

Lymphomas Involving Waldeyer's Ring: Placement, Paradigms, Peculiarities, Pitfalls, Patterns and Postulates

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Abstract

Introduction: This review revisits Waldeyer's ring lymphomas as classified by the World Health Organisation. **Materials and Methods:** Sources of data include international studies on Waldeyer's ring lymphomas as well as from personal observations gleaned from lymphoma statistics of Singapore General Hospital, Changi General Hospital, Tan Tock Seng Hospital and National University Hospital within the last decade or so. **Results:** Waldeyer's ring shares many of the histopathological trends of the rest of mucosa-associated lymphoid tissue (MALT), such as the high frequency of diffuse large B-cell lymphomas, and the relative rarity of follicular lymphomas in spite of its rich endowment with reactive lymphoid follicles. However, extranodal marginal zone lymphoma or "MALToma" may not be as frequently encountered as in other mucosal sites. Furthermore, the placement of Waldeyer's ring is unique in that stark comparisons with the lymphopathology of the immediately anterior oronasal cavities can be made, with intriguing peculiarities such as the abrupt reversal of the ratio of B-cell to T/NK-cell lymphoma frequency upon crossing the imaginary line that separates the 2 regions. The differential diagnosis with regionally common lymphoma mimics, in particular reactive parafollicular hyperplasia and nasopharyngeal undifferentiated (lymphoepithelial) carcinoma of Schmincke pattern, both often aetiologically related to Epstein-Barr viral infection, is also discussed. **Conclusions:** Recognition of the peculiarities and patterns of Waldeyer's ring lymphomas is important for accurate pathologic assessment. Postulates that attempt to account for the patterns and peculiarities of Waldeyer's ring lymphopathology can be used to direct further research.

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Introduction

As the histopathological diagnosis of any lymphoma still largely hinges upon the demonstration of lymphoid architectural abnormality, the pathologist must first be cognizant of the histology of normal and reactive lymphoid tissue in all contexts, particularly in extranodal tissue such as Waldeyer's ring where unfamiliarity with lymphoid histological landmarks potentiates diagnostic difficulty.

Waldeyer's ring will now be reviewed in terms of its anatomical, immunophysiological and histoarchitectural paradigms, in order to interrelate these properties to its lymphoma pathology, as classified according to the current diagnostic criteria of the World Health Organisation (WHO), thereby allowing identification of characteristic

patterns and peculiarities which can be used to guide diagnosis and further research.

Waldeyer's Ring: Anatomical Placement

Waldeyer's ring consists of the lymphoid tissue of the nasopharynx and oropharynx. The former, in turn, comprises the adenoids ("pharyngeal tonsil") and the lymphoid tissue around the pharyngeal openings of the Eustachian tubes (tubal or Gerlach's tonsils), while the latter consists of "the" (palatine) tonsils, as well as the lymphoid tissue of the soft palate and posterior third or base of the tongue (lingual tonsil).^{1,2} Together, these form a roughly circular threshold to the opening of the upper aerodigestive tract. Hence, Waldeyer's ring represents the initial locus of contact

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between inhaled or ingested, exogenous antigen and the mucosa-associated lymphoid tissue (MALT) of the aerodigestive tract.

Lymphoid Tissue: Immunophysiological and Histoarchitectural Paradigms

The immunophysiological function of peripheral lymphoid tissue, including lymph nodes, MALT and splenic white pulp, has well-defined histoarchitectural correlates. B-cells proliferate, are clonally selected, and mature in follicles, whereas T-lymphocytes home into and reside in the richly-vascularised, interfollicular and paracortical (or parafollicular) zones.^{3,4} The paradigm of an antigen-sampling “percolator” exemplified by the lymph node,⁴ through which body fluids trickle and are filtered by the B- and T-cell components of the immune system (Fig. 1), may be applied essentially to any peripheral lymphoid organ for a more complete, correlative understanding of the lymphoid system (Table 1), and of pathology occurring therein.

As Waldeyer's ring represents the initial locus of contact between exogenous antigen and the (MALT of the) aerodigestive tract, it invokes the immunophysiological paradigms of MALT,² including a reactive lymphoid tissue structure similar to that of the lymph node, except that modifications are present to allow antigen sampling from luminal content rather than from percolating lymph (Fig. 2).

WHO Lymphoma Classification: Principles

The current WHO lymphoma classification characterises distinct lymphoma entities based on a multiparametric integration of morphology, immunoarchitecture and phenotype, cytogenetics and molecular genetics, as well as clinical behaviour.⁵ This therefore has advantages over preceding lymphoma classification systems, which were often limited to morphology and minimal immunophenotyping, such that distinct entities that closely resembled one another were either confused with each

other or were difficult to categorically separate, e.g. small lymphocytic lymphoma versus mantle cell lymphoma, mantle cell lymphoma versus low-grade follicular lymphoma, and follicular lymphoma with marginal zone differentiation versus marginal zone lymphoma with follicular colonisation.⁵

The nomenclature of lymphomas by such multiparametric analysis has thus become correspondingly complex, although in the current WHO classification system, it is still based largely on reference of the lymphoma cells to the components of normal or reactive lymphoid tissue that they most closely resemble, i.e. their postulated normal or reactive counterparts (Fig. 3).⁵ While this system has obvious limitations in that some lymphoproliferations bear no resemblance whatsoever to any normal or reactive lymphoid component, an alternative system of nomenclature would be difficult to devise, let alone establish. In addition, the full potential of the usefulness of the current system of nomenclature has probably not been realised, as many aspects of the normal immune system are still not completely understood and continue to be elucidated.

Waldeyer's Ring: Peculiarities in Lymphoma Pattern

Let us now turn to the patterns in lymphoma pathology that make Waldeyer's ring distinctive. Where possible, large international and local series of Waldeyer's ring lymphomas are quoted to support the inferences made. Local series include lymphoma statistics drawn from 4 major hospitals in Singapore – namely Singapore General Hospital (SGH), Changi General Hospital (CGH), Tan Tock Seng Hospital (TTSH) and National University Hospital (NUH) – over the decade of the 1990s. Data from the first 3 hospitals were presented at the 32nd Singapore-Malaysia Congress of Medicine incorporating the 9th Annual Scientific Meeting of the Chapter of Pathologists, Academy of Medicine, Singapore and the Singapore Society of Pathology in 1998 (Tan L, Sng I. Waldeyer's ring lymphomas – a preliminary histopathologic and immunophenotyping study). Data from the Department of Pathology, National University of Singapore (Tan LHC, unpublished data) from 1991 to 1999 were gleaned retrospectively, with the help of the Singapore Cancer Registry.

