Lymphoid Lesions of the Head and Neck: A Model of Lymphocyte Homing and Lymphomagenesis

Elaine S. Jaffe, M.D.

Hematopathology Section, Laboratory of Pathology, National Cancer Institute, Bethesda, Maryland

Lymphoid lesions of the head and neck mainly affect the nasopharynx, nasal and paranasal sinuses, and salivary glands. These three compartments each are affected by a different spectrum of lymphoid malignancies and can serve as model for mechanisms of lymphomagenesis. The type of lymphoma seen reflects the underlying biology and function of the particular site involved. The nasopharynx and Waldeyer's ring are functionally similar to the mucosal associated lymphoid tissue (MALT) of the gastrointestinal tract and are most commonly affected by B-cell lymphomas, with mantle cell lymphoma being a relatively frequent subtype. The most prevalent lymphoid lesion of the salivary gland is lymphoepithelial sialadenitis, associated with Sjögren's syndrome. Lymphoepithelial sialadenitis is a condition in which MALT is acquired in a site not normally containing lymphoid tissue. Patients with Sjögren's syndrome are at increased risk to develop B-cell lymphomas, most commonly MALT lymphomas. The nasal and paranasal sinuses are the prototypical site for the development of extranodal natural killer (NK) /T-cell lymphoma, nasal type. This condition must be distinguished from other conditions causing the clinical picture of lethal midline granuloma, including Wegener's granulomatosis and infectious disorders. Lymphomatoid granulomatosis is common in the lung but is rarely seen in the midline facial structures.

KEY WORDS: B-cell, Epstein Barr virus, Follicular lymphoma, Immunophenotyping, Lymphocyte homing, Lymphoma, Lymphomagenesis, MALT lymphoma, NK-cell lymphoma, T-cell.

Mod Pathol 2002;15(3):255–263

VOL. 15, NO. 3, P. 255, 2002 Printed in the U.S.A.
Date of acceptance: September 27, 2001.
Address reprint requests to: Elaine S. Jaffe, M.D., Building 10, Room 2N202, 10 Center Drive MSC-1500, Bethesda, MD 20892; e-mail: ejaffe@mail.nih.gov; fax: 301-402-2415.

Lymphomagenesis is not a random event but is usually site specific. It is dependent on lymphocyte homing, as well as the underlying biology and function of the resident lymphoid tissues. The head and neck region contains several compartments: the nasopharynx, nasal and paranasal sinuses, and salivary glands, each of which is affected by a different subset of benign and neoplastic lymphoid proliferations (Table 1). These three sites can serve as a model of lymphomagenesis that can be extended to other organ systems. Indeed, the head and neck region can serve as a microcosm for understanding the principles of lymphoma classification and the distribution of lymphoma subtypes in other organ systems.

The nasopharynx normally contains abundant lymphoid tissue. This site is functionally equivalent to the lymphoid tissue of the gastrointestinal tract or mucosal-associated lymphoid tissue (MALT). The most common benign process is follicular hyperplasia, and the most common lymphomas are the "small B-cell lymphomas," most commonly mantle cell lymphoma. By contrast, the nasal region and paranasal sinuses do not contain lymphoid tissue normally. NK/T-cell lymphomas are most common in this site, nearly always associated with Epstein-Barr virus (EBV). The prevalence of EBV in this subset of lymphomas may relate to the fact that the nasopharynx is a reservoir for EBV infection. Interestingly, however, most nasopharyngeal lymphomas are negative for EBV sequences.

The salivary gland does not normally contain lymphoid tissue but is a site predisposed to the acquisition of acquired MALT upon appropriate antigenic stimulation. It is a frequent target in patients with autoimmune disease, such as Sjögren's syndrome (SS). The most common lymphoma of the salivary gland is MALT lymphoma.

