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Introduction

Lymphomas are a diverse group of neoplasms that comprise 4% of all new cancers annually. Once the diagnosis is established, most care is rendered by radiation oncologists and medical oncologists. The role of the otolaryngologist is usually limited to biopsy. However, for many patients the otolaryngologist serves as the entry point into the medical system. Awareness of the current knowledge and the proper workup of lymphomas is important for the otolaryngologist to assure timely care of these cancer patients and to prevent the otolaryngologist from being a mere technician in the multidisciplinary care of these patients.

Immunology Review

To understand the pathophysiology of lymphoid neoplasia, an understanding of normal lymphocyte activity is necessary. White blood cells are comprised of neutrophils, monocytes, eosinophils, basophils, and lymphocytes. Lymphocytes are subdivided into three types: B-cells, T-cells, and NK, or natural killer cells.

The path to becoming a lymphocyte begins with a pluripotent stem cell. Once it begins differentiating, a number of molecular changes take place. Cells that mature in the thymus are destined to become T-cells (the "T" refers to thymus). These cells express initially neither CD4 and CD8, then both, and finally one or the other. In the thymus a process of "thymic education" occurs in which the cells, which each express a different random rearrangement of the T-cell receptor (TCR) are culled out by inducing apoptosis in all cells except those which do not recognize "self" as foreign and which additionally are capable of reacting with the major histocompatibility complex (MHC). The cells that then remain are those in which foreign antigens are recognizable, and the cells can then interact with other immune cells to initiate appropriate responses.

T-cells are subdivided into CD4⁺ cells, which are *helper*, or T_H cells, and CD8⁺ cells, which are *cytotoxic* or T_C-cells. The helper T-cells serve primarily regulatory

functions, whereas the cytotoxic T-cells serve primarily effector functions. When an antigen is presented in an MHC class II molecule by an antigen-presenting cell (which is usually a macrophage, but can also be B-cells, dendritic cells of the spleen, and Langerhans cells of the skin), the helper T-cells are activated. The activated T_H-cell then serves a variety of functions, mostly mediated by cytokines. The three main functions effected by T_H-cells are to 1) help B-cells activate 2) activate CD8⁺ T-cells and 3) effect delayed hypersensitivity. T_{H1} cells mediate the latter two functions, whereas T_{H2} cells mediate the first function. T_{H1} cells primarily use IL-2 and IFN-gamma, whereas T_{H2} cells primarily use IL-4 and IL-5. Cytotoxic T-cells interact with antigens presented in MHC class I molecules, which are present in all cells. When activated, cytotoxic T-cells serve to induce cell death by inserting proteins known as perforins into the cell membrane of the recipient cell, most commonly in virus, tumor, and allograft cells. Some CD8⁺ cells also serve to suppress certain cell functions and are called *suppressor*, or T_S cells. CD4⁺ cells comprise about 65% of peripheral T-cells, and CD8⁺ cells compromise about 35%.

B-cells are so named for the Bursa of Fabricius, an organ found in birds rich in these lymphocytes. The equivalent in humans is thought to be in gut-associated lymphoid tissue. These cells do not require the thymus for maturation, and they exist in germinal centers of lymph nodes, in the spleen, in the bone marrow, and in mucosa-associated lymphoid tissue (MALT). They evolve from pre-pre-B cells to pre-B cells to B-cells, and upon activation they then mature into plasma cells. Through rearrangement of areas of DNA known as the V, D, and J segments, cells with a random variety of different immunoglobulins are produced, each cell having a unique arrangement of its own particular immunoglobulin. When stimulated by an appropriate antigen, the B-cell undergoes clonal expansion and matures into immunoglobulin-secreting plasma cells. Some then persist as memory cells which provide a rapid response upon antigen reintroduction. Approximately 30% of peripheral lymphocytes are B-cells, and they have a short lifespan. Approximately one billion new ones are made each day.

Natural killer cells, or NK-cells, are cytotoxic to cells, but they do not require prior exposure to antigen, are not enhanced by exposure, and are not specific to a particular antigen. They do not require antibody, but their action is enhanced by antibody through a process known as antibody-dependent cellular cytotoxicity (ADCC). They do not mature in the thymus. Approximately 5-10 % of peripheral lymphocytes are NK-cells.