Lymphomas of Small B-cells

Despite its rich endowment with reactive lymphoid follicles, lymphomas of small B-cells that differentiate towards each of the 3 zones of the lymphoid follicle – namely, the marginal zone, mantle zone and germinal centre – are rare in Waldeyer's ring.^{2,5} As such, the salient morphologic, immunophenotypic, genetic and aetiological features⁵ have been summarised in Table 2 and will not be further dealt with here.

Table 1. “Immunological Percolator” Paradigm of Lymph Node, Spleen and MALT, Including Waldeyer's Ring

Organ (“percolator”)	Fluid filtered	Transport system	External interface
Lymph node	Tissue fluid (lymph)	Sinuses	Capsule
Spleen	Blood	Sinusoids (red pulp)	Capsule
MALT	Luminal content	Lamina propria	Epithelium

MALT: mucosa-associated lymphoid tissue

Table 2. Cardinal Features of Waldeyer's Ring Lymphomas Recognised by the World Health Organisation

Type	%*	Architecture	Cytology	Immunophenotype†	Cytogenetics	Aetiology
ENMZL of MALT	0-3.6%	marginal, nodular, follicular colonisation, diffuse, LEL	polymorphous, monocytoid, "centrocyte-like", plasmacytoid	non-germinal centre B	heterogenous; largely unknown for Waldeyer's ring	chronic antigenic stimulation
MCL	3-4%	mantle, nodular or diffuse	small to medium, irregular	non-germinal centre B CD5+ CD23-	t(11;14)(q13;q32)	promotion of <i>Cyclin D1/bcl-1</i> gene on 11q13 by juxtaposed <i>IgH</i> gene on 14q32
LGFL	6-9%	follicular ± diffuse	majority centrocytes, minority centroblasts	germinal centre B	t(14;18)(q32;q21)	promotion of antiapoptotic gene <i>bcl-2</i> on 18q21 by juxtaposed <i>IgH</i> gene on 14q32
DLBCL	66-75%	diffuse or pseudonodular	centroblasts, immunoblasts, or mixture	germinal centre B or non-germinal centre B	heterogenous	largely unknown; ? transformed low-grade B-cell lymphomas
BL	3-5%	diffuse	medium-sized centroblasts	germinal centre B	t(8;14)(q24;q32) t(2;8)(q11;q24) t(8;22)(q24;q11)	promotion of <i>c-myc</i> on 8q24 by juxtaposed <i>Ig</i> genes; role of EBV uncertain (see text)
PT/NKCL	6-19%	diffuse, parafollicular/interfollicular	spectrum of cells with nuclear irregularity, often with clear cytoplasm	T-cell phenotype ± variable loss of pan-T cell Ag ± NK phenotype	variable	"Nasal"-type NK-cell lymphomas highly associated with EBV
EP	3-10%	diffuse or interfollicular	mature plasma cells	cytoplasmic Ig with light-chain restriction; CD138+ with variable loss of surface pan-B cell Ags	not known	? extreme maturation of ENMZL of MALT

BL: Burkitt's lymphoma; DLBCL: diffuse large B-cell lymphoma; EBV: Epstein-Barr virus; ENMZL: extranodal marginal zone lymphoma; EP: extraosseous plasmacytoma; LEL: lymphoepithelial lesions; LGFL: low-grade follicular lymphoma; MALT: mucosa-associated lymphoid tissue; MCL: mantle cell lymphoma; PT/NKCL: peripheral T/natural killer-cell lymphoma;

Footnotes

* Frequencies derived from sources quoted in text, except where definition of entity in particular source does not satisfy criteria of WHO classification⁵

† Pan-B cell antigens (Ags) include CD20 and CD79a

Germinal centre B-cells are pan-B Ag+, CD10+, bcl-6+, CD5-, CD23-

Non-germinal centre B-cells are pan-B Ag+, CD10-, bcl-6-

Pan-T Ags include CD2, CD3, CD5 and CD7

NK cell phenotype includes expression of CD56 and T-cytotoxic markers (e.g. CD8+, Granzyme B+)

Extranodal Marginal Zone Lymphoma of MALT

Although common in other MALT sites, where they often arise in a background of chronic inflammation or autoimmune disease (e.g. gastric MALT lymphoma arising in *Helicobacter pylori* gastritis, salivary MALT lymphoma in Sjogren's syndrome and thyroid MALT lymphoma in Hashimoto's thyroiditis),^{2,5} these lymphomas constitute only a minority in Waldeyer's ring, the percentages derived from various large series being 3.6% of 329 cases,⁶ 1.3% of 79 cases⁷ and 0% of 65 cases (SGH/TTSH/CGH, 1992-1996).

Mantle Cell Lymphoma

This again, is a rare entity in Waldeyer's ring, quotable

percentages being: 11% "centrocytic" of 79 cases,⁷ 4% of 77 cases⁹ and 3% of 65 cases (SGH/TTSH/CGH 1992-1996).

One of the outcomes of the recent change in lymphoma classification is that mantle cell lymphoma under the current WHO classification has been found to correspond largely to what used to be called "centrocytic lymphoma" in the preceding Kiel classification.⁸ However, it is difficult to ascertain from Menarguez's series⁷ if the term "centrocytic" had incorporated other lymphomas of small, irregular B-cells ("centrocytes"), especially low-grade follicular lymphomas, since their study was done before the establishment of the current criteria formulated for the WHO classification.⁵

Mantle cell lymphoma is also uncommon in other MALT sites, although in the large bowel, it is the most common lymphoma subtype associated with lymphomatous polyposis,^{2,5} and has been found to express the mucosal-homing integrin $\alpha_4\beta_7$, in contradistinction to its nodal counterpart, which does not.⁵

Low-grade Follicular Lymphoma

Quoted figures for the frequency of follicular lymphoma in Waldeyer's ring lymphoma series are: 6% of 79 cases,⁷ 6% of 77 cases⁹ and 9% of 65 cases (SGH/TTSH/CGH, 1992-1996).

Follicular lymphomas are also uncommon in other MALT sites,² the duodenum being most recently reported to be the commonest primary site within the gastrointestinal tract,^{10,11} where expression of the mucosal-homing integrin $\alpha_4\beta_7$ may also play a role in its localisation.¹²

The reasons for these peculiarities in lymphoma distribution are yet unknown, but whatever molecular genetic events responsible for lymphomatous transformation in MALT sites appear distinct from those operating in lymph nodes, despite their common B-follicle-rich paradigm.²

High-grade B-Cell Lymphomas

Diffuse Large B-Cell Lymphoma

These are lymphomas composed of patternless sheets of large, transformed lymphoid cells with variable cytoplasmic content and enlarged, vesicular nuclei containing dispersed (activated) chromatin that allows one-to-several nucleoli to become visible in each nucleus (Fig. 4). This turns out to be the largest group of lymphomas involving Waldeyer's ring, quoted figures in large series being: 57% "centroblastic" (i.e. morphologically resembling the B-blasts of the germinal centre) of 79 cases,⁷ 66% of 77 cases⁹ and 75% of 65 cases (SGH/TTSH/CGH, 1992-1996).