NASOPHARYNGEAL LYMPHOID HYPERPLASIA AND LYMPHOMA

As Waldeyer's ring is the site of abundant lymphoid tissue, the nasopharyngeal lymphoid tissues can be the sites of both lymphoid hyperplasia and

TABLE 1. Common Lymphoid Lesions of the Head and Neck

Nasopharynx and Waldeyer's ring
Lymphoid hyperplasia
Lymphomas, B cell ≫ T cell
Mantle cell lymphoma
Follicular lymphoma
Small lymphocytic lymphoma
Nasal and paranasal sinuses, palate
Extranodal natural killer/T-cell lymphoma, nasal type
Wegener's granulomatosis
Oral cavity and gingiva
Plasmablastic lymphoma
Lymphomatoid granulomatosis
Burkitt lymphoma (usually extension from bone)
Salivary gland
HIV-associated cystic hyperplasia
Lymphoepithelial sialadenitis
Marginal-zone B-cell lymphoma of mucosa-associated lymphoid tissue type
Warthin's tumor

TABLE 2. World Health Organization Classification of Lymphoid Neoplasms

B-cell neoplasms
Precursor B-cell neoplasm
Precursor B-lymphoblastic leukemia/lymphoma
Mature (peripheral) B-cell neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
B-cell prolymphocytic leukemia
Lymphoplasmacytic lymphoma
Splenic marginal zone B-cell lymphoma
Hairy cell leukemia
Plasma cell myeloma/plasmacytoma
Extranodal marginal-zone B-cell lymphoma of mucosa-associated lymphoid tissue type
Nodal marginal-zone B-cell lymphoma/follicular lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma
Mediastinal large B-cell lymphoma
Primary effusion lymphoma
Intravascular large B-cell lymphoma
Burkitt lymphoma/Burkitt cell leukemia
T- and natural killer cell neoplasms
Precursor T-cell neoplasm
Precursor T-lymphoblastic lymphoma/leukemia
Mature (peripheral) T-cell neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Aggressive natural killer cell leukemia
Adult T-cell lymphoma/leukemia
Hepatosplenic T-cell lymphoma
Extranodal natural killer/T-cell lymphoma, nasal type
Enteropathy-type T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides/Sezary syndrome
Primary cutaneous anaplastic large-cell lymphoma
Peripheral T-cell lymphoma, not otherwise characterized
Angioimmunoblastic T-cell lymphoma
Anaplastic large-cell lymphoma

lymphoma. In many respects, the lymphoid tissue of the nasopharynx is functionally similar to the lymphoid tissues of the gastrointestinal tract and is considered part of the MALT system. Follicular hyperplasia is the most common pattern of lymphoid reaction seen. Lymphocytes often infiltrate the overlying epithelium, producing lymphoepithelial lesions, and should not be considered suspicious for evolving lymphomas. Lymphoepithelial lesions are common in sites containing normal MALT, such as the tonsil and ileum. In contrast, when lymphoepithelial lesions are seen in acquired MALT, such as in the stomach, they are more often an indication for an evolving lymphoproliferative process (1).

The most common lymphomas of the nasopharynx are the small B-cell lymphomas, mantle cell lymphoma (MCL), small lymphocytic lymphoma/chronic lymphocytic leukemia (SLSL/CLL), and follicular lymphoma (FL; Table 2). The histologic and immunophenotypic features of these lymphomas mirror those of other sites.

MCL is among the more common lymphomas affecting the nasopharynx. It frequently involves the gastrointestinal tract, producing polypoid lesions throughout the small bowel. This pattern of gastrointestinal tract involvement has been referred to as lymphomatous polyposis (2). Twenty percent of patients with MCL present with overt gastrointestinal tract involvement, but with endoscopic evaluation, the incidence increases to 88% (3, 4). As the nasopharynx is functionally and developmentally linked to the gastrointestinal tract, it is not surprising that this site is commonly involved as well. Waldeyer's ring is involved at presentation in 20% of patients, but the incidence may be greater with a thorough ear, nose, and throat exam and blind biopsies of nasopharyngeal lymphoid tissue (3). The overlying mucosal epithelium is commonly undisturbed. MCL is composed of CD5+, B−cells, usually negative for CD23. They are cyclin D1 positive as a result of the associated chromosomal translocation, t(11;14) (5). Immunophenotypic studies are very helpful in differential diagnosis, as especially in small biopsy specimens, morphologic details of architecture and cytology may be limited.