Classification of Lymphomas

The term “malignant lymphoma” was first used by Billroth in 1871. Of course, this is now somewhat redundant, as there are no “benign lymphomas”. Lymphomas can be considered a subset of the larger group *lymphoproliferative disorders*. This group includes benign reactive lymphoproliferative disorders, histiocytosis X (more recently termed Langerhans-cell histiocytoses), plasma cell neoplasms, as well as Hodgkin’s disease and non-Hodgkin’s lymphomas. The latter two will be the focus of this discussion.

Classification of lymphoid neoplasms remains one of the most challenging and controversial subjects in pathology. Rappaport conceived one of the first useful systems in 1956. He divided non-Hodgkin's lymphomas according to whether the cell type appeared to be a lymphocyte or histiocyte, and by whether the histologic architecture was nodular or diffuse.

Subsequently other systems arose, including the Kiel, Lukes-Collins, British National Lymphoma Investigation (BNLI), World Health Organization (WHO), and Dorfman classification systems. This resulted in some degree of chaos, as trials and outcomes from one system were difficult to apply to another. Of these, the Kiel classification remained active the longest, particularly in Europe and Asia. Interestingly, as part of the NCI proposal of the Working Formulation (discussed shortly), these systems were examined by looking at test-retest reproducibility for the individual pathologists shown previously reviewed slides a second time, and the reproducibility varied from 0.53 to 0.93. Also, when concordance among different pathologists was examined, it varied from 0.21 to 0.65.

In 1982, a group from the National Cancer Institute proposed a "Working Formulation", which was intended to be a way to translate among the different systems. Instead, people began using this as a freestanding classification system and began designing trials based upon it. This system was largely based upon the Rappaport system, with "histiocytic" becoming "large cell" and being subdivided into "large cell" and "large cell immunoblastic". It segregates the different categories into low-grade, intermediate grade, high grade, or miscellaneous.

Some problems with the Working Formulation were noted, however. For one thing, it is not based upon the cell of origin of the neoplasm, as is the Kiel system. Also, different groups were segregated according to treatment outcome, not by disease pathogenesis. Thus, in 1994 the International Lymphoma Study Group proposed the Revised European-American Lymphoma classification (REAL). This system segregates lymphomas initially by the cell of origin (B-cell or T-cell), and it uses morphologic features, immunophenotype and/or stage of differentiation, genotype, etiology, epidemiology, and clinical behavior. It also includes Hodgkin's disease in its classification, as the line between NHLs and HD is occasionally difficult to discern. The authors recognize that it is a work in progress and that later modifications may need to be made. Currently, the World Health Organization is working on an updated system based largely on the REAL classification.

Hodgkin's disease (HD) is named for Thomas Hodgkin who described the disease in 1832. At the time, lymphadenopathy was generally thought to be caused by syphilis, inflammation, tuberculosis, or by spread from cancer. He described a series of patients who appeared to have nodal spread of tumor in the absence of a primary tumor or inflammation. He noted, "This enlargement of the glands appeared to be a primitive affection of those bodies rather than the result of an irritation propagated to them from some ulcerated surface or other inflamed texture." Although known more in his time for other accomplishments, such as public health initiatives, introduction to England of the

stethoscope, and clinicopathologic correlations, the disease that bears his name was initially described by him (before common use of the microscope, amazingly enough) and then assigned his name in later publications by Wilks. Hodgkin noted that Malpighi had actually described this sometime earlier.

Hodgkin’s disease is characterized by the presence of the pathological cell known as the *Reed-Sternberg* cell. This cell was originally described decades earlier, but Carl Sternberg (1898) and Dorothy Reed (1902) published thorough descriptions and illustrations of this cell, and it thus bears their names today. (Interestingly, Sternberg thought the process to be tuberculous in origin, and Reed inflammatory. As late as the 1940s, many considered HD to be infectious in origin.) The Reed-Sternberg cell (also known as the Hodgkin cell) is characterized by its large size and its classically bilobulated nucleus with eosinophilic “owl-eyed” nucleoli surrounded by a clear halo. It often is sparsely found throughout a field of reactive lymphocytes. Although considered necessary for diagnosis in the past, some pathologists may call Hodgkin’s disease without it if enough other corroborative data are present. Conversely, presence of Reed-Sternberg cells alone is not pathognomonic for HD, as a variety of other conditions may produce Reed-Sternberg cells (such as infectious mononucleosis). A variant of the Reed-Sternberg cell exists which is called the L&H cell, or the popcorn cell. This is so-named because of the lymphocytes and histiocytes seen in the background in the nodular

