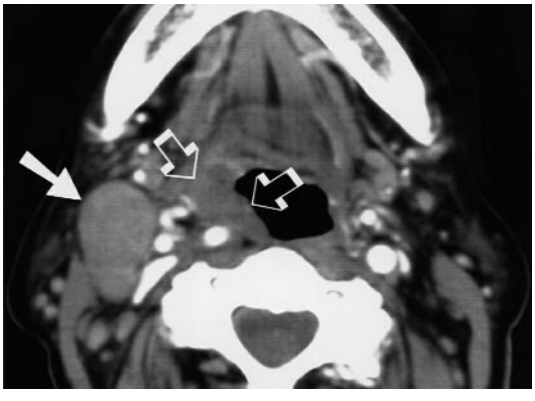

Figure 1. Axial computed tomography (CT) scan showing a biopsy proven B-cell non-Hodgkin's lymphoma of the tonsil (hollow arrows) with adjacent nodal involvement (solid arrow) in a 70-year-old female patient.

SINONASAL LYMPHOMA

Sinonasal lymphomas (SNLs) arise from the nasal cavity and paranasal sinuses. There is a definite male preponderance and it occurs more often with advancing age (Liang et al, 1990). The incidence of the different immunophenotypes of SNL, B-cell, T-cell and NK/T-cell show a distinct geographic variation. In Western populations B-cell type predominates (Cleary and Batsakis, 1994), whereas in Asia and certain parts of the Americas NK/T-cell type is most common. The reason for this has yet to be elucidated. This immunophenotypic distinction is important because they have a different clinical picture, response to therapy and prognosis (Kim et al, 2004).

B-cell SNL tends to involve the paranasal sinuses with a prolonged history of sinogenic symptoms including sinusitis, post-nasal drip, nasal obstruction or epistaxis. As the disease progresses, adjacent structures become involved and external nasal deformity, orbital or cheek involvement may be apparent (*Figures 2 and 3*). This is not dissimilar to carcinomas and other malignancies in the sinonasal region. Most large series reporting T-cell and NK/T-cell SNL have emanated from Asia or South America, where they are most often seen.

NK/T-cell lymphoma is one of a number of pathological entities that were grouped as midline lethal granulomas, non-healing granuloma or polymorphic reticulosis inter alia. This clinical entity, characterized by a progressive, relentless course with ulceration and destruction of midline structures, was previously believed to be inflammatory in nature. However, it is now recognized that the majority of these cases are NK/T-cell lymphomas. The male predominance is more pronounced than the other SNL immunophenotypes with a male to female ratio of 3:1 (Kim et al, 2004). It tends to occur in a slightly younger cohort, with median age at presentation reported to be 49 years (Liang et al, 1990).

While B-cell SNL tends to affect the sinuses, NK/T-cell tends to involve the nasal cavity. It is strongly associated with Epstein-Barr virus which is seen in 95% of NK/T-cell SNL. It pursues a rapidly progressive course, tends to

disseminate to the testis, lung, liver and central nervous system, responds poorly to doxorubicin-based combination chemotherapy and has a dismal overall prognosis (Rodriguez et al, 2000). Regardless of SNL subtype, lymphomas of this region appear to have a less favourable outcome compared to other extranodal NHL sites.

One of the diagnostic difficulties for the otolaryngologist is that NK/T-cell SNLs are characterized by large volumes of necrotic or ischaemic tumour. Therefore, even large biopsy samples may yield only non-viable tissue from which diagnosis is not possible (Young and Rogers, 2000). Even with a viable tissue biopsy, there may be a marked inflammatory infiltrate but a paucity of malignant cells, therefore impeding correct diagnosis. Wegener's granulomatosis has a similar clinical presentation to NK/T-cell SNL and must be borne in mind as a diagnostic possibility.

PAROTID GLAND LYMPHOMA

Salivary or partoid gland lymphoma is an uncommon lesion. The parotid gland is the most frequently affected salivary gland. It accounts for 10% of extranodal NHL in the head and neck (Barnes, 1998). Previous authors reported the incidence of lymphoma in parotidectomy specimens to be between 0.7% and 2.4% (Grage and Lober, 1962; Patey et al, 1965). More recently, a higher incidence has been noted in parotid series (von Stritzky et al, 1998)

Most patients present with a unilateral, painless, progressive parotid swelling, possibly involving the overlying skin (*Figure 4*). Regional adenopathy may be found and rarely encountered findings include trismus, facial nerve dysfunction and pain. A rapid increase in size may be a clinical feature that is more commonly seen in parotid lymphomas than other tumours arising within the gland. An antecedent history of Sjögren's syndrome or rheumatoid arthritis may be observed in a quarter of patients with parotid lymphoma, particularly the mucosa associated lymphoid tissue subtype (MALToma) (Dunn et al, 2004).