Follicular lymphoma is not uncommon in the palatine tonsils but is more infrequent in the nasopharynx. Although follicular lymphomas are generally rare in children, the nasopharyngeal and palatine tonsils are among the most common sites of follicular lymphomas in children (6). In contrast to follicular lymphomas in adults, these tumors are usually *bcl-2* protein negative and lack *BCL-2* gene rearrangements (Table 3). They are typically Grade 3, with a predominance of centroblasts, and a high mitotic rate. The differential diagnosis with florid follicular hyperplasia can be difficult. Stains for *bcl-2,* commonly employed in the diagnosis of FL, are not helpful. Documentation of monoclonality, either by light-chain expression or molecular studies, is most useful in diagnosis. Some cases appear to show evidence of plasmacytoid differentiation, and therefore, immunohistochemistry in paraffin sections may be useful. FL in children usually presents with localized disease and has an excellent prognosis (7). It is more common in males than

TABLE 3. Characteristics of Pediatric Follicular Lymphoma: a Distinctive Disease Entity

Rare lymphoma subtype in children (1–2%)
60% present in head and neck
Tonsils, nasopharynx
Other sites: lymph nodes, gastrointestinal tract, testis
Many differences with follicular lymphoma in adults
Usually Grade 2–3
Bcl-2 protein negative
BCL-2 rearrangement not seen
Male–female ratio, 3:1
85% present with Stage I or II disease
75% complete remission with low relapse rate

females (M:F ratio, 3:1), in contrast in adult follicular lymphomas, which show a slightly greater prevalence in females.

The Revised European-American Lymphoma classification (8), and its successor, the World Health Organization classification of tumors of the hematopoietic and lymphoid tissues (9), have as a basic principle the recognition of specific disease entities by use of morphologic, clinical, immunophenotypic, and genotypic criteria. By this standard, pediatric follicular lymphomas should be considered a separate disease entity from the more common follicular lymphomas seen in adults. These tumors have a different molecular pathogenesis from adult follicular lymphomas, and the majority of patients will have a sustained complete clinical remission with appropriate treatment. Bone marrow involvement is rare, and presentation in extranodal sites, such as the testis or gastrointestinal tract, is not uncommon. They do seem to be of germinal center origin, based on the expression of bcl-6 by the neoplastic cells (10).

Although Hodgkin's disease (HD) overall is rare in Waldeyer's ring, occasional cases of HD have been reported in this site (11). Epstein-Barr virus (EBV) appears to be more often found in the neoplastic cells in contrast to HD presenting in other sites. This finding may relate to the nasopharynx as a reservoir for EBV. Most reported patients had localized disease, Stage I or II. Nodular lymphocyte predominant HD also may occur but is rare.

Diverse lymphomas of both T and B-cell types also occur in this site. These include T-cell–rich large B-cell lymphomas, diffuse large B-cell lymphoma, peripheral T-cell lymphoma, unspecified, and specific types of T-cell malignancy, such as adult T-cell lymphoma/leukemia (12–14).

EXTRANODAL LYMPHOMAS OF THE SINONASAL AND ORAL REGIONS

In contrast to the nasopharynx itself, T-cell or natural killer (NK)-cell lymphomas, rather than B-cell lymphomas, more often affect the sinonasal area and palate. The most common lymphoma in this site is nasal NK/T-cell lymphoma. However, B-cell lymphomas, including plasmablastic lymphoma and Burkitt lymphoma, may present with gingival involvement. Burkitt lymphoma involving the gingiva usually represents extension from the mandible or maxilla.

Extranodal NK/T-cell lymphoma, nasal-type (nasal NK/T) was formerly known as *angiocentric lymphoma* because of the propensity of this tumor to show angioinvasion and necrosis. However, because angioinvasion is not seen in all cases, and because other pathogenetic mechanisms have been implicated in causing the necrosis, the name *extranodal NK/T-cell lymphoma, nasal type,* was proposed in the WHO classification (9, 15). It is a distinct clinicopathologic entity highly associated with EBV (16–19).

The most common clinical presentation is with a destructive nasal or midline facial tumor, so-called *lethal midline granuloma.* Palatal destruction, orbital swelling, and edema may be prominent (20). Nasal NK/T lymphomas often spread to other extranodal sites, including skin, soft tissue, testis, upper respiratory tract, and gastrointestinal tract. Tumors with an identical phenotype and genotype may appear primarily outside the nasal region. For this reason, the term *extranodal NK/T-cell lymphoma, nasal type* is preferred. Additionally, there are aggressive NK and NK-like T-cell leukemias that have a similar phenotype and genotype (21). Most of these cases also are EBV positive, suggestive that they might represent a leukemic counterpart of this disease (19, 21, 22).