REAL Classification
<u>B-CELL NEOPLASMS</u>
<i>Precursor B-cell neoplasms</i>
Precursor B-lymphoblastic leukemia/lymphoma
<i>Peripheral B-Cell Neoplasms</i>
1) B-cell CLL/PLL/SLL
2) Lymphoplasmacytoid lymphoma/immunocytoma
3) Mantle cell lymphoma
4) Follicular center lymphoma, follicular Provisional cytologic grades: I (small), II (mixed), III (large) Provisional subtype: diffuse, predominantly small cell
5) Marginal zone B-cell lymphoma Extranodal (MALT +/- monocytoid B-cells) Provisional category: Nodal (+/- monocytoid B-cells)
6) Provisional entity: Splenic marginal zone lymphoma
7) Hairy cell leukemia
8) Plasmacytoma / myeloma
9) Diffuse large B-cell lymphoma
10) Burkitt’s lymphoma
11) Provisional entity: high-grade B-cell lymphoma, Burkitt’s-like
<u>T-CELL AND PUTATIVE NK-CELL NEOPLASMS</u>
<i>Precursor T-cell neoplasms</i>
Precursor T-lymphoblastic leukemia/lymphoma
<i>Peripheral T-Cell and NK-Cell Neoplasms</i>
1) T-cell CLL/PLL
2) Large granular lymphocyte leukemia
3) Mycosis fungoides/Sézary syndrome
4) Peripheral T-cell lymphomas, unspecified

Provisional categories: medium, mixed, large, lymphoepithelioid
Provisional subtypes: Hepatosplenic $\gamma\delta$ T-cell lymphoma
Subcutaneous panniculitic T-cell lymphoma
5) Adult T-cell lymphoma/leukemia
6) Angioimmunoblastic T-cell lymphoma
7) Angiocentric lymphoma / nasal T/NK-cell lymphoma
8) Intestinal T-cell lymphoma
9) Anaplastic large cell lymphoma
10) Provisional: ALCL Hodgkin's-like
<u>HODGKIN'S DISEASE</u>
1) Lymphocyte predominance (nodular +/- diffuse)
2) Nodular sclerosis
3) Mixed cellularity
4) Lymphocyte depletion
5) Lymphocyte-rich classic HD (provisional subtype)
Suggested Groupings
<u>I. INDOLENT LYMPHOMAS AND LYMPHOID LEUKEMIAS</u>
<i>B-cell</i>
B-CLL/SLL
Lymphoplasmacytoid lymphoma
Follicular center lymphoma, follicular (small and mixed)
Marginal zone B-cell lymphoma
Hairy cell leukemia
Plasmacytoma / myeloma
<i>T-Cell</i>
Large granular lymphocyte leukemia
ATL/L (smoldering)
Mycosis fungoides/Sézary syndrome
<u>II. MODERATELY AGGRESSIVE LYMPHOMAS AND LYMPHOID LEUKEMIAS</u>
<i>B-cell</i>
B-PLL
Mantle cell lymphoma
Follicular center lymphoma (follicular large cell)
<i>T-Cell</i>
T-CLL/PLL
ATL/L (chronic)
Angiocentric lymphoma
Angioimmunoblastic lymphoma
<u>III. AGGRESSIVE LYMPHOMAS</u>
<i>B-cell</i>
Large B-cell lymphoma
<i>T-Cell</i>
Peripheral T-cell lymphomas
Intestinal T-cell lymphoma
Anaplastic large cell lymphoma

IV. HIGHLY AGGRESSIVE LYMPHOMAS AND LYMPHOID LEUKEMIAS	
<i>B-cell</i>	
Precursor B-lymphoblastic leukemia/lymphoma	
Burkitt's lymphoma	
High-grade B-cell lymphoma, Burkitt's-like	
<i>T-Cell</i>	
Precursor T-lymphoblastic leukemia/lymphoma	
ATLL (acute and lymphomatous)	

Table 1. Revised European-American Lymphoma Classification and Suggested Clinical Grouping of Entities

lymphocyte-predominant HD in which it mainly occurs. Another variety is the lacunar cell, which mainly occurs in the nodular sclerosis type.