Since the current WHO lymphoma classification does not require sub-categorisation of diffuse large B-cell lymphomas, numbers are large probably because this group is heterogeneous and incorporates more than 1 disease entity, as suggested by the presence of differences in gene expression profile and prognosis between a "germinal centre-like" (better prognosis) and an "activated B-cell like" (poorer prognosis) subgroup using microarray technology.¹³ Whether these would turn out to correspond respectively to "centroblasts" and "immunoblasts" as they are morphologically recognised remains to be seen; at present, there appears to be no such correlation.⁵

Further evidence for the heterogeneity of this group comes from our own local series of 65 cases collated in SGH from 1992 to 1996, incorporating case inputs from TTSH and CGH (then representing the Toa Payoh Hospital

catchment area as well). In this series, there were a total of 30 cases confined to Waldeyer's ring (Stage 1E) and 30 cases with regional (cervical) lymph node involvement concurrent with, subsequent to, or not more than 6 months prior to involvement of Waldeyer's ring (Stage 2E, Table 3). Their ethnic compositions were similar and their gender ratios not significantly different. However, the mean ages of Stages 1E and 2E patients were 46 and 59 years, respectively, with the difference of 13 years being statistically significant ($P = 0.005$, Student's *t*-test). As the majority of cases in both stages (67% of Stage 1E and 83% of Stage 2E) were diffuse large B-cell lymphomas, which progress rapidly, such a disparity in mean age between the 2 groups suggests that they might not represent different stages of the same disease, but different diseases altogether.

Moreover, the mean age of our Stage 1E patients appears to match closely that of Ye et al's series of Chinese patients (45 years),¹⁴ while that of our Stage 2E patients is more in keeping with the mean ages in the studies done by Menarguez et al in Spain (55 years)⁷ and Krol et al in the Netherlands (66 years),⁹ implying that clinicopathologic heterogeneity may also be related to divergent ethnicity. Proof of these impressions awaits additional clinicopathologic and molecular genetic correlation.

Burkitt's Lymphoma

In its non-endemic forms, Burkitt's lymphoma is rare in Waldeyer's ring,⁵ locally (3% of 65 cases, SGH/TTSH/CGH, 1992-1996) as well as overseas (5% of 79 cases⁷). However, it is important to recognise as an oncologic emergency, being a highly aggressive lymphoma characterised primarily by activation of the *c-myc* oncogene that drives its cell proliferation fraction to virtually 100%, thereby rendering it also highly chemosensitive and prone to the tumour lysis syndrome.⁵ Activation of the *c-myc* oncogene on chromosome 8q24 occurs by translocation to 1 of the immunoglobulin (Ig) gene promoters (the μ heavy chain gene [*vide infra*] on chromosome 14q32 and the kappa and lambda light chains on chromosomes 2q11 and

Table 3. Stage 1E/2E Lymphomas of Waldeyer's Ring in SGH, TTSH and CGH from 1992 to 1996 Inclusive

Stage	1E (Nodes-)	2E (Nodes+)
Total no.	n = 30	n = 30
Age range (y)	5 to 82	15 to 85
Mean age (y)	46*	59*
M:F ratio	1:1.3	1.5:1
% Chinese	76.7	63.3
No. of DLBCL (%)	20 (66.7%)	25 (83.3%)

CGH: Changi General Hospital; DLBCL: diffuse large B-cell lymphoma; E: extranodal; M:F: male:female; SGH: Singapore General Hospital; TTSH: Tan Tock Seng Hospital

* $P = 0.005$ (Student's *t*-test)

22q11, respectively), corresponding to consistently recurrent cytogenetic abnormalities: usually t(8;14)(q24;q32) and less commonly t(2;8)(q11;q24) or t(8;22)(q24;q11).^{2,5}

Morphologically and phenotypically, Burkitt's lymphoma is a B-cell lymphoma that recapitulates the early blast cell stage of the germinal centre. Common to both these neoplastic and reactive counterparts is a germinal centre phenotype (bcl-6 and CD10+), as well as the presence of ongoing somatic hypermutation in the variable regions of their Ig genes.⁵ However, unlike low-grade follicular lymphoma, these counterparts are not protected from apoptosis, being bcl-2-negative⁵ which, coupled with a high proliferation fraction, results in a high cell turnover imparting the well-known "starry sky" appearance of tingible-body macrophages^{2,5} ("stars") against a basophilic background of proliferating blasts ("sky"). Although by no means specific to Burkitt's lymphoma,^{2,5} this forms the basis of the morphological similarity between Burkitt's lymphoma (Fig. 5a) and the dark (proliferative) zone of the germinal centre (Fig. 5b).

Although latent Epstein-Barr (EB) viral infection has been a long-standing association, this is true mainly for the endemic form in which all cases harbour the virus, and is rare outside the African continent; the rates of latent EB viral infection in the sporadic and immunodeficiency-associated forms are much lower, being less than 30% and 25% to 40% respectively.⁵ Furthermore, the virus resides in the lymphomatous cells in Latency I (Lat I),^{15,16} expressing only EB nuclear antigen (EBNA)-1 which is required for replication of the viral episome, but does not provoke a cytotoxic T-lymphocytic reaction.¹⁵ The major transforming viral oncoprotein, latent membrane protein (LMP)-1, which can be recognised by T-lymphocytes, is not expressed in Burkitt's lymphoma, but in acute infectious mononucleosis (IM) which represents the first contact of the unprimed immune system with the virus,^{16,17} as well as in entities harbouring the virus in higher latency states (Lat II and III) that are associated with some form of deficiency in T-cell immunosurveillance.^{15,16} In the latter entities, LMP-1 functions as a constitutively active (autonomous) tumour necrosis factor (TNF) receptor that perpetually activates DNA transcription via the nuclear factor-kappa-B (NF-κB) pathway.^{15,16}

Moreover, *in situ* hybridisation studies for EB-encoded small RNAs (EBERs) in acute IM,¹⁷⁻¹⁹ latently-infected reactive lymphoid tissue from both human immunodeficiency virus (HIV)-negative¹⁹ and HIV-positive²⁰ individuals, acquired immune deficiency syndrome (AIDS)-related non-Hodgkin's lymphoma (NHL),^{20,21} as well as Hodgkin's lymphoma²² have indicated that the virus preferentially localises outside germinal centres, whose

environment appears to be relatively non-permissive to it, particularly if LMP-1 is expressed,^{17,20} as in acute IM^{16,17} as well as in Lat II and III.^{15,16} Conversely, LMP-1 expression has been found to suppress germinal centre formation,^{16,17} probably through downregulation of bcl-6 which is essential for the germinal centre reaction²³ (see "Reactive Hyperplasia Simulating Lymphoma") and whose expression has been found to be inversely related to that of LMP-1 in NHL, albeit in the AIDS setting.^{20,21} These observations are entirely consistent with the germinal centre (bcl-6+) phenotype of Burkitt's lymphoma and the Lat I state of the EB virus that it harbours (i.e., lacking LMP-1 expression).

