Selected Topics on Lymphoid Lesions in the Head and Neck Regions

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Abstract Lymphoid tissue located in the head and neck region include multiple regional lymph node chains as well as mucosa associated lymphoid tissue of the conjunctiva, buccal and nasopharyngeal cavities (Waldeyer's ring), and thyroid and salivary glands. This region is a rich source of antigenic stimuli including infectious agents coming from the outside environment. Many reactive conditions that affect lymphoid tissue in this region may mimic neoplasia. In fact, distinguishing between benign and malignant lymphoid proliferations in the head and neck region is a relatively frequent diagnostic challenge and in many instances, this distinction is not straightforward. It therefore behooves the practicing pathologist to be able to recognize the benign lymphoproliferative disorders that affect this region so as to effectively guide the appropriate clinical management of such patients. Kimura disease, Epstein Barr lymphadenitis, HIV associated salivary gland disease and chronic sialadenitis are benign conditions that not infrequently affect lymphoid tissue in the head and neck region and that share certain overlapping features with malignant lymphoma. In this brief review, we discuss these conditions and highlight clinicopathological features that may help distinguish them from neoplastic lymphoproliferations that may share similar features.

Keywords Kimura · HIV · EBV · Chronic sialadenitis · MALT

Introduction

The head and neck region represents about 10% of the total body surface area and contains several mucosal surfaces, including buccal, nasopharyngeal and ocular, that can serve as ports of entry for antigens into the body's internal environment. Consequently, this region is rich in lymphoid tissue that is strategically located to surveil, process and eliminate potentially harmful antigens. Head and neck lymphoid tissue includes mucosa associated lymphoid tissue (MALT) of the buccal and nasopharyngeal cavities (Waldeyer's ring), conjunctiva, and thyroid and salivary glands. There are also multiple regional lymph node chains. These are constantly bombarded by external antigenic stimuli and are frequently enlarged or tender in response to viral, bacterial and other infectious lymphadenitis. Non-neoplastic lymphadenopathy such as those associated with autoimmune diseases and iatrogenic causes (such as certain drugs) also frequently affect head and neck lymphoid tissue. In fact, it is not uncommon for the practicing pathologist to be faced with the challenge of distinguishing between reactive and neoplastic lymphoid proliferations in this region [1]. From a histopathological stand point, it is important to consider both the overall architecture of the lymphoid tissue as well as the cytological features of the proliferating cells in order to help make the distinction between a reactive and neoplastic process. Reactive conditions generally show overall preservation of normal lymphoid architectural features including intact B-cell (lymphoid follicles) and T-cell (inter-follicular and paracortical) areas, even if there is overall expansion (lymphoid hyperplasia) or partial distortion of one or more of the components. Neoplastic processes, on the other hand, frequently disrupt or replace the normal architecture. In addition, cytologic evaluation in

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conjunction with ancillary studies such as immunophenotyping by flow cytometric analysis of fine needle aspirate (FNA) specimens for B- and T-cell clonality can greatly enhance the ability of pathologists to distinguish benign from malignant lymphoproliferative disorders [2, 3]. Indeed, FNA is often the initial method used to acquire material for pathologic assessment of these lesions. Molecular studies such as polymerase chain reaction (PCR) for clonal B- and T-cell receptor gene rearrangements also represents an additional tool in the pathologist's arsenal in this regard. However, as we shall discuss, there are limitations and pitfalls associated with these modalities that must be considered when applying data derived from these tests for diagnosis.

Here we review four selected non-neoplastic entities that affect head and neck lymphoid tissue and can mimic lymphoid neoplasia.

Kimura Disease

Kimura disease is a rare chronic inflammatory disorder with a predilection for the head and neck region. First described in the Chinese literature in 1937 as “eosinophilic hyperplastic lymphogranuloma”, the disease acquired its current eponymous designation from Kimura who published a series in the Japanese literature in 1948 [4–6]. However, the true incidence of Kimura disease is not known. Most cases have been described in mainland China and Japan where the disease occurs predominantly in young males [7–9]. Sporadic cases have been described in most geographic regions around the world including North and South America, Europe and Africa. The largest series reported in the United States by Chen et al. [10] from The Armed Forces Institute of Pathology (AFIP) included 21 patients of different ethnicities including Caucasian (7), Black (6), Asian (6), Hispanic and Arabic (1 each) with a male: female ratio of 6:1 and a mean age of 31 years (range 8–64). These findings are comparable to those described in similar case series reported in the Japanese and Chinese literature [8, 9].