Nasal NK/T-cell lymphoma is characterized by a broad cytologic spectrum. The atypical cells may be small or medium in size. Large atypical and hyperchromatic cells may be admixed, or may predominate. If the small cells are in the majority, the disease may be difficult to distinguish from an inflammatory or infectious process. In early stages, there may also be a prominent admixture of inflammatory cells, further causing difficulty in diagnosis (23). Necrosis, with or without evidence of angioinvasion, is seen in 50–60% of nasal NK/T-cell lymphoma. The presence of extensive necrosis can make diagnosis difficult, especially in small biopsy specimens. Multiple biopsies are sometimes required for correct diagnosis.

Because all cases of nasal NK/T-cell lymphoma are positive for EBV, *in situ* hybridization studies with probes to EBV-encoded small nuclear RNA (EBER 1/2) may be very helpful in diagnosis and can detect even small numbers of neoplastic cells (24, 25). However, LMP-1 is not a sensitive indicator of EBV positivity, and is often negative.

Although the cells express some T-cell–associated antigens, most commonly CD 2, other T-cell markers, such as surface CD 3, are usually absent (18).

Cytoplasmic CD 3 can be found in paraffin sections. However, cytoplasmic CD 3 can be found in NK cells and is not specific for a T-cell lineage. In addition, molecular studies in most cases have not shown a clonal T-cell gene rearrangement, despite clonality being shown by other methods (17, 26, 27). In favor of an NK-cell origin, the cells are nearly always CD 56+; however, CD 16 and CD 57, other NK-cell antigens, are usually negative. Rare cases with identical histologic and clinical features may be of true T-cell derivation. Thus, the term *NK/T-cell lymphoma* is favored. Both NK and T-cell variants are EBV positive (28–30).

Little is known about the molecular pathogenesis of nasal NK/T-cell lymphoma. However, a few studies have shown some recurring cytogenetic abnormalities, both by conventional cytogenetics and comparative genomic hybridization (31–33). p53 mutations and deletions are a common feature, as well as overexpression of the p53 protein (34). Frequent deletions at 6q and 13q have been found.

Nasal NK/T-cell lymphoma is much more common in Asians than in individuals of European background. Clusters of the disease have also been reported in Central and South America and in Mexico, in individuals of Native American heritage (35, 36). Thus, a racial predisposition appears to play a role in the pathogenesis of angiocentric NK/T-cell lymphoma.

Nasal disease may be controlled with radiotherapy, but the relapse rate is high. Chemotherapy is generally used in conjunction with radiation therapy, but many cases are chemotherapy resistant. The neoplastic cells are frequently positive for p53, which has been associated with resistance to therapy in other lymphomas (34). The most common site of relapse is skin and subcutaneous tissue. A hemophagocytic syndrome is a common clinical complication, which adversely affects survival in angiocentric NK/T-cell lymphoma (37). It is likely that EBV plays a role in the pathogenesis of the hemophagocytic syndrome.

Not all T-cell lymphomas occurring in the nasal region are nasal NK/T-cell lymphomas. Peripheral T-cell lymphomas of other types, (peripheral T-cell, unspecified, anaplastic large-cell lymphoma) may also be seen. These tumors are generally EBV negative and may or may not have a cytotoxic T-cell immunophenotype (38–40). In addition, B-cell lymphomas, most commonly aggressive B-cell lymphomas, may be seen (38, 41).

Lymphomatoid granulomatosis (LYG) exhibits many similarities both clinically and pathologically to extranodal NK/T-cell lymphoma, nasal type (42). In the past, it was considered to be part of the same disease spectrum, angiocentric immunoproliferative lesions (AIL; 23, 43). However, recent data indicate that LYG is an EBV-positive B-cell proliferation associated with an exuberant T-cell reaction (44, 45).

LYG also presents in extranodal sites, but the most common site of involvement is the lung (45, 46). The kidney and central nervous system are also frequently involved, as are skin and subcutaneous tissue. The pattern in necrosis in both LYG and NK/T-cell lymphoma is very similar, emphasizing the role of EBV in mediating the vascular damage (15).

LYG is rare in the nasal area. However, we have encountered EBV-positive lymphoproliferative disorders with features of LYG commonly in the oral cavity and gingival region (Fig. 1). They usually contain marked necrosis. As with LYG in other sites, immunodeficiency is a predisposing feature. These lesions may occur in the setting of HIV, and in patients receiving iatrogenic immunosuppression for other disorders (methotrexate, steroids).