In addition, the immunodominant antigens, namely EBNA3A, 3B and 3C that are seen only in acute IM and Lat III and are the main targets of cytotoxic T-cell recognition,¹⁵ are also not expressed in Lat I.^{15,16} As a result, Burkitt's lymphoma can arise in fully immunocompetent hosts, in whom expression of viral proteins that would otherwise contribute to oncogenesis are being held in check by a functioning immune system.^{5,15} Therefore, EB virus may represent only a "passenger" in Lat I and may not be an essential contributor to the genesis of Burkitt's lymphoma⁵ which, after all, is already driven by a powerful, translocation-promoted, oncogene (*c-myc*) that hardly requires any "assistance" to effect neoplastic transformation!¹⁵

Last but not least, another latent viral protein, EBNA2, is also not expressed in classical Lat I, i.e. it is not found in Burkitt's lymphoma cells *in vivo*.^{15,16} However, *in vitro* activation of EBNA2 in a Burkitt's lymphoma cell line was found to lead to growth arrest, because EBNA2 suppressed transcription of the Ig μ heavy chain gene which, in turn, was responsible for driving the translocationally-linked *c-myc* oncogene!²⁴ Besides the obvious therapeutic implication, this experiment suggested that EBNA2 protein expression is not compatible with Burkitt's lymphoma cell proliferation, another reason for the lymphoma to be associated with only the most rudimentary of EB viral latency states.

Peripheral T/NK (Natural Killer)-Cell Lymphomas

As a rule, these are also rare in Waldeyer's ring. Only 4 (6%) of the 65 cases from SGH, TTSH and CGH seen from 1992 to 1996 were of T-cell phenotype. Separate data accumulated from 1991 to 1999 came from NUH (Table 4). Of 26 Waldeyer's ring lymphomas, only 5 (19%) were of T-cell phenotype, resulting in a B:T-cell lymphoma ratio of 4.2, which compares with that of the gastrointestinal tract, at 7.3. During the same period, 7 (70%) of 10 sinonasal lymphomas displayed a T-cell phenotype, yielding an inverted B:T-cell lymphoma ratio of 0.4, agreeing closely with the ratio of 0.3 in the series of Ye et al,¹⁴ and

Table 4. Comparative Phenotyping of Extranodal Lymphomas in NUH from 1991 to 1999 Inclusive (n = 45)

Site	B	T	Total No. (%)	B:T ratio
Tonsil	14	0	14 (31)	∞
Oropharynx	2	2	4 (9)	1.0
Nasopharynx	5	3	8 (18)	1.7 (1.05*)
Total Waldeyer's	21	5	26 (58)	4.2
Gastrointestinal	29	4	33	7.3
Sinonasal	3	7	10 (22)	0.4 (0.3*)
Skin	2	3	5	0.7

*Ye et al¹⁴ (n = 54)

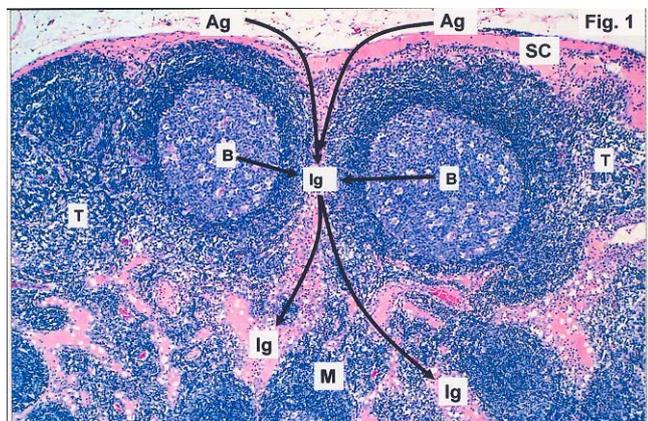


Fig. 1. The lymph node filters antigens (Ag) in tissue fluid through a system of sinuses: afferent lymph collects within the subcapsular sinus (SC), where it proceeds to bathe the B-follicles (B) and trickle towards the nodal medulla (M), in which sinuses coalesce and their fluid contents, rich in immunoglobulin (Ig) finally exit as efferent lymph. "T" denotes interfollicular/parafollicular zone of T-lymphocytes. [haematoxylin and eosin (H & E), x20]

resembling that of NUH-diagnosed cutaneous lymphomas at 0.7. These comparisons are also in agreement with the personal observations of Jaffe (Jaffe ES, personal communication, *Tutorial on Neoplastic Hematopathology* organised by the Department of Pathology, Weill Medical College of Cornell University, 3 to 7 February 2003) and appear particularly striking in a country such as Singapore, whose regional geographic placement and ethnic constitution appear to engender the predominance of extranodal over nodal lymphomas.

What could account for these striking trends? The imaginary line that separates the elements of Waldeyer's ring, including the nasopharynx (postnasal space) and oropharynx, which incorporates the soft palate superiorly and posterior third (or "base") of the tongue inferiorly; from the anterior sinonasal spaces and the buccal cavity,

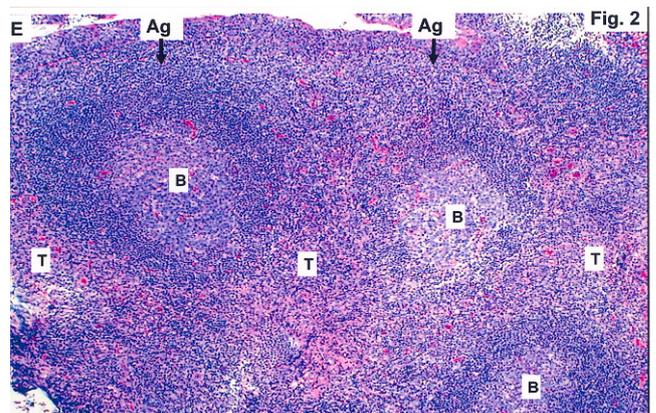


Fig. 2. In MALT, including Waldeyer's ring, there is a reactive lymphoid tissue structure similar to that of lymph nodes, except that the capsule is replaced by epithelium (E) and sinuses are absent, allowing Ag sampling from luminal content rather than from percolating lymph (H&E, x20).