The etiology of Kimura disease is unknown. It is considered to represent a chronic inflammatory disorder, possibly due to a hitherto unidentified antigenic stimulus. Infectious agents such as viruses, parasites and *Candida albicans* and toxins have been proposed as possible triggers, but there is no conclusive evidence to support any specific inciting factor [11].

Patients usually present with single or multiple painless subcutaneous masses in the head and neck region, including the face, neck and periauricular areas [8]. Enlarged regional lymph nodes are frequently present and the reported frequency of clinically detectable regional lymphadenopathy ranges from 32 to 100% [8, 12]. Subcutaneous tissue and

lymph node groups outside of the head and neck region may also be involved, at times without apparent head and neck disease [8, 9, 12]. Unilateral or bilateral involvement of parotid and submandibular salivary glands may lead to swelling and lacrimal gland involvement has been reported in at least one patient [8]. In addition, peripheral blood eosinophilia, frequently above 10%, and elevated serum IgE and eosinophil cationic protein levels are invariably present [9, 13, 14]. Renal disease, usually in the form of nephrotic-level proteinuria, is seen in up to 16% of patients [15]. The histopathologic correlate includes a number of patterns including mesangioproliferative glomerulonephritis, membranous nephropathy and minimal change disease, among others [15–18].

Histologically, Kimura disease is characterized by follicular lymphoid hyperplasia with prominent germinal centers and expanded interfollicular areas containing increased eosinophils (Fig. 1). These features are seen both in subcutaneous tissue and lymph nodes. Focally, tight clusters of eosinophils or eosinophilic microabscesses are present and are frequently associated with intra- or extracellular Charcot-Leyden crystals. Warthin-Finkeldey type giant-cells, when present, are also a characteristic finding. The eosinophilic infiltrate may partially disrupt reactive follicles to give a moth-eaten appearance (“folliculolysis”). Vascular hyperplasia with flattened or low cuboidal endothelial cells is also a characteristic feature of Kimura disease and vessels are sometimes seen within germinal centers. Other common features include concentric perivascular and periductal sclerosis as well as dense stromal fibrosis associated with plasma cells and eosinophils [8]. Infrequent findings include extracapsular extension into perinodal fat and collapsed sub-capsular sinuses. Immunohistochemical studies show preservation of the overall lymph node architecture with B-cell dominated follicles and T-cell predominant interfollicular areas. Special stains for microorganisms are negative.

Historically, Kimura disease has been confused with angiolymphoid hyperplasia with eosinophilia (ALHE). However, it is now well established that these two represent separate unrelated entities with distinct clinicopathological features [12, 19]. ALHE, renamed epithelioid hemangioma, is a benign vascular tumor characterized by proliferation of small, capillary-sized vessels with plump, epithelioid endothelial cells (in contrast to Kimura disease) which can be highlighted with immunohistochemical stains for CD31, CD34 and factor VIII. Furthermore, ALHE is usually localized to the skin without regional lymph node involvement and despite the frequent presence of a rich inflammatory milieu including eosinophils and lymphocytes, peripheral blood eosinophilia and elevated IgE are not seen. Several malignant lymphomas including classical Hodgkin lymphoma (CHL), peripheral T-cell lymphomas,

Fig. 1 Lymph node involved by Kimura disease **a** and **b** shows florid follicular lymphoid hyperplasia and an interfollicular expansion by vascular proliferation and eosinophil infiltrate (**a**); and a follicle is replaced by numerous eosinophils and a marked vascular proliferation

(**b** and inset). A case of early angioimmunoblastic T-cell lymphoma (AITL) shows an expanded interfollicular area with a maintained architecture (**c**); florid follicular hyperplasia is often seen in early AITL, with absence of a mantle zone (**d**)

especially angioimmunoblastic T-cell lymphoma (AITL) (Fig. 1) and non-Hodgkin B-cell lymphomas may be accompanied by prominent eosinophilia and should always be considered in the differential diagnosis of Kimura disease. In particular, differentiating Kimura disease from early forms of AITL and interfollicular CHL can be extremely challenging. These lymphoid neoplasms may not demonstrate significant disruption of the normal lymph node architecture or easily identifiable neoplastic cells such as Hodgkin/Reed-Sternberg (HRS) cells of CHL and clear cells of AITL in early stages. If interfollicular CHL is suspected, IHC for CD30, CD15, and Pax5 will be helpful to identify HRS cells. On the other hand, if early AITL is suspected, IHC for CD3, CD4, CD8, CD10, PD-1 will help to identify proliferation of neoplastic cells with a follicular T-helper immunophenotype. In addition, in situ hybridization for Epstein Barr virus (EBV) encoded RNA (EBER) may highlight EBV positive cells. It is perceivable that these lesions may undergo fine needle aspiration with immunophenotypic analysis by flow cytometry, as this is a common first-line investigational method used in head and neck lesions. Both CHL and Kimura disease would demonstrate a polyclonal pattern of surface immunoglobulin (Ig) kappa and lambda light chain expression. By flow cytometry, the neoplastic cells of AITL can frequently be