The Rye classification has been the dominant system for classifying HD for the last 25 years. This includes the categories of nodular sclerosis (NSHD), mixed cellularity (MCHD), lymphocyte predominant (LPHD), and lymphocyte depletion (LDHD). Recently the REAL classification (and now apparently the WHO classification) has made subtle modifications, recognizing the different biology of nodular lymphocyte-predominant HD.

Staging

Staging can be defined as determining the extent of the malignant disease within a given patient. For lymphomas, traditional TNM staging is difficult to apply, as one is often not able to distinguish between T, N, and M. The Ann Arbor system, proposed in 1971, has been the gold standard for both HD and NHLs since that time. Staging is important for assessing prognosis and determining the best course of treatment.

Ann Arbor staging classification	
<i>Stage</i>	<i>Characteristics</i>
I	Involvement of a single lymph node region (I), or a single extranodal organ or site (I_E)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II), or localized involvement of an extranodal site or organ (II_E) and one or more lymph node regions on the same side of the diaphragm.
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by either localized involvement of an extranodal site or organ (III_E), involvement of the spleen (III_S), or both (III_{ES})
IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymphatic involvement. The organs may be designated by a symbol: H for liver, L for lung, M for bone marrow, P for pleura, O for bone, D for skin.
	The absence or presence of any of the following: fever > 38°, night sweats, or weight loss of >10% body weight over prior 6 months should be designated with the suffix A or B , respectively.

Table 2. Ann Arbor staging classification

Lymphatic structures include lymph nodes, spleen, thymus, appendix, Peyer's patches, and Waldeyer's ring. These do not therefore count as extranodal (or more

properly extralymphatic) sites, although this is not uniformly reflected in the literature, with the more recent trend to classify Waldeyer's ring as extranodal. Extralymphatic sites may also be characterized as local or diffuse. This has relevance inasmuch a localized extralymphatic site may be considered for treatment with radiation. In practice there is disagreement among clinicians about what constitutes a localized extralymphatic site. Prior designations of "CS" for clinical stage and "PS" for pathologic stage have been largely abandoned as the staging workup has become less invasive over time and there has thus been less pathologic tissue and less need to point out the difference, as the quality of clinical (non-invasive) staging is currently high.

The Ann Arbor system does have limitations, especially for NHLs. For one thing, the prognosis is not always very different among the stages, especially between IV and III, and to some degree even II. Prognosis may be better assessed by indirect measures of tumor burden such as number of nodal and extranodal sites, size of tumor masses (>10 cm is considered bulky disease), percentage of bone marrow involvement, and performance status. Also, NHLs are a diverse set of tumors which do not all behave similarly and, as such, are difficult to stage with a "one-size-fits-all" system. They often present extralymphatically, which is less well addressed by the Ann Arbor system. Also, whereas HD patients present somewhat evenly by stage, NHL patients tend to present with advanced disease. Although a number of tertiary cancer centers are investigating newer staging systems, none have supplanted the Ann Arbor system at present.

Epidemiology

Hodgkin's Disease

Hodgkin's disease has a bimodal age-incidence curve that is more common among economically advantaged populations such as in the United States. This bimodal peak has led some to speculate that an infectious agent is responsible for the younger cluster whereas the later peak represents cellular changes of aging. HD is more common in men than women, and by race it is more common in whites than in blacks and is least common in Asians. Geography also plays a role in the incidence of HD that is independent of race. There are about 7,500 new cases in the US annually and about 1,500 deaths. This corresponds to an age-adjusted incidence rate of 2.9 in the US. The incidence has decreased about 16% since the 1970s. This decrease is partly due to prior misclassification of NHL as HD, but much of the reason for this decrease is not known. Mortality has decreased about 65%, largely due to improved treatment and technology. Among the subtypes, nodular sclerosis has increased in incidence, particularly among young white women. It also is the subtype that shows an association with economic advantage. The subtypes ranked according to incidence are: NSHD>MCHD>LPHD>LDHD.