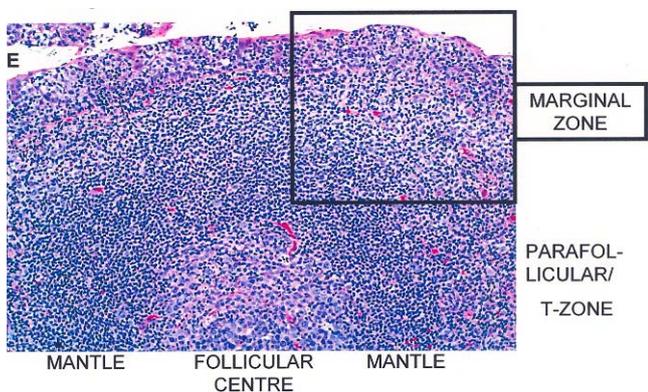


Fig. 3. The current WHO lymphoma classification system is still based largely on reference of lymphoma cells to the components of normal or reactive lymphoid tissue that they most closely resemble, i.e. their postulated normal or reactive counterparts, shown here in the context of Waldeyer's ring. "E" denotes epithelium (H&E, x40).

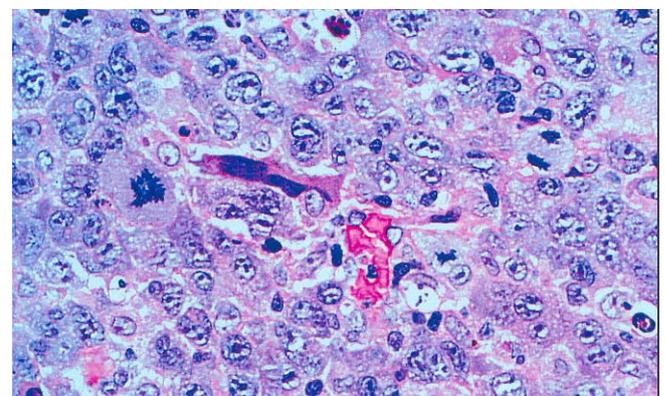


Fig. 4. A diffuse large B-cell lymphoma is composed of patternless sheets of large, transformed lymphoid cells with enlarged, vesicular nuclei, each containing dispersed (activated) chromatin and one-to-several visible nucleoli (H&E, x600).

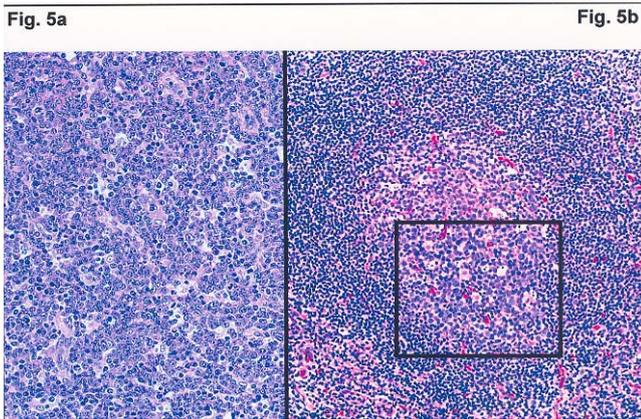


Fig. 5. The well-known “starry sky” appearance of tingible-body macrophages (“stars”) against a basophilic background of proliferating blasts (“sky”) forms the basis of the morphological similarity between (a) Burkitt’s lymphoma (H&E, x100) and (b) the dark (proliferative) zone (boxed) of the germinal centre (H&E, x40). This morphological impression is supported by their shared expression of germinal centre markers (CD10 and *bcl-6*, not shown), and by the presence of ongoing somatic hypermutation in the variable regions of their Ig genes.

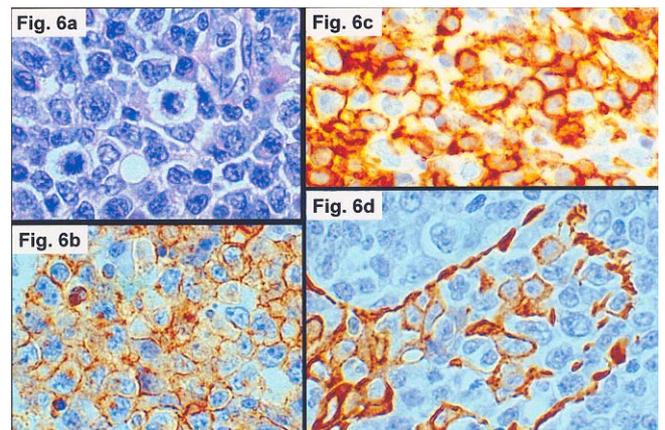


Fig. 6. Being epitheliotropic, T/NK-cell lymphomas, shown here by (a) routine histology (H&E, x600) and positivity for (b) CD8 (immunoperoxidase, x600) and (c) CD56 (immunoperoxidase, x600), may also produce (d) lymphoepithelial lesions mimicking those of MALT lymphomas, which are of B-lineage (cytokeratin immunoperoxidase, x600), removing from this histological phenomenon any connotation of “lineage specificity” in lymphomas.

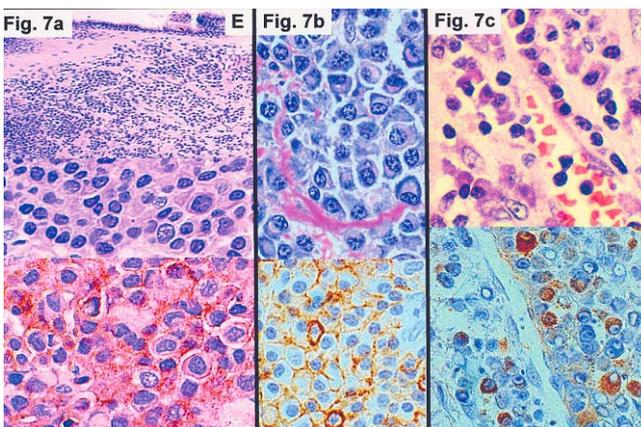


Fig. 7. Plasma cell infiltrates by routine H&E staining (top row) and immunoperoxidase for CD56 (bottom row). (a) An unusual case of multiple myeloma presenting with proptosis and a nasopharyngeal mass (respiratory epithelium is marked “E”, top, x20), retaining strong CD56 immunoreactivity (bottom, x600) despite extramedullary dissemination. (b) Extrasosseous plasmacytoma may also be CD56-positive, although the staining pattern is patchier, with a more variable intensity than in myeloma of osseous origin (x600). (c) Scattered, weakly CD56-immunoreactive plasma cells, seen here in their typical perivascular arrangement, may be encountered in reactive plasmacytosis (x600).

including the hard palate superiorly and anterior two-thirds of the tongue inferiorly, represents where the regressed buccopharyngeal membrane used to lie in embryonic life, marking the cephalic plane of fusion between the endoderm and the ectoderm respectively.¹ Waldeyer’s ring is therefore an endodermal derivative while the anterior oronasal spaces are lined by ectodermal derivatives; perhaps the peculiar distribution of B- and T/NK-cell lymphomas in the head and neck can be linked to characteristic homing patterns, possibly generated by distinct cytokine networks and adhesion molecules that may be associated with the