identified as immunophenotypically aberrant T-cells, usually expressing CD2, CD4, CD5, CD10 and CD45RO [20, 21]. CD3 is frequently dimly expressed or negative. Although T-cells have been shown to be increased in Kimura disease by immunohistologic methods, their immunophenotypic profile by flow cytometric analysis remains unclear at this time [10, 22]. Molecular studies may show clonal T-cell receptor rearrangement in AITL, in contrast to Kimura disease which would typically show a polyclonal pattern. However, routine molecular studies for B-cell clonality are not helpful in distinguishing CHL from Kimura disease, as both entities lack clonal Ig heavy chain rearrangement by PCR.

The natural history of Kimura disease is not well described. In most patients, the disease shows a prolonged, indolent clinical course. In the AFIP series, the majority had complete remission with no evidence of disease even with long term follow up while one patient still had evidence of disease more than 12 years after initial presentation. Long-term oral corticosteroids seem to be the mainstay of treatment of Kimura disease whereas surgical resection and radiation have limited roles in localized disease. Multifocal disease outside of the parotid glands, eosinophils >50% and IgE levels >10,000 IU/ml have been shown to be associated with recurrent disease [9].

More aggressive therapy with immunosuppressive agents like cyclosporine and azathioprine may play a role in the treatment of patients with renal disease [23, 24].

HIV Associated Lymphoepithelial Cysts

The term HIV-associated salivary gland disease usually refers to lymphoproliferative disorders that lead to parotid gland enlargement in HIV infected patients [25, 26]. The overwhelming majority of these lesions are lymphoepithelial cystic lesions [25–28]. The term lymphoepithelial cyst (LEC) was first introduced by Bernier and Bhaskar et al. [29] and the first report of bilateral multicystic lesions in HIV-infected patients was by Morris et al. [30]. Like many other HIV/AIDS-related disorders, the incidence of HIV-related salivary gland disease has progressively declined since the introduction of highly active antiretroviral therapy (HAART). Nevertheless, LEC remains the most common cause of parotid gland enlargement in HIV-positive patients and is estimated to occur in up to 10% of this patient group, which is ten times more than the incidence of sporadic LECs in the general population (<1%) [28, 31, 32]. Therefore, the discovery of parotid gland LECs in any patient should trigger an investigation into their HIV status. Any age group may be affected, and HIV-related LECs have been reported in patients as young as 2 months of age [31, 33].

Over the years, there has been much controversy regarding the pathogenesis and appropriate terminology for these lesions. Some terms previously used include benign lymphoepithelial cyst (BLEC), benign lymphoepithelial lesion (BLEL), AIDS-related lymphadenopathy and cystic lymphoid hyperplasia [32]. Historically, most authors have suggested that the cystic lesions arise in hyperplastic intraparotid lymph nodes affected by persistent generalized lymphadenopathy as part of the spectrum of the HIV-associated syndrome, while others have suggested that the changes represent an autoimmune process akin to that seen in Sjögren's syndrome [31, 34, 35]. In 1996, however, Ihrler et al. [31] used immunohistochemistry and 3-D reconstruction of histologic sections to show that LECs represent an advanced stage of generalized lymphocytic infiltration and lymphoepithelial lesions of the salivary parenchyma. They showed that the cystic lesions represent dilated striated ducts which develop due to compression by markedly hyperplastic lymphoid tissue [36]. It is unclear why such prominent lymphocytic infiltration of the parotid glands occurs in only a subset of HIV-positive patients, and although an infectious trigger has been postulated, definitive evidence is lacking. HIV p24-antigen can be found in follicular dendritic cells and multinucleated giant-cells but not in lymphocytes in lymphoepithelial cystic lesions;

however, the significance of this is unclear [37]. Other viruses like EBV and CMV do not seem to play a pathogenic role [37]. Given the morphologic similarities with the salivary gland changes seen in Sjögren's syndrome, a chemokine-mediated autoimmune reaction has also been proposed by some. Itesco et al. [38] even demonstrated an increased prevalence of HLA-DR5 in a series of patients with HIV-related LECs [35]. However, to date, a clear etiology remains unknown.