Non-Hodgkin's Lymphomas

Non-Hodgkin's lymphoma is the fifth-most common cancer in the US, with about 55,000 cases in the year 2000. From 1973 to 1997, the age-adjusted incidence rates rose about 80%. This is faster than most other cancers, and it is not known why this increase

is occurring. HIV-associated NHLs account for some, but not all, of this increase. Over the same period the mortality of NHLs has increased by about 45%. The rise in incidence is worldwide, independent of the higher incidence rates observed in developed countries such as Western Europe, North America, and Australia. Family history plays a role, and the odds ratio for persons with a first-degree relative with lymphoma is 3.0 (95% CI 1.7-5.2). Within NHLs, 90% are B-cell derived.

Etiologic Factors

HIV/immunosuppression: While any form of immunodeficiency increases the risk of acquiring lymphoma, the current HIV epidemic has caused its own explosion of NHLs. Between 1982 and 1990, NHL incidence rates increased nearly 800% among men aged 20 to 59 in San Francisco County. HD, although not as strong an association initially, is now thought to be about 10 times as common among persons with HIV that in the general population. The risk of NHL in AIDS patients is 72 times that of the general population. It is estimated that 3% of AIDS cases present with NHL as the AIDS-defining condition. The increases appear to be mostly in the higher-grade lymphomas, and there is a higher incidence of extralymphatic disease. Since 1996, the incidence rate of NHLs in the HIV population has been falling dramatically, and this is thought to be due to the introduction of highly active antiretroviral therapy (HAART).

Recipients of bone marrow transplant are 5-6 times more likely to develop HD, supporting the link of immunosuppression to lymphomas. Other organ transplant recipients are also at risk, but the risk appears to be getting smaller as the science of transplantation has improved and resulted in better matches and less immunosuppression. Additionally, survivors of HD treatment are at increased risk to develop NHLs, which may in part be due to immunosuppression. Genetic immunodeficiency syndromes such as common variable immunodeficiency and Wiskott-Aldrich syndrome are at increased risk of developing a number of malignancies, of which NHLs comprise about 50%.

EBV: Epstein-Barr virus was originally isolated in a cell line developed from African Burkitt's lymphoma. Denis Burkitt recognized that a previously unrecognized cancer affecting the jaws of African children had a distribution similar to that of endemic malaria, and he hypothesized that an infectious agent might be at work. This led Tony Epstein and Yvonne Barr in 1964 to examine tumor biopsies with electron microscopy where they identified a new herpesvirus, later named Epstein-Barr virus (EBV). Since then EBV has been clearly implicated as a factor in both HD and NHLs. In HD, it is most strongly associated with MCHD and LDHD subtypes. A diagnosis of infectious mononucleosis increases the risk of HD development between 2 and 13-fold. It can be isolated in between 20 and 50% of Reed-Sternberg cells. In NHLs, EBV is most strongly associated with Burkitt's lymphoma. In the endemic (African) form, EBV association approaches 100%, whereas in the sporadic form, it is in the 10-20% range. It appears to transform the *c-myc* oncogene. EBV has also been associated with a number of other lymphomas (post-transplant, AIDS-related, T-cell/NK-cell (nasal and non-nasal), and anaplastic large cell) and a number of other malignancies (nasopharyngeal carcinoma, sinonasal undifferentiated carcinoma, lymphoepithelial carcinoma of salivary glands, oral squamous cell carcinoma, and basaloid squamous cell carcinoma).

HTLV-I: Human T-cell lymphotropic virus-I has been associated with an excess of peripheral T-cell NHL in the Caribbean and Japan. HTLV infection is rare in the US.

Helicobacter pylori: *H. pylori* has been associated with MALT lymphoma. One study found that individuals with a diagnosis of peptic ulcer had a relative risk of 5.6 for gastric NHL, mostly of the MALT variety.