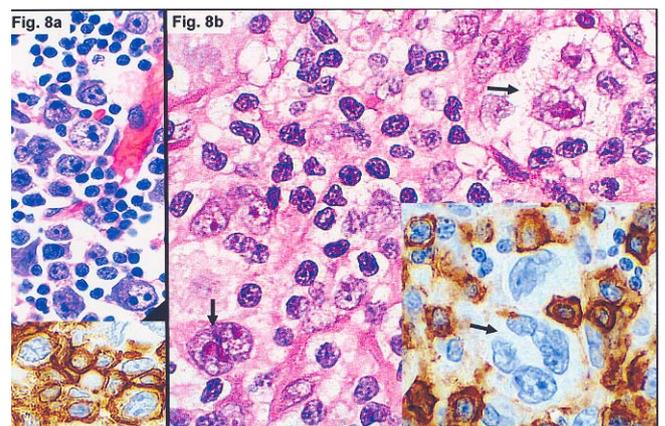


Fig. 8. (a) Extrafollicular activated B-cells (immunoblasts) in parafollicular hyperplasia demonstrate a spectrum of plasmacytic maturation (H&E, top, x600), often with positivity for LCA (immunoperoxidase, bottom, x600), both features being absent in (b) classical Hodgkin’s lymphoma, in which RS cells (H&E, arrow, x600) stand out against the reactive cellular background and are LCA-negative (immunoperoxidase, inset, x600).

derivatives of the different germ layers.

Although lymphoepithelial lesions have characteristically been associated with extranodal marginal zone B-cell lymphomas of MALT,^{2,5} T/NK-cell lymphomas, being often epitheliotropic, may also produce lymphoepithelial lesions (Fig. 6), removing from this histological phenomenon any connotation of “lineage specificity” in lymphomas.²⁵ Furthermore, since the presence of lymphoepithelial complexing merely reflects the antigen-sampling behaviour of reactive (non-neoplastic) marginal zone or memory B-cells (Fig. 3),² the presence of lymphoepithelial lesions alone in Waldeyer’s ring is bereft

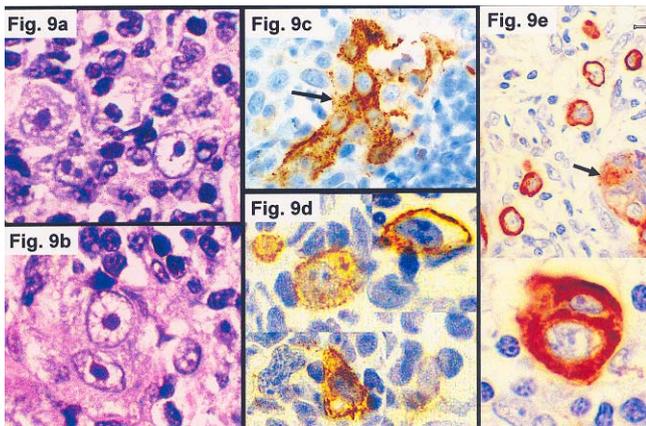


Fig. 9. Schmincke-pattern undifferentiated (lymphoepithelial) carcinoma of nasopharyngeal origin may present as a cervical lymph node metastasis, mimicking classical Hodgkin's lymphoma (a) histologically (H&E, x600) and (b) cytologically, with RS-like cells (H&E, x600), as well as immunophenotypically by expression of (c) CD15 (immunoperoxidase, x600) and (d) CD30 (immunoperoxidase, x600). (e) Immunoreactivity for cyokeratin confirms the carcinomatous nature of the tumour cells, and excludes a lymphoma (immunoperoxidase, x600). Note that immunostaining, as in (c) and (e), may also "unmask" short-range intercellular cohesion in the form of microscopic tumour cell clusters (arrow), further belying their epithelial (carcinomatous) nature.

even of neoplastic connotations.^{6,7}

Extraosseous Plasmacytoma

The WHO now groups plasma cell neoplasms, including myeloma and extraosseous⁵ (extramedullary) plasmacytoma (plasmacytic lymphoma),² under mature B-cell neoplasms by their immuno-ontogeny, although in the past, extraosseous plasmacytomas have not been consistently included in "lymphoma" series, particularly in Waldeyer's ring. Thus, while approximately 80% of all extraosseous plasmacytomas arise in the upper respiratory tract, including Waldeyer's ring sites,^{2,5} some lymphoma studies,⁷ including our local series, from SGH/TTSH/CGH in 1992 to 1996, and from NUH in 1991 to 1999, have excluded this tumour, making it difficult to compare its relative frequency between series. In overseas studies that have included extraosseous plasmacytoma, incidences quoted are 3% of 77 cases⁹ and 10% of 41 cases¹⁴, although the latter figure is restricted to a nasopharyngeal location. The WHO concedes that some extraosseous plasmacytomas may represent MALT lymphomas with extreme plasmacytic differentiation;⁵ perhaps this could account (or "compensate") for the rarity of MALT lymphomas diagnosed in Waldeyer's ring sites.

Two of the problems that may be encountered in the overall clinicopathologic evaluation of extraosseous plasmacytoma are its differentiation from florid reactive plasmacellular (chronic inflammatory) infiltrates, which occur fairly often in Waldeyer's ring sites, as well as the exclusion of extramedullary dissemination of multiple

myeloma, which is a different disease.⁵ Although the former has traditionally been done by demonstration of Ig light chain restriction and the latter by clinicoradiological assessment, recent immunohistological studies have alluded to differences between plasma cells of reactive (polyclonal) and neoplastic (monoclonal) nature, as well as between those of osseous and extraosseous origin, in their expression of certain adhesion molecules of the Ig supergene family²⁶ – namely, CD31 or platelet-endothelial cell adhesion molecule-1 (PECAM-1)²⁶ and CD56 or neural cell adhesion molecule (N-CAM).^{5,27}

Govender et al²⁶ found strong, extensive CD31 immunoreactivity in all 20 extramedullary cases of reactive plasmacytosis, while only 50% of 10 extramedullary plasmacytomas and none of 8 extramedullary deposits and 12 medullary cases of multiple myeloma stained positively. Although they do not advocate the use of CD31 immunostaining to differentiate between reactive and neoplastic plasma cells,²⁶ it would appear from their results that in the context of an extramedullary plasmacellular neoplasm, positivity for CD31 would exclude an extraosseous deposit originating from a multiple myeloma and favour the diagnosis of a primary extraosseous plasmacytoma, although the converse – a negative CD31 immunostaining result – would not be helpful.