Patients with HIV-related LECs typically present with slow growing, painless, bilateral parotid gland swelling [31]. Unilateral involvement can also be seen, but this is more common in sporadic LECs not related to HIV infection. Submandibular gland involvement has also been rarely reported [39]. In most cases, the disorder is brought to the attention of the patient or physician because of the cosmetic effect of an enlarging mass in the neck. However; more serious complications like xerostomia or facial nerve compression may rarely occur [40]. By ultrasound, computerized tomography or magnetic resonance imaging, multiple thin cysts are usually identified [32]. Enlarged regional lymph nodes may accompany parotid gland enlargement, but these do not usually show cystic formations [41].

Histologically, HIV-related LEC is characterized by atrophic glands, follicular lymphoid hyperplasia and cystic ductal dilatation with squamous metaplasia. Histiocytes and plasma cells are usually present in the cyst walls and multinucleated giant-cells may also be seen [39]. However, the full spectrum of histopathological changes in LEC is rarely seen because salivary glands with these lesions are rarely completely excised. In the elaborate study by Ihrler et al., the authors used computer-assisted reconstruction of autopsy and surgical specimens to show that the lesions are composed of complex three-dimensional cystic structures with numerous peripheral branches that communicate with preserved intercalated ducts and salivary acini [31]. They showed that well developed LECs in fact represent an advanced stage of a generalized lymphoid infiltration with lymphoepithelial lesions of the salivary gland parenchyma. Earlier stages without cystic development were demonstrated in autopsy specimens, and showed similar features with Sjögren disease such as lymphoepithelial duct lesions and follicular hyperplasia with atrophic salivary gland parenchyma. Please refer to below "chronic sialadenitis and early extranodal marginal zone lymphoma (ENMZBCL)" to see the distinction of lymphoepithelial lesions and ENMZBCL. Immunohistochemical stains highlight preservation of intact B- and T-cell areas and polytypic plasma cells by Ig kappa and lambda light chain expression. HIV p24-antigen may be detected in multinucleated giant-cells [37]. LECs frequently undergo fine needle aspiration for cytologic evaluation. This typically

shows desquamated squamous cells associated with a polymorphous population of lymphocytes, histiocytes and plasma cells in an amorphous, proteinaceous background [37, 39, 42].

Benign LECs may also occur in the setting of several non-HIV related disorders such as chronic sialadenitis (Sjögren disease), sarcoidosis, and Hashimoto disease [32, 43]. The histologic appearance of these lesions may be virtually indistinguishable from that of HIV-associated LEC. However, some features such as the presence of squamous metaplasia and bilateral lesions, although not entirely specific, are more characteristic of HIV-related LECs. In addition, some authors suggest that a markedly decreased interfollicular CD4:CD8 T-cell ratio may help to distinguish HIV-associated LEC from HIV-negative cases [44]. Warthin's tumor (or papillary cystadenoma lymphomatosum) is the most common bilateral neoplasm of the parotid glands. Histologically, Warthin's tumor is characterized by a double layer of oncocytic epithelium growing in a cystic or papillary pattern and a dense stromal lymphoid infiltrate.

Malignant squamous cell cystic lesions, unlike benign LECs, show cytologic atypia of the squamous epithelial cells. It is important to note that p16 appears to be intrinsically expressed by the squamous cells of LECs and therefore immunohistochemical expression for this protein seems to play a limited role in differentiating LECs from malignant cystic squamous cell lesions [45].

Surgical resection, frequently by enucleation of the cystic lesions of HIV-related LECs usually results in resolution. Aspiration of the cystic contents may also result in partial relief. There have been reports of complete regression with antiretroviral treatment only, and there is no increased risk for malignancy [46].

Lymphoepithelial Sialadenitis and Extranodal Marginal Zone B-cell Lymphoma (ENMZBCL)

Lymphoepithelial sialadenitis is a component of Sjögren syndrome and represents an autoimmune process characterized by a benign lymphoid infiltrate with lymphocytic epitheliotropism in salivary glands. Sjögren syndrome predominantly affects women in the fourth to seventh decades of life, with a male to female ratio of 3:1. The parotid glands are affected in about 90% of cases [47]. Bilateral disease is typical, but one gland may be more severely affected than the other. Patients with Sjögren syndrome have a markedly increased risk of developing secondary lymphoma, which may be 44 times greater than in the general population [48]. Lymphoepithelial sialadenitis is characterized by a lymphocytic infiltrate, parenchymal atrophy, and foci of epithelial proliferation

associated with lymphoepithelial lesions. However, the lobular architecture of the salivary gland is usually preserved. In the early stages, the extent of lymphocytic infiltration may be variable among the parotid gland lobules, but in late stage disease, nearly all of the lobules are affected. Reactive follicles vary in number from few to numerous. Lumens are sometimes evident within the lymphoepithelial lesions, but most times, only irregularly shaped islands of polygonal and spindled cells are seen. The hyperplastic epithelium predominantly consists of ductal basal cells that lack immunohistochemical markers specific for myoepithelium. The lymphocytic infiltrate represents acquired mucosa-associated lymphoid tissue (MALT) in salivary gland with predominance of T-cells. However, the lymphocytes in and around the lymphoepithelial lesions are mainly B-cells with monocytoid features or centrocyte-like morphology (Fig. 2).