Unfortunately, these clinical features are indistinguishable from other neoplastic entities within the parotid gland, the most common of which is pleomorphic adenoma. With regard to the diagnosis of parotid lesions, a thorough history and examination will yield the diagnosis in 90% of cases (Fee and Tran, 2003).

Adjunctive modalities such as imaging and fine needle aspiration cytology (FNAC) may slightly improve on this diagnostic accuracy.

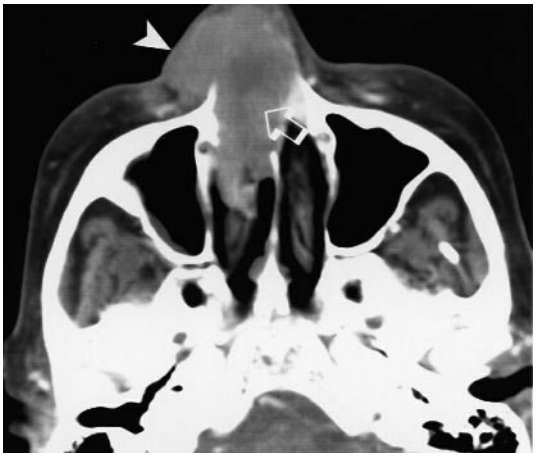

Figure 2. Axial computed tomography (CT) scan of a 67-year-old female patient with sinonasal B-cell lymphoma. The lesion originated in the ethmoid sinuses and had extended anteriorly through the frontal bones (hollow arrow) to involve the overlying skin (arrow head). The patient's presenting complaint was external nasal deformity.

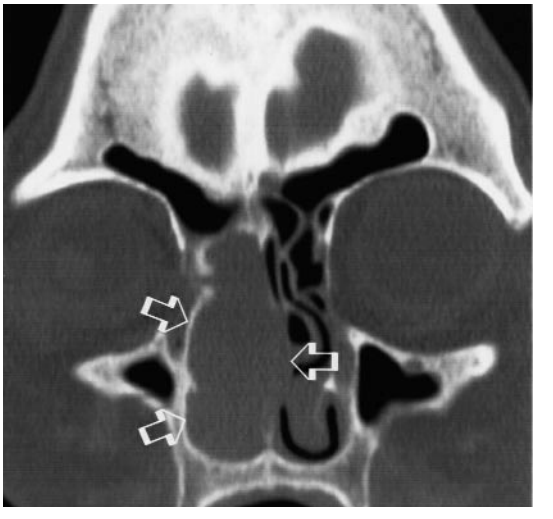

Figure 3. Coronal computed tomography (CT) scan of the same patient as in Figure 2. Notice the lateral and medial extent of the lymphoma (hollow arrows), traversing the septum and extending superiorly to the frontal recess.

Notwithstanding this, the majority of parotid mass lesions are subjected to parotidectomy which is the gold standard for diagnosis and is therapeutic in most cases. In the case of lymphoma, however, parotidectomy serves only as an extended biopsy, has no therapeutic benefit and has attendant risks such as facial nerve damage and Frey's syndrome. This may be avoided if there is loco-regional nodal involvement, where excision biopsy of the node may suffice or where there is invasion of overlying skin, where an incision biopsy can be performed without violating surgical oncological principles.

THYROID LYMPHOMA

Primary thyroid lymphoma accounts for 1–5% of all thyroid lesions (Kossev and Livolsi, 1999). There is a well described association with Hashimoto's thyroiditis, which accounts for the fact that women are affected more often than men (Widder and Pasieka, 2004). Most are of B-cell origin, of which 25% are MALToma subtypes. It most often presents as a rapidly enlarging thyroid mass. Symptoms referable to this lesion include dyspnoea, dysphagia, or in some cases acute respiratory embarrassment. The gland itself is classically smooth and firm with a rubbery consistency.

The association with Hashimoto's thyroiditis, when present, can raise the suspicion of lymphoma in the thyroid. Traditionally, thyroid lymphoma has been difficult to discern from other malignant thyroid neoplasms, particularly anaplastic carcinoma. FNAC appears to be a valuable diagnostic tool in the work up of these lesions (Wirtzfeld et al, 2001). Although a definitive diagnosis may not be reported, it may outrule carcinoma, which in itself is valuable information.