Medical conditions: NHLs have been associated with a number of medical conditions, including hepatitis C, diabetes mellitus, prior blood transfusion, Sjögren's syndrome, rheumatoid arthritis, lupus, pyelonephritis, tuberculosis, malaria, and psoriasis, although not all reported associations have been later validated. Of note to the otolaryngologist, lymphomas associated with Sjögren's syndrome appear to be low-grade marginal zone lymphomas and are not associated with viruses.

Genetic Factors: Certain HLA phenotypes have been associated with lymphomas, such as DPB1*0301 and HD. A study of monozygotic twins who developed HD showed a relative risk of 128 (95% CI:42-299) in the other twin. Familial clustering of NHLs is much less common.

Occupational risk: Although many occupational exposures have been studied and suggested as etiologic factors, the most compelling data appear to show an association of woodworking with HD and show an association of pesticide and herbicide exposure (mostly in farmers) with NHLs.

Negative/Weak Associations: Investigations have failed to show any definitive link between NHLs and smoking, radiation exposure, and physical activity. A possible link between tonsillectomy and HD has been suggested but appears to have been refuted in later studies. Some suggestions have been made that body-mass index over 30, certain dietary factors, prior blood-transfusion, phenytoin use, and long-term black or brown hair dye use may increase the risk of developing NHLs. Human herpesvirus-6 (HHV-6) has been found in both HD and NHLs, but causality remains speculative at present. Another more recently discovered herpesvirus, HHV-8, is also being investigated as a cause of lymphomas.

Workup

As always, the medical evaluation begins with the history and physical examination. The classic presenting sign is painless adenopathy. Other items to note in the history include age, gender, presence or absence of fever and its duration, unexplained night sweating and its severity, unexplained weight loss and its magnitude and timecourse, unexplained pruritus, alcohol-induced pain, family history of cancers, prior immunosuppressive illness, and prior cancer and cancer treatments. Alcohol-induced pain is a phenomenon of unknown etiology that causes affected lymph node groups to have significant pain upon consumption of even a little ethanol. This phenomenon is relatively specific for lymphoma.

Unexplained constitutional symptoms, adenopathy that persists greater than 2-3 weeks, increasing adenopathy, or patients at high risk should be considered for tissue evaluation. At our institution, fine-needle aspiration (FNA) is the usual initial investigation. This is particularly important in the head and neck- if the FNA suggests lymphoma an excisional biopsy is often indicated, whereas if it suggests squamous cell carcinoma (the most common head and neck cancer) excisional biopsy is usually contraindicated. Excisional biopsy is needed in lymphoma to examine tissue for architecture and acquire tissue for additional studies such as flow cytometry.

Comparing HD to NHLs, HD has more of a tendency to present in a localized set of nodes, whereas NHLs tend to present in multiple sites. HD spreads in an orderly, contiguous fashion, whereas NHLs have more likelihood of noncontiguous spread. NHLs are more likely to involve Waldeyer's ring, and they are more likely to be extranodal.

Once the diagnosis is made, appropriate staging investigations are undertaken. Appropriate staging is important to avoid the morbidity of overtreatment or the mortality of undertreatment. In addition to a CBC with smear, LFTs with LDH, blood chemistries, ESR, and serum β_2 -microglobulin, a CT of the chest, abdomen, and pelvis should be obtained. Many patients will also need bone marrow biopsies, and some will need a spinal tap to assess for meningeal involvement. MRI images bone marrow well and has the possibility of decreasing false-negative bone marrow aspirations by providing directed sites for biopsy.

Adjunctive imaging modalities include bone scanning, gallium scanning, ultrasound, and FDG-PET scanning. Also, lymphangiography is an older imaging technique that is being used less often today. Gallium-67 is a nuclear medicine isotope that has an affinity for lymphomas. Studies have shown that gallium scanning is highly sensitive and specific. One study by Kaplan found that when gallium-positive tumors become gallium-negative after treatment, a complete and lasting remission was likely.