Extranodal marginal zone B-cell lymphoma (ENMZBCL) of the parotid gland usually arises in the context of lymphoepithelial sialadenitis of Sjögren syndrome [27, 34, 49–51]. The distinction between benign lymphoepithelial sialadenitis and early ENMZBCL can be challenging and in some cases not possible. This suggests a histologic, immunophenotypic and genotypic continuum from a polyclonal lymphoid proliferation to the development of a clonal neoplasm. Similar to ENMZBL, lymphoepithelial sialadenitis shows monocytoid and centrocyte-like B-cells present within lymphoepithelial lesions and frequently accompanied by immunoblasts, plasmacytoid lymphocytes and plasma cells. Additionally, reactive follicles can be seen in both conditions. In up to 50% cases of benign lymphoepithelial sialadenitis, some foci of intra-epithelial B-cell infiltration are clonal, as demonstrated by PCR for Ig heavy chain gene rearrangement; [51, 52] and in some cases, focal plasmacytoid lymphocytes or plasma cells within the lymphoepithelial lesions show kappa or lambda light chain excess by in situ hybridization or immunohistochemistry (IHC) [27, 51]. Therefore, it is controversial whether the demonstration of clonality in the absence of an expansion of these B-cell clones represents the very early manifestation of lymphoma, and a diagnosis of ENMZBCL is discouraged in such cases. In early ENMZBCL, there is an expansion of monocytoid B-cells, which form broad halos and bands around the lymphoepithelial islands, [27, 51] and clonality is demonstrable either by gene rearrangement studies by PCR or Ig light chain restriction by flow cytometry. If clonality is absent, a diagnosis of early ENMZBCL is also discouraged and close follow-up of such patients is recommended. As early ENMZBCL progresses, monocytoid B-cells form coalescing wide bands which alter the normal lobular salivary gland architecture by expanding the interglandular spaces, replacing acini and ducts, growing around nerves, and infiltrating interlobular

Fig. 2 Chronic sialadenitis shows a maintained lobular architecture (**a**) and present of lymphoepithelial lesions (**b**). The lymphocytes inside the epithelium have a monocytoid appearance, they are often B-cells. An early extranodal marginal zone lymphoma (ENMZBCL)

developed in a patient with chronic sialadenitis shows an expansion of the monocytoid B-cells in halos circling around the epithelial islands (**c** and **d**); and as the early ENMZBCL progresses, the monocytoid B-cells form coalescing strands and broad bands (**e** and **f**)

and periglandular fat and connective tissue. The monocytoid B-cells are positive for pan-B-cell markers CD20, CD79a and Pax5 and negative for CD5, CD10 and cyclin D1. Aberrant expression of the T-cell marker CD43 is present in a high proportion of cases (60–70%). Monoclonal plasma cells as demonstrated by monotypic Ig light chain expression can be seen in 50% of cases. Overall, salivary ENMZBCL lymphoma is rather indolent and usually remains localized. However, as the disease progresses, regional lymph node involvement or other extranodal site involvement may occur. The presence of t(14;18)(q32;q21) involving *IGH* and *MALT1* may be demonstrated in a minor subset of parotid gland

ENMZBCL by fluorescence in situ hybridization [53]. However, t(11;18)(q21;q21) and t(1;14)(p22;q32) which are frequently seen in gastric and pulmonary marginal zone lymphomas are rare in ENMZBCL of salivary glands [53].