Wedge biopsy in such cases is preferable to thyroidectomy with its potential risks to the recurrent laryngeal nerves and parathyroid glands. Previously thyroidectomy was felt to be an appropriate treatment modality for TL but this is not now believed to be the case. Some reports suggest that while the role of surgery is largely diagnostic, a few patients with significant upper aerodigestive tract obstructive symptoms may benefit from palliative surgical removal of the gland if a delayed response to non-surgical treatment, combination chemotherapy and/or radiation, would be poorly tolerated (Sippel et al, 2002). This would represent a minority of patients with this rare disease and does not obviate the need for postoperative combined modality treatment as appropriate.

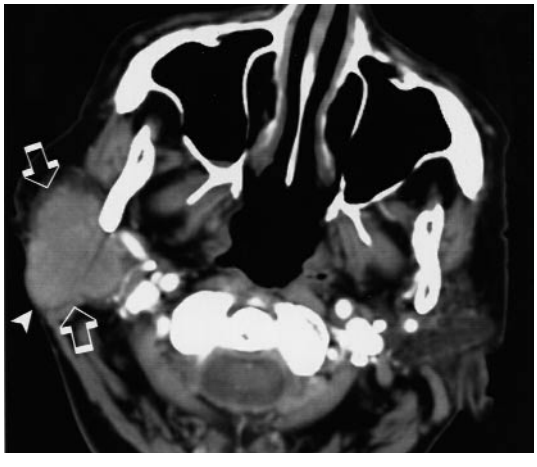

Figure 4. Axial computed tomography (CT) scan of a 65-year-old patient with B-cell non-Hodgkin's lymphoma of the parotid gland involving superficial and deep lobes, and overlying skin (arrow head). Notice the infiltrative ill-defined tumour margins (hollow arrows).

DIAGNOSTIC CHALLENGES

Diagnosis of extranodal NHL of the head and neck in the aforementioned sites can often prove challenging. Lymphomatous lesions within these sites closely resemble other tumours that can also occur. A history of rapid enlargement of the parotid or thyroid can suggest the possibility of lymphoma.

A positive history for Sjögren's syndrome, rheumatoid arthritis, Hashimoto's thyroiditis, immunosuppression and previous NHL should alert the clinician to the increased likelihood of lymphomatous disease. Computer tomography (CT) and magnetic resonance imaging (MRI) appearances of extranodal NHL in the head and neck are not specific. Modern immunocytopathological techniques have improved the accuracy of FNAC diagnosis of these lesions and may facilitate a diagnosis in a high proportion of cases, particularly if flow cytometry and clonality analysis is available (Cannon and Richardson, 2000).

It is important to bear in mind that, within the affected tissue, large areas of inflammatory tissue may be present and fine needle aspiration (FNA) biopsy may miss malignant cells. The gold standard of diagnosis still remains tissue biopsy. However, even with extensive tissue biopsy, it can be difficult for the pathologist to confirm lymphoma. In the case of NK/T-cell NHL, large amounts of ischaemic or necrotic tissue may be present rendering the biopsy specimen non-diagnostic. It is important that all surgical specimens are handled in a gentle manner to avoid distorting the architecture for the pathologist and sent directly to the laboratory to the awaiting pathologist.

CONCLUSIONS

Extranodal NHL of the head and neck is often seen by otolaryngologists. It can mimic other malignant lesions in its symptoms and clinical examination. It is important to be aware that any head and neck lesion may represent extranodal lymphomatous disease. As the incidence of NHL continues to rise worldwide, extranodal disease of the head and neck will be increasingly encountered.

A full history for patients with head and neck lesions should include risk factors for

lymphomatous disease and the presence or absence of B symptoms. In addition to locoregional lymph nodes, particular care should be taken to identify any lymphadenopathy in the major peripheral nodal groups. FNA biopsy should be performed but tissue biopsy remains the gold standard for diagnosis of these lesions. **HM**

Conflict of interest: None

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KEY POINTS

- The head and neck is the second most common site of presentation of extranodal non-Hodgkin's lymphoma (NHL).
- The most affected sites are Waldeyer's ring, nose/paranasal sinuses, major salivary glands, thyroid gland, in descending order of frequency.
- The presentation of extranodal NHL is often similar to carcinomas and other malignant entities that can occur in these regions
- Most are B-cell lymphomas but racial variations include the predominance of T-cell and NK/T-cell subtypes in nasal lymphomas in Asian and some South American races.
- The role of the surgeon is mainly diagnostic as these lesions are both chemosensitive and radiosensitive.
- Improving immunocytopathology techniques may obviate the need for extensive surgical diagnostic procedures such as parotidectomy for parotid lymphoma or thyroidectomy for thyroid lymphoma.
- Worldwide increasing incidence of NHL would suggest that extranodal manifestations in the head and neck region will also be increasingly encountered. Extranodal NHL should be considered in the differential diagnosis of all head and neck masses.