CD56 expression in multiple myelomas mimics its expression in normal osteoblasts, and is thought to mediate aberrant homophilic adhesion of myeloma cells to bone, being associated with lytic bone lesions,²⁷ and tending to be lost in those with extramedullary spread,²⁸ and in high-grade (plasmablastic) myelomas.²⁹ Nonetheless, the author has encountered a case of multiple myeloma that had retained strong CD56 immunopositivity despite extramedullary dissemination, this one presenting with proptosis and a nasopharyngeal mass (Fig. 7a). Furthermore, contrary to a recent study by Ely and Knowles²⁷ that had obtained negative staining for CD56 in 2 extramedullary plasmacytomas, the author has found that positive staining for this marker may also be seen in this entity, although the staining pattern is patchier, with a more variable intensity (Fig. 7b) than in myeloma of osseous origin. Ely and Knowles' study do, however, confirm the author's impression that occasional, weakly CD56-positive plasma cells may be encountered in reactive plasmacytosis²⁷ (Fig. 7c). Clearly then, further experience has to be accumulated for the use of CD56 immunostaining in the evaluation of plasma cell lesions.

Pitfalls in Immunophenotyping

Given the importance that immunophenotyping has gained with the development of the current WHO lymphoma classification, it is inevitable that pitfalls resulting from the

increased use of immunohistochemistry will become more frequent in routine diagnostic practice.

Reactive Hyperplasia Simulating Lymphoma

Reactive lymphoid hyperplasia usually results in expansion of both B- and T-cell compartments, giving rise to the well-recognised follicular architecture of reactive lymphoid tissue featuring prominent germinal centres containing tingible-body macrophages cuffed by distinct mantles (Figs. 1 to 3).^{3,4} On occasion, however, the B-cell compartment is diminutive and might be overshadowed by diffuse parafollicular (T-zone) hyperplasia, for example in cell-mediated immune responses to viral infections, particularly in acute IM,^{30,31} in which LMP-1 expression has been found to suppress germinal centre formation,^{16,17} probably through downregulation of bcl-6,²³ as alluded to earlier. This unfamiliar, diffuse-looking, extrafollicular proliferation, although reactive, may therefore masquerade as a lymphoma to the unwary, because of apparent loss of the better-recognised follicular landmarks of reactive lymphoid tissue.^{30,31}

On closer examination, such a mucosal T-zone hyperplasia can be seen to recapitulate all the features of lymph nodal T-zone (paracortical) hyperplasia, with the exception of the presence of sinuses. Thus, there would be a predominantly small, mature lymphocytic population with compact chromatin and indiscernible nucleoli, amongst which may be found scattered, large, transformed or “activated” lymphoid cells and histiocytes, including antigen-presenting interdigitating dendritic cells, with intervening high-endothelial venules.^{3,30,31} The activated lymphoid cells with dispersed chromatin should have minimal nuclear irregularity, and would usually comprise a mixture of B- and T-cells by immunophenotyping.³⁰ The B-cell subset of these large, transformed cells ought to demonstrate a spectrum of plasmacytic maturation in terms of nuclear eccentricity, chromatin clumping towards a “clockface” configuration, diminution of nucleoli and accrue of cytoplasm with increasing amphophilia as well as the development of perinuclear hofs (Fig. 8a);^{32,33} thus, they are the extrafollicular precursors of plasma cells and can therefore be termed B-immunoblasts.^{4,32,33}

In acute IM, these immunoblasts have long been known to be capable of assuming the cytomorphology of Reed-Sternberg (RS) cells of classical Hodgkin's lymphoma.³²⁻³⁷ This has recently been shown to be due to downregulation of the adhesion molecule CD99 by EB viral LMP-1,^{38,39} which is also expressed by RS cells in a variable proportion of classical Hodgkin's lymphoma cases (75% of the mixed cellularity type and 10% to 40% of the nodular sclerosing type).⁵ Thus, EB virus-infected B-immunoblasts, in common with RS cells of classical Hodgkin's disease, may evade the

immune system by deactivating the following functions of CD99: (1) expression on reactive memory T- and B-lymphocytes,⁴⁰ (2) regulation of leukocyte function antigen (LFA)-1/intercellular adhesion molecule (ICAM)-1-mediated lymphocyte adhesion,⁴¹ (3) promotion of T-cell receptor (TCR)/CD3-dependent cell activation and T_H1-restricted cytokine production,⁴² and (4) enhancement of CD4+ peripheral T-cell proliferation and activation.⁴³

Immunoblasts and RS cells, in common with other “activated” cells, whether reactive or neoplastic, express the activation marker CD30, which is routinely used to highlight RS cells in diagnostic histological sections,^{5,36,37,44,45} and is, like EB viral LMP-1, related to the TNF receptor group of molecules.⁴⁵ (Unlike LMP-1 which is constitutively active¹⁶, however, CD30 intracellular signalling is amenable to regulation and can be deactivated when necessary.⁴⁵) In cytomegaloviral infection, the immunoblasts, which may also have an “owl-eye” and therefore RS cell-like configuration, are known to further imitate RS cells by expressing CD15 (Leu-M1),⁴⁶ another non-specific activation antigen that also marks granulocytes,⁴⁶ histiocytes⁴⁶ and epithelial cells (the latter being thus discriminated from mesothelial cells in the context of effusion cytology,⁴⁷ vide infra), although absent from the immunoblasts of acute IM.^{36,37,48}

There are 3 “giveaways” to the correct diagnosis, especially in Waldeyer's ring sites such as the tonsil:

1. Hodgkin's lymphoma rarely presents initially in extranodal sites without contiguous nodal disease,⁵ and although it has been reported in Waldeyer's ring without cervical node involvement,⁴⁸ a differential diagnosis should be entertained in this location.
2. In classical Hodgkin's lymphoma, although mature plasma cells are present in the reactive cellular background, a spectrum of immunoblastic-to-plasmacytic maturation is not seen and, if present, tends to exclude Hodgkin's lymphoma.^{33,48} It is as though the RS cells were the neoplastic counterpart of immunoblasts that had been “frozen” in their neoplastic state and somehow lost the ability to complete the process of plasmacytic differentiation (Fig. 8b). Such has been the morphological acumen of Dr Robert Lukes for at least three decades.³³ Recent research has given support to his intuitions, because the maturation block in RS cells is also evident at the level of Ig expression, which is curtailed by various transcription factor deficits.^{49,50} Therefore, the presence of RS cells is only half the definition of Hodgkin's lymphoma, and it is worth remembering that the presence of “an appropriate cellular background” is equally, if not more, important in making this diagnosis.^{5,33,34}
3. The RS cells of classical Hodgkin's lymphoma are

negative for leukocyte common antigen (LCA, or CD45, Fig. 8b),^{5,36,37,48} whereas reactive immunoblasts often are positive (Fig. 8a),^{36,48} (although they may lose expression of this surface antigen³⁷ if committed towards more terminal stages of plasmacytic differentiation, since plasma cells have completed the B-lineage selection process and do not require many of the surface signalling molecules that regulate the survival of less mature B-lymphocytes).⁵¹ Thus, demonstration of LCA expression by RS-like cells tends to exclude classical Hodgkin's lymphoma. The RS cells in the nodular lymphocyte predominant variant of Hodgkin's lymphoma may express LCA,^{5,48} but this is even rarer in Waldeyer's ring,^{5,48} and is a proliferation based on abnormal germinal centres^{5,22,30} rather than on the parafollicular (T-)zone.^{5,22,30}