Positron emission tomography (PET), which uses 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG), detects tissues that are actively metabolizing glucose. It, too, has been shown to have a high sensitivity and specificity. Early data suggest that it may be particularly useful for extralymphatic tumors. It is also helpful in assessing the post-treatment mass, as this may represent either residual tumor or sterilized, fibrotic tumor, and FDG-PET can help differentiate between the two metabolically. Also, some have suggested that using carbon-11 methionine instead of fluorine-18 may improve the sensitivity. Research into the applications of PET is ongoing.

The role of staging laparotomy has been evolving and debated over the last few decades. The concept is this: if a potential Stage I or II supradiaphragmatic disease has crossed the diaphragm, then it is a Stage III disease and the treatment may need to be altered (e.g. it is no longer a candidate for localized radiation only). Risks include overwhelming sepsis by encapsulated organisms in both the immediate and late post-operative period. As non-invasive imaging techniques have improved, the role of staging

laparotomy has decreased. Laparoscopy may be a newer technique that is less morbid yet still allows for tissue diagnosis.

Treatment

Treatment options for both HD and NHLs include observation, involved-field radiation, subtotal lymphoid radiation, chemotherapy with or without radiation, and bone marrow transplant. Also, newer biologic therapies are being applied in the treatment of HD and NHLs.

Chemotherapy: The first chemotherapeutic agent was found when an explosion in Bari, Italy during World War II exposed US servicemen to an intense amount of mustard gas. Profound marrow and lymphoid aplasia were noted, and nitrogen mustard was isolated and applied to humans by Goodman and Gilman. The first six patients treated had HD and lymphosarcoma, and striking dissolution of the tumor masses was noted (unfortunately to return shortly thereafter).

With failure of monotherapy, combinations of chemotherapeutic agents arose. The first popular treatment regimen for HD was MOPP – cyclophosphamide, vincristine, procarbazine, and prednisone. Although revolutionary in the treatment of HD, certain treatment failures led to the search for other regimens. This led to the development of ABVD – doxorubicin, bleomycin, vinblastine, and dacarbazine. This proved to have similar efficacy as MOPP but different toxicities. It was also found to be effective in salvaging MOPP failures.

Since then, other chemotherapeutic agents and combinations have been developed and been efficacious in the chemotherapeutic treatment of lymphomas. Some regimens may have similar efficacy but be selected for different toxicities. The first regimen to show efficacy in NHLs was CHOP – cyclophosphamide, doxorubicin, vincristine, and prednisone. CHOP therapy is still employed today.

Radiation therapy: The first reported treatment of HD with XRT was by Dr. William Pusey, a dermatologist at the University of Illinois in 1901. He reported successful shrinkage of nodes in HD patients. Since then radiation alone or in combination with chemotherapy has been a mainstay of treatment of lymphomas. Much controversy exists regarding the optimum treatment of lymphomas, particularly for early-stage HD where monotherapy (either chemo or XRT alone) is likely to be efficacious.

Bone marrow transplant: One of the limiting factors in chemotherapy is myelosuppression. If this restriction is removed, it is possible to escalate the dose of chemotherapy agent, which is beneficial for certain agents. However, hematologic reconstitution must occur to avoid a fatal outcome. This is accomplished with marrow transplant. It can either be autologous, in which the patient's own marrow is harvested, or allogeneic, from a matched donor. Autologous donors avoid the problem of graft-versus-host disease but may run the risk of transplanting disease back in. Also, much of the efficacy in allogeneic transplants is thought to come from a graft-versus-tumor effect, as the tumor cells are less hardy than the native cells. Bone marrow transplants are usually

performed for NHLs rather than for HD, as NHLs are frequently more difficult to treat conventionally. Allogeneic stem cells have been traditionally harvested from the iliac crest, but newer techniques involve leukopheresis after marrow stimulation with G-CSF.

Novel therapies: Novel therapies involving immunotherapy, vaccination, radioimmunoconjugates, interferons, immunotoxins, vascular targeting, and other novel therapies are currently under investigation. The monoclonal antibody rituximab (trade name Rituxan) became the first FDA-approved monoclonal antibody for treatment of cancer. It selectively targets CD20, a protein found on malignant and normal B-cells but not on other normal tissues.