Plasmablastic lymphoma, a variant of diffuse large B-cell lymphoma, often presents in the oral cavity. These lymphomas are usually positive for EBV and also occur in a setting of immunodeficiency, most commonly HIV infection (47). The most common sites of involvement are the gingiva, floor of the mouth, and palate. Plasmablastic lymphomas are more monomorphic than LYG, without an inflammatory background. They also lack the vascular destruction and necrosis frequently seen in LYG. They exhibit an aggressive clinical course, with frequent spread to other extranodal and nodal sites in most patients.

The cells typically have a markedly plasmacytoid appearance. As expected for cells with plasmacytic differentiation, they are typically CD20 negative but express the plasma cell–associated marker VS38c+, which is found in cells equipped for protein production with abundant rough endoplasmic reticulum. EBV has been identified in approximately 60% of cases (47). Although many cases will contain monoclonal Ig sequences, some cases appear Ig negative. EBV often interferes with the ability of a cell to produce Ig and also leads to the downregulation of other B-cell associated antigens (48).

The differential diagnosis of Wegener's granulomatosis with nasal NK/T-cell lymphoma presents a more significant issue. The majority of patients with Wegener's granulomatosis present with head and neck disease. The nasal and paranasal sinuses are most commonly affected, but other sites may be involved, including the larynx, oral region, periorbital region, middle and external ear, and salivary gland (49).

The histological features usually permit the differential diagnosis of Wegener's granulomatosis and LYG, despite clinical similarities. Lymphoid cells usually do not form a significant component of the infiltrate. The most common histologic features of Wegener's granulomatosis are vasculitis, necro-