Lymphoepithelial Carcinoma Simulating Hodgkin's Lymphoma

One final differential diagnosis deserves our attention, particularly in the locoregional ethnic context.^{52,53} Undifferentiated "lymphoepithelial" carcinoma, most commonly in the nasopharynx,^{52,53} but also in other Waldeyer's ring sites,⁵⁴ may occasionally lose its conventional epithelial cohesiveness to spread as individual neoplastic cells amidst a lymphoplasmacellular reactive background^{48,52,53,55} – the so-called "Schmincke pattern"^{53,55} – thereby mimicking Hodgkin's lymphoma,^{48,55} particularly if presenting as a nodal metastasis (Figs. 9a and b). The mimicry of classical Hodgkin's lymphoma continues at the immunophenotypic level since the neoplastic cells in both entities lack expression of leukocytic markers including LCA^{5,48,53,55} and can be positive for CD15⁵ (Fig. 9c), which also highlights epithelial cells⁴⁷ as alluded to previously. Furthermore, Schmincke-pattern undifferentiated carcinoma cells can occasionally be positive for CD30⁴⁴ (Fig. 9d), since this is really a non-specific activation marker and is by no means restricted to lymphoid lineages.^{44,45} The neoplastic cells in both entities may also harbour the EB virus,^{5,48,52,53,55} and if so, in Lat II with expression of LMP-1.^{16,56}

These similarities notwithstanding, a distinction between these 2 entities is most easily made using immunohistochemistry for cytokeratins, which will highlight epithelial (including carcinoma) cells and not RS cells^{48,53,55} (Fig. 9e). "Epithelial" membrane antigen (EMA) expression may statistically favour a carcinoma, but may be of limited use since lymphocyte predominant Hodgkin's lymphoma expresses EMA in at least 50% of cases,^{5,57} and positivity for the latter does not even completely exclude classical Hodgkin's lymphoma.^{5,57} In addition, a recent study suggests that the pattern of leukotactic cytokine and chemokine gene expression is very different between the 2 tumours,⁵⁶

although the authors did not specifically separate out the Schmincke variant, which more closely resembles Hodgkin's lymphoma than – and may therefore interact with host immune cells in a fundamentally different way from – the more conventional, cohesive, "Regaud" variant.^{53,55}

The author has also encountered 1 such case of CD30-positive, Schmincke-pattern undifferentiated (lymphoepithelial) carcinoma of nasopharyngeal origin in a 27-year-old man, presenting as a cervical lymph node metastasis that had been excised and mimicked classical Hodgkin's lymphoma histologically (Tan LHC, Sng ITY; unpublished observation). At the time of presentation, the postnasal space had not been biopsied even though a postnasal mass had been noted on a staging computerised tomographic scan, and since the possibility of a metastatic carcinoma had not been considered, immunohistochemistry for cytokeratins was initially not performed in addition to the usual Hodgkin's lymphoma panel. The patient was treated with 4 courses of chemotherapy for Hodgkin's lymphoma (adriamycin, bleomycin, vinblastine and dacarbazine, ABVD), but during the fourth course developed recrudescence of cervical lymphadenopathy. Biopsy of the postnasal space then showed undifferentiated/lymphoepithelial carcinoma in its classical, cohesive (Regaud) pattern, and fine needle aspiration of an enlarged cervical node also demonstrated metastatic carcinoma compatible with the nasopharyngeal primary. Retrospective immunostaining for cytokeratins was then found to be positive in the individually-dispersed, metastatic tumour cells seen in the cervical node that had been excised at presentation.

Conclusion and Future Direction

Recognition of the peculiarities and patterns of Waldeyer's ring lymphomas, their mimics, and potential diagnostic pitfalls, is important for accurate pathologic diagnosis. It has also raised questions that may be used to guide further research. The immunohistochemical armamentarium enabling the pathologist to identify various cellular proteins in formalin-fixed, paraffin-embedded tissue continues to expand⁵⁸ and further experience in using the more newly-available markers, such as CD56, needs to be accrued in order to temper diagnostic interpretation. Furthermore, although gene expression profiling has begun to stratify the clinically heterogeneous diffuse large B-cell lymphomas,¹³ correlations with epidemiologic patterns, immunomorphologic phenotypes and clinical behaviour are, as yet, very incomplete and often apparently conflicting.⁵

The paradigm of Hodgkin's lymphoma as a disease of "cytokine espionage" and resultant immune evasion^{38-43,59} has taught us not to restrict our attention only to the neoplastic cell population, but also to study the host reaction,

which has revealed aberrancy at the cellular level⁵ as well as in terms of the molecules mediating various cellular interactions.^{5,38-43,59} This approach may eventually also prove useful in developing a more holistic understanding of the biology of non-lymphoid neoplasms such as nasopharyngeal carcinoma.⁵⁶ In addition, cytokine and cell adhesion molecular profiling may, in future, provide additional information to cell surface marker phenotyping in the subclassification of peripheral T/NK-cell lymphomas, perhaps providing a more accurate and reproducible prediction of their clinical behaviour and patterns of spread, as alluded to by the stark reversal of B:T-cell lymphoma ratio across the line of the embryonic buccopharyngeal membrane.

The role of the EB virus in the genesis of lymphoid and non-lymphoid neoplasms harbouring it in various latency states needs to be further clarified, and the resultant findings may perhaps be exploited for therapeutic benefit.^{16,24} Finally, what needs to be unraveled is the fundamental mystery of the rarity of lymphomas corresponding to the various follicular zones in Waldeyer's ring, despite its abundance of lymphoid follicles, which parallels that in other MALT sites and in nodal tissue where the respective neoplasms are much commoner.^{2,5} These include MALT lymphoma^{6,7} of the marginal zone, mantle cell lymphoma^{2,7,9} of the follicular mantle, follicular^{2,7,9} and Burkitt's^{5,7} lymphomas of the germinal centre, and even Hodgkin's lymphoma which is also thought to have emerged from the germinal centre.⁵⁰ This may then provide further clues to differential aetiopathogenesis⁶⁰ and perhaps even new therapeutic approaches.

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