Epstein-Barr Virus Lymphadenitis and Lymphoproliferative Disorders

Epstein-Barr Virus (EBV) is a ubiquitous gamma herpes virus with a double stranded DNA genome and is exclusively found in humans. Over 95% of adults worldwide are infected with EBV. The virus is primarily transmitted in

Fig. 3 EBV lymphadenitis (infectious mononucleosis) shows a markedly expanded paracortex with proliferation of immunoblasts (a); the interfollicular area contains lymphocytes of variable size and many plasma cells (b); CD20 shows that the B-cells are scattered not

in sheets, ranging from small, medium to large (c). A case of EBV-associated lymphoma in elderly shows overtly malignant cells in sheets with focal necrosis (d)

saliva by direct human contact, hence the colloquial term “kissing disease” for Infectious Mononucleosis (IM) [54]. After a 2–7-week incubation period, a lytic phase of infection leads to high levels of viral shedding in saliva which can persist for up to 18 months. Although EBV can infect epithelial cells, it is unclear whether infected oropharyngeal epithelial cells play a role in this phase of infection, since several authors were unable to detect EBV infection in tonsillar epithelium in patients with IM [55, 56]. Within the immune system, B-cells are preferentially infected and results in a striking secondary increase of CD8+ suppressor T-lymphocytes. In developing countries, primary infection of EBV almost always occurs in early childhood and is either asymptomatic or manifests itself as a mild nonspecific upper respiratory tract viral infectious syndrome. In more developed countries, the majority of primary infections occur during adolescence or early adulthood and about 30–50% of patients develop IM syndrome [56]. IM is a self-limited lymphoproliferative disorder characterized by pharyngitis and lymphadenopathy associated with fever, fatigue and malaise [57]. Non-tender enlargement of anterior and posterior cervical lymph nodes is most frequently observed. But diffuse lymphadenopathy can also be seen. Splenomegaly and hepatomegaly may be seen in about 50% of patients [58, 59]. A fatal or

nearly-fatal clinical course of IM with fulminant multiorgan failure is usually associated with immunodeficient states such as AIDS, congenital immunodeficiency syndromes, most notably X-linked lymphoproliferative disorder, and treatment with immunosuppressive drugs, [60] but is rarely seen in previously healthy patients.

Chronic active Epstein–Barr virus (CAEBV) disease has been defined as a systemic EBV-positive lymphoproliferative disease (LPD) characterized by fever, lymphadenopathy, and splenomegaly, developed after primary viral infection in patients without known immunodeficiency [61]. Antibody titers show evidence of primary EBV infection with anti-EBV viral capsid antigen IgG $\geq 5,120$, anti-EBV early-antigen IgG ≥ 640 , and or anti-EBNA < 2 . High levels of EBV DNA in the blood, histological evidence of organ disease, and elevated levels of EBV RNA or viral proteins in affected tissues are also observed. In CAEBV, EBV infection can involve B-, T-, or NK-cells. The term CAEBV should be applied to systemic LPDs that are not frank lymphomas and that arise during primary infection and persist for over 6 months [62]. CAEBV of B-cell origin has also been referred to as chronic (or persistent) IM. Ohshima K et al. [63] described the spectrum of CAEBV of T- or NK-cell origin as polymorphic LPD without clonal proliferation of EBV-infected cells,

polymorphic LPD with clonal proliferation of EBV-infected cells and monomorphic LPD (either peripheral T-cell lymphoma or NK-cell lymphoma/leukemia) with a clonal proliferation of EBV-infected cells. The term ‘systemic EBV-positive T-cell LPD’, as adopted by the WHO classification, is the preferred pathologic designation over CAEBV for those cases that are clearly clonal (polymorphic LPD with clonal proliferation of EBV-infected cells and monomorphic LPD), as they are generally associated with an aggressive clinical course and require aggressive treatment [64].

In recent years, it has been noted that defective immune surveillance of EBV may occur late in life and can be associated with the development of EBV-positive B-cell LPD in individuals who otherwise have no apparent immune deficiency. These are often due to EBV reactivation as demonstrated by increased anti-EBV viral capsid antigen IgG, anti-EBV early-antigen IgG, and positive anti-EBNA. The spectrum of EBV-associated B-cell LPD as recently described by Jaffe et al. [62] include: (i) lymph node-based reactive hyperplasia with increased EBV-positive B-cells, (ii) EBV-positive nodal B-cell lymphoproliferations resembling post-transplant LPD (PTLD), (iii) EBV-positive extranodal B-cell lymphoproliferations resembling PTLD, (iv) EBV-positive diffuse DLBCLs, and (v) EBV-positive B-cell proliferations resembling CHL. The reactive hyperplasia process-category (i) is self-limited in most patients, with only rare cases showing progression to a more aggressive lymphoproliferative process.

Although there are no evidence-based or consensus guidelines for the clinical work-up of possible EBV infection, a combination of clinical, serologic data and possible tissue biopsy is necessary [59]. Laboratory evaluation of EBV infection includes EBV-specific serologic analysis for anti-viral capsid antigen (VCA)-IgG and IgM, anti-early antigen IgG and anti-EBNA, EBV DNA and RNA. Pathologic evaluation of a tissue biopsy specimen in order to rule out another etiology or a malignant process may be performed when there are atypical clinical features such as absence of atypical lymphocytosis or high titers of EBV antibodies, an enlarging neck mass and age >30 years [65].