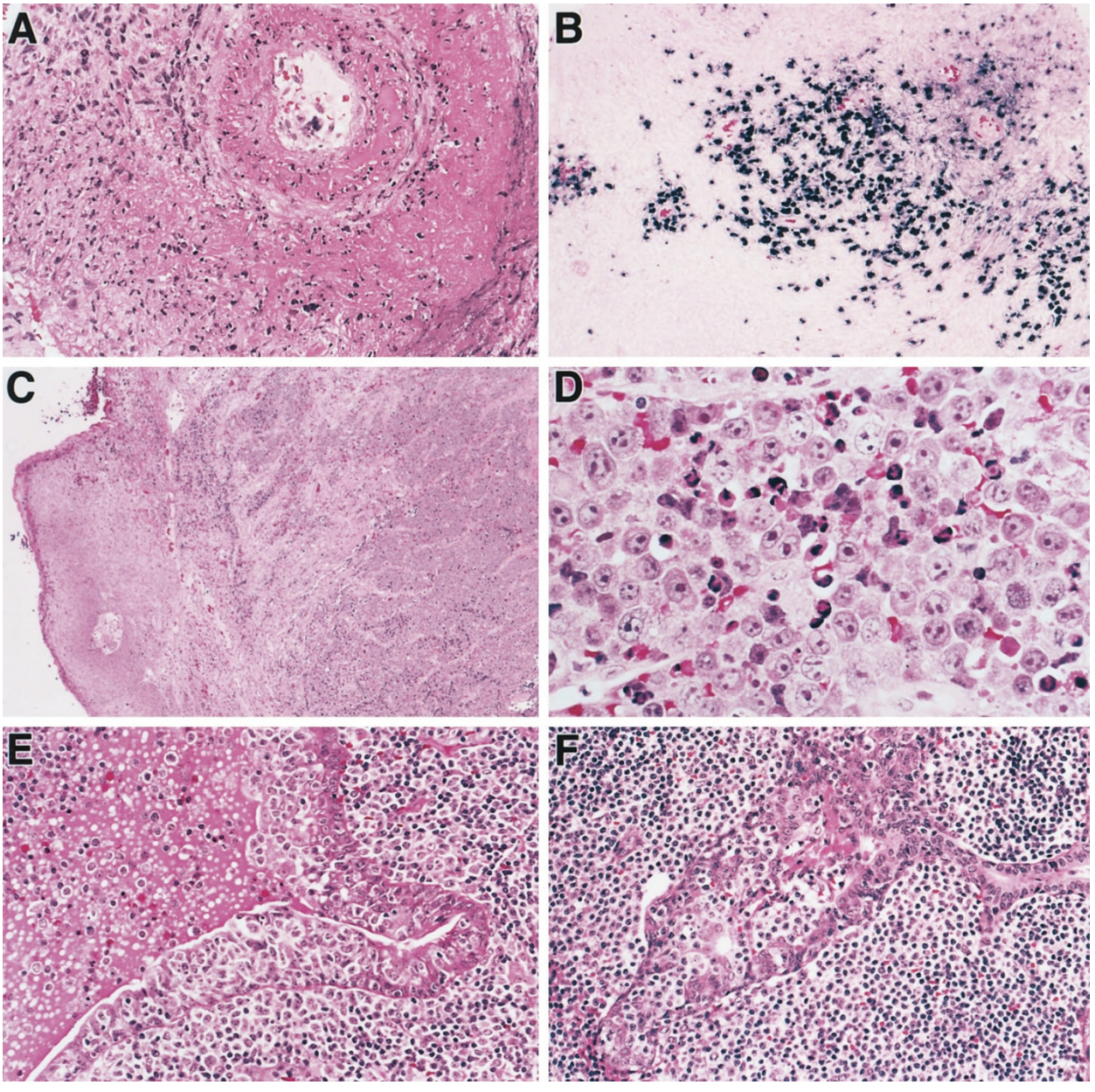

FIGURE 1. Lymphoid lesions of the head and neck. **A** and **B,** EBV-associated B-cell lymphoproliferative process presenting as a gingival lesion. This lesion has some features of lymphomatoid granulomatosis, including marked necrosis and vascular damage. **B,** the EBER1 *in situ* hybridization shows scattered positive cells, more numerous around blood vessels. **C** and **D,** plasmablastic lymphoma of the oral cavity. A dense monomorphic infiltrate is seen beneath the oral mucosa. The cells have an immunoblastic or plasmablastic appearance and were CD20 negative and EBER positive. **E,** lymphoepithelial cyst of the salivary gland in an HIV-positive patient. Lymphoid cells with clear cytoplasm infiltrate the epithelium. **F,** extranodal marginal-zone lymphoma of the salivary gland. Broad coronas of monocytoid cells surround the altered ducts.

sis, and granulomatous inflammation. However, it is rare that all of these features are seen in a single biopsy specimen (49). Neutrophils are usually abundant, in contrast to their rarity in nasal NK/T-cell lymphoma. The absence of EBV-positive cells in the infiltrate is another helpful diagnostic feature (24).

Salivary Gland Lymphoid Hyperplasia and Lymphoma

Lymphoid hyperplasia affecting the salivary glands and periparotid lymph nodes is commonly seen in the setting of HIV infection (50, 51). The parotid gland is most often affected, but other salivary glands may be involved as well. The lesions are cystic in nearly 100% of cases, in contrast to SS, in which cysts are found in only 3% (52). The salivary gland and adjacent lymph nodes are affected by marked lymphoid hyperplasia with features of HIV-associated lymphadenopathy. In a careful study performed by Ihrler *et al.*, they showed that the cystic lesions are of true salivary origin and not derived from salivary gland rests within periparotid lymph nodes (52). The cysts are composed of epi-

thelial cells from the striated ducts of the salivary gland. Lymphoepithelial lesions may be seen, but monocytoid B cells are not prominent. Compression of salivary gland ducts by markedly hyperplastic lymphoid tissue may play a role in the evolution of the cystic lesions but is unlikely to fully explain their pathogenesis. The lymphoid infiltrates are polyclonal and generally do not progress to lymphoma. Of course, patients with HIV infection are at increased risk for development of aggressive B-cell lymphomas, most commonly Burkitt lymphoma and diffuse large-cell lymphoma.

In pediatric patients with HIV infection, lymphoepithelial cystic lesions of the salivary gland may more closely resemble MALT lymphomas, and monoclonality may be found (53). Interestingly, despite the rarity of MALT lymphomas in children, MALT lymphomas have been described at a variety of sites (lung, salivary gland, and stomach) in pediatric patients with HIV (54). The salivary gland infiltrates in pediatric HIV disease show some similarities to lymphocytic interstitial pneumonitis (LIP) and cystic hyperplasia of the thymus gland seen in this clinical setting (55–57).

The most common lymphoid lesion of the salivary gland is lymphoepithelial sialadenitis (LESA). (58). This term was recently proposed as an alternative to *myoepithelial sialadenitis* and *benign lymphoepithelial lesion* (BLEL), based on the absence of true myoepithelial cells in these lesions and confusing nature of the last term (BLEL), as many of the cases described as BLEL were probably lymphomas.