Prognosis

It is estimated that approximately 80% of patients with HD will be cured of their disease. Early-stage, favorable HD, has a cure rate of over 90%. After treatment, HD survivors have a higher incidence of death from cardiac, infectious, and second malignancies. One problem in estimating prognosis is that disease-specific survival has not been separated from overall survival in many of the studies. Advanced stage has been shown to have a negative impact on prognosis. Tumor histology has been shown to have prognostic implications as MCHD/LDHD had an inferior overall survival than NSHD/LPHD. This is thought to be due to the former subtypes tendency to relapse infradiaphragmatically, which is usually bulkier and harder to salvage. Factors that segregate early-stage HD into the unfavorable category (which may mean adding chemo to radiation) include age over 50, ESR>50, B-symptoms with ESR>30, and a large mediastinal mass.

NHLs have a worse prognosis than HD. Five-year survival rates (considering all NHLs) are around 50%, but this varies by subtype and by aggressiveness. Ten-year survival rates for low, intermediate, and high-grade lesions are approximately 45, 26, and 23%, respectively. In general, follicular (or nodular) architecture is better than diffuse architecture on histology. In low-grade NHLs approximately 30% will undergo a process known as *Richter's transformation* in which a clone of high-grade aggressive cells will emerge. Median survival is less than one year after this occurs. Ironically, the low-grade lymphomas are much less curable than the high-grade lymphomas. They may not move quickly, but due to the small percentage of the cells in the growth phase, therapy is not usually as effective as in high-grade, aggressive lymphomas. Many will elect to observe certain low-grade lymphomas until treatment becomes necessary due to symptoms.

One study by Shipp et al identified risk factors for poor prognosis. They were age greater than 60, late-stage disease, elevated LDH levels, impaired performance status, and extralymphatic involvement. Five-year survival by number of risk factors was: 0—73%, 1—51%, 2—43%, 3—26%. Ki-67 has been shown to be a negative prognostic factor when this nuclear proliferation antigen was present in greater than 60% of cells. The faster one achieves a complete remission has a positive prognosis for survival. Gallium-negativity after treatment improves survival, as well. β_2 -microglobulin, a component of the MHC class I molecule detectable in serum, has a negative prognostic correlation when elevated.

Issues for the Otolaryngologist / Head & Neck Surgeon

While squamous cell carcinoma represents the most common malignancy in the head and neck, lymphoma comprises the second-most common. As discussed before, FNA is essential prior to consideration of excisional biopsy to exclude squamous cell.

A recent study by Hanna et al summarized 98 patients with extranodal lymphomas of the head and neck. They found that Waldeyer's ring was the most common site of presentation at 36%, followed by the sinonasal tract (25%). Fifty percent of patients had nodal disease, and only 20% had B-symptoms. Tonsillar lymphoma had a 20% chance of having associated GI lymphoma. Two-thirds of patients had intermediate grade lymphomas, and three-fourths had Stage I or II disease. Overall and disease-free survival was 60 and 50%, respectively. High grade and advanced stage had the worst prognosis.

Burkitt's Lymphoma: One type of lymphoma that presents in the head and neck is Burkitt's lymphoma. This was originally described by Burkitt in Africa (see the section on EBV). This endemic form is clinically distinct from a sporadic form, which occurs in the US, although they are histologically identical. The African form usually presents as a mass in the maxilla or mandible, whereas abdominal presentation is more common in the sporadic form. These respond relatively well to aggressive chemotherapy although long-term relapse is not uncommon.

Lethal Midline Granuloma: Lethal midline granuloma, which has also been called lymphomatoid granulomatosis and polymorphic reticulosis, is now known to be a T-cell lymphoma. Some feel that idiopathic midline destructive disease is a separate entity, whereas others feel it is another variant of this disease. Men are affected more than women, and this usually occurs in the 5th and 6th decade of life. Patients commonly present with cough, shortness of breath, and hemoptysis. On exam the patient has ulcerating lesions of the upper respiratory tract, usually in the sinonasal cavity. Clinically this is impossible to distinguish from Wegener's, but histologically it lacks granulomas and palisading histiocytes. Mortality is relatively high.

Conclusion

A summary of the classification, etiology, epidemiology, staging, workup, and treatment of lymphomas is presented.

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