Histologically, EBV lymphadenitis (IM) is characterized by a prominent interfollicular/paracortical expansion associated with variable degrees of follicular hyperplasia and distended sinuses (Fig. 3). The paracortex has a mottled or “moth-eaten” appearance with increased high endothelial venules and a mixed population of small, medium and large lymphocytes, histiocytes, and variable numbers of plasma cells and eosinophils. Increased large immunoblasts are a characteristic feature and may be polylobated or show prominent nucleoli reminiscent of HRS cells. Immunoblasts may sometimes form confluent sheets, closely mimicking large B-cell lymphoma. Single

cell or confluent necrosis may also be seen. Follicles may be hyperplastic or relatively atretic and usually contain prominent germinal centers with numerous mitoses and tingible body macrophages. Marginal zone monocytoid B-cell hyperplasia is also occasionally observed. Sinuses are frequently distended with histiocytes and/or lymphocytes and plasma cells or with acellular eosinophilic proteinaceous fluid. It is not uncommon for the lymphoid proliferation to extend beyond the lymph node capsule into extranodal fat. However, the overall lymph node architecture, with preservation of B- and T-cell areas as highlighted with immunohistochemical stains, is generally preserved. Immunohistochemical stains also show that immunoblasts represent a mixture of B- and T-cells and also express CD45 and CD30. Analysis for EBV small-encoded RNA (EBER) by in situ hybridization shows a variable number of positive cells and is usually more sensitive than immunohistochemical staining for EBV LMP1. Molecular studies show polyclonal B and T-cells by immunoglobulin and T-cell receptor gene rearrangements respectively. Furthermore, Southern blot analysis usually shows a polyclonal pattern of EBV. Of note, however, fatal IM (sporadic or associated with immunodeficiency) may show monoclonal EBV in association with monoclonal B- or T-cell proliferations [60, 66]. In one series, histologic evaluation of autopsy specimens from these patients demonstrated marked infiltration of polymorphous lymphocytes and histiocytes in lymph nodes, spleen, liver and bone marrow, occasionally associated with prominent hematophagocytosis and necrosis.

IM-like syndromes can be caused by several other infectious agents including cytomegalovirus (CMV), HIV, adenoviruses, hepatitis A virus, adenoviruses, diphtheria and *Toxoplasma gondii*. Serologic testing is an important tool to help distinguish these etiologies. CMV mononucleosis is probably the most common mimicker of EBV infection and can show a clinical and hematologic picture indistinguishable from EBV-related IM. CMV lymphadenitis typically shows a paracortical expansion with immunoblastic and perivascular monocytoid B-cell proliferation. However, scattered large atypical cells with pleomorphic nuclei and characteristic “owl’s eye” intranuclear viral inclusions are unique to CMV infection. In addition, immunohistochemical or in situ hybridization analysis for CMV can be helpful. *Toxoplasma* infection most commonly presents in the general population as localized posterior cervical lymphadenopathy associated with mild constitutional symptoms. *Toxoplasma* lymphadenitis is characterized by a triad of reactive follicular hyperplasia, intrasinusoidal monocytoid B-cell hyperplasia and singly scattered and clusters of inter and intra-follicular epithelioid histiocytes. Paracortical expansion with immunoblastic proliferation is not a prominent feature.

The atypical immunoblastic proliferation of EBV lymphadenitis may mimic diffuse large B-cell lymphoma (DLBCL), or HRS cells of classical Hodgkin lymphoma. Prominent intrasinusoidal immunoblastic proliferation may mimic anaplastic large cell lymphoma (ALCL). Expert hematopathologic evaluation in conjunction with immunophenotypic and molecular studies for B-, T-cell or EBV clonality and clinical correlation may be required in cases of EBV reactivation in elderly, CAEBV infection, and EBV infection in congenital immunodeficiency in order to reach an accurate diagnosis.

Summary

Biopsy specimens from the head and neck region that contain lymphoid tissue are commonly encountered in the daily surgical pathology practice. The lymphoid tissue may represent a normal component of the oral pharyngeal region, reactive lymphoid hyperplasia or a malignant lymphoma. Lymphoproliferative lesions in this region can be prominent, and it is important to recognize whether the process represents a lymphoproliferative disorder that requires further comprehensive immunophenotypic and molecular studies and possible hematopathologic consultation, or if the process is benign, in which case it may represent reactive lymphoid hyperplasia secondary to viral infection, autoimmune disease, drug/toxin exposure or an unidentified etiologic agent (idiopathic), or may be part of an underlying lesion such as Warthin's tumor or nasopharyngeal carcinoma that might explain the clinical manifestation of a mass-like lesion or enlarged organ.

References

- Jaffe ES. Lymphoid lesions of the head and neck: a model of lymphocyte homing and lymphomagenesis. *Mod Pathol*. 2002; 15:255–63.
- Allen EA, Ali SZ, Mathew S. Lymphoid lesions of the parotid. *Diagn Cytopathol*. 1999;21:170–3.
- Chhieng DC, Cangiarella JF, Cohen JM. Fine-needle aspiration cytology of lymphoproliferative lesions involving the major salivary glands. *Am J Clin Pathol*. 2000;113:563–71.
- Ioachim HL, Medeiros LJ. Ioachim's lymph node pathology, vol. 4. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2009.
- Kim HT, Szero C. Eosinophilic hyperplastic lymphogranuloma, comparison with Mikulicz's disease. *Chin Med J*. 1937;23: 699–700.
- YS Kimura T, Ishikawa E. On the unusual granulation combined with hyperplastic changes of lymphatic tissue. *Trans Soc Pathol Jpn*. 1948;37:179–80.
- Hui PK, Chan JK, Ng CS, Kung IT, Gwi E. Lymphadenopathy of Kimura's disease. *Am J Surg Pathol*. 1989;13:177–86.
- Li TJ, Chen XM, Wang SZ, Fan MW, Semba I, Kitano M. Kimura's disease: a clinicopathologic study of 54 Chinese patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1996;82:549–55.
- Iwai H, Nakae K, Ikeda K, et al. Kimura disease: diagnosis and prognostic factors. *Otolaryngol Head Neck Surg*. 2007;137: 306–11.
- Chen H, Thompson LD, Aguilera NS, Abbondanzo SL. Kimura disease: a clinicopathologic study of 21 cases. *Am J Surg Pathol*. 2004;28:505–13.
- Terada N, Konno A, Shirotori K, et al. Mechanism of eosinophil infiltration in the patient with subcutaneous angioblastic lymphoid hyperplasia with eosinophilia (Kimura's disease). Mechanism of eosinophil chemotaxis mediated by candida antigen and IL-5. *Int Arch Allergy Immunol*. 1994;104(Suppl 1):18–20.
- Kuo TT, Shih LY, Chan HL. Kimura's disease. Involvement of regional lymph nodes and distinction from angiolymphoid hyperplasia with eosinophilia. *Am J Surg Pathol*. 1988;12:843–54.
- Ohta N, Okazaki S, Fukase S, Akatsuka N, Aoyagi M, Yamakawa M. Serum concentrations of eosinophil cationic protein and eosinophils of patients with Kimura's disease. *Allergol Int*. 2007; 56:45–9.
- Tsukadaira A, Kitano K, Okubo Y, et al. A case of pathophysiologic study in Kimura's disease: measurement of cytokines and surface analysis of eosinophils. *Ann Allergy Asthma Immunol*. 1998;81:423–7.
- Rajpoot DK, Pahl M, Clark J. Nephrotic syndrome associated with Kimura disease. *Pediatr Nephrol*. 2000;14:486–8.
- Nakahara C, Wada T, Kusakari J, et al. Steroid-sensitive nephrotic syndrome associated with Kimura disease. *Pediatr Nephrol*. 2000; 14:482–5.
- Matsuda O, Makiguchi K, Ishibashi K, et al. Long-term effects of steroid treatment on nephrotic syndrome associated with Kimura's disease and a review of the literature. *Clin Nephrol*. 1992; 37:119–23.
- Danis R, Ozmen S, Akin D, et al. Thrombosis of temporal artery and renal vein in Kimura-disease-related nephrotic syndrome. *J Thromb Thrombolysis*. 2009;27:115–8.
- Armstrong WB, Allison G, Pena F, Kim JK. Kimura's disease: two case reports and a literature review. *Ann Otol Rhinol Laryngol*. 1998;107:1066–71.
- Chen W, Kesler MV, Karandikar NJ, McKenna RW, Kroft SH. Flow cytometric features of angioimmunoblastic T-cell lymphoma. *Cytometry B Clin Cytom*. 2006;70:142–8.
- Merchant SH, Amin MB, Viswanatha DS. Morphologic and immunophenotypic analysis of angioimmunoblastic T-cell lymphoma: emphasis on phenotypic aberrancies for early diagnosis. *Am J Clin Pathol*. 2006;126:29–38.
- Kimura Y, Pawankar R, Aoki M, Niimi Y, Kawana S. Mast cells and T cells in Kimura's