LESA is most commonly seen in the setting of SS. Similar infiltrates affect the lacrimal glands in many patients, producing the clinical picture of dry eyes and dry mouth. In LESA, markedly hyperplastic lymphoid tissue infiltrates the salivary gland, with loss of most acinar structures. The altered ducts are surrounded by and infiltrated by lymphoid cells. Within the ducts themselves, monocytoid B cells may be prominent, even in the absence of lymphoma. However, if the ducts are surrounded by broad coronas of monocytoid cells, the index of suspicion for extranodal marginal zone lymphoma of MALT-type, so-called MALT lymphoma, should be raised (1, 59). Other worrisome features favoring MALT lymphoma over LESA include extensive infiltration of the interfollicular region by monocytoid cells or atypical plasma cells containing Dutcher bodies (59).

Early studies showed that patients with SS were at increased risk for B-cell lymphomas (60). These were generally aggressive B-cell lymphomas outside the salivary gland; the low-grade lymphoproliferative process in the salivary gland itself had not been recognized as malignant. It was only later that the salivary gland lesions with features of LESA were shown to harbor monoclonal B-cell populations (61). Despite the presence of monoclonality at the genetic level, the infiltrates usually pursued a benign clinical course, and in fact different clones could be found at different points in time. This situation is analogous to lymphocytic gastritis associated with *Helicobacter pylori*, which can show monoclonality by polymerase chain reaction (PCR)–based techniques in the absence of overt lymphoma. Therefore, finding a clone by PCR alone is not sufficient to diagnosis MALT lymphoma in the salivary gland in the absence of other evidence of malignancy (62). More than 50% of cases of LESA will contain monoclonal B cells by PCR, in the absence of histological or clinical features of lymphoma.

The demonstration of monoclonality at the immunophenotypic level, either by flow cytometry or immunohistochemistry, is stronger evidence of progression to lymphoma (63, 64). In addition, if regional lymph nodes contain sinusoidal and parasinusoidal infiltrates of monocytoid B cells, this finding favors MALT lymphoma, as it indicates spread beyond the salivary gland (65). The risk of lymphoma in LESA and SS has been estimated at 4–7% (58). MALT lymphoma begins as an antigen-driven lymphoid proliferation, which progresses first to monoclonality and then, with the acquisition of secondary genetic changes, to MALT lymphoma (1). The development of an aggressive B-cell lymphoma is associated with an adverse prognosis (66).

Immunophenotype is helpful in the differential diagnosis of MALT lymphomas from cytologically similar lymphomas such as B-CLL/SLL and MCL. MALT lymphomas are positive for B-cell–associated antigens CD 19, CD 20, and CD 22 but are usually negative for CD 5, in contrast to most systemic small lymphocytic malignancies. Rare cases of MALT lymphoma may be CD5 positive (67, 68). They are negative for CD10 and cyclin D 1.

MALT lymphomas also have a commonly recurring cytogenetic abnormality, the t(11;18) observed in up to 50% of extranodal cases (69–71). The genes involved in the translocation have been identified as *c-IAP2*, a gene encoding for an inhibitor of apoptosis, and a novel gene on 18q21 named *MLT* (of unknown function; 70, 72). It has been speculated that the fusion protein may lead to increased inhibition of apoptosis conferring a survival advantage to the neoplastic cells.

The translocation t(11;18)(q21;q21) is associated exclusively with low-grade extranodal MALT, and it is not detected in cases with simultaneous low, and high grade tumors or in "primary" extranodal large-cell lymphomas, raising the question of whether these primary extranodal B-cell lymphomas are related to low-grade MALT. The translocation is found in tumors of the salivary gland and lacrimal gland, as well as other MALT-associated sites (73). Identification of this genetic abnormality may

prove to be of diagnostic utility in distinguishing LESA with a small monoclonal B-cell population from true MALT lymphoma with the potential for spread outside the salivary gland. MALT lymphomas tend to spread to regional lymph nodes, as well as other extranodal sites, including the stomach, lung, and bladder. The putative cell of origin of marginal zone lymphomas is a memory B cell (post-germinal center; 74, 75).

Warthin's tumor contains variable amounts of lymphoid tissue. It can be a site of involvement by malignant lymphoma and, rarely, malignant lymphoma may present in a Warthin's tumor. The most common lymphoma in this site is follicular lymphoma (76, 77). Hodgkin's lymphoma is occasionally seen (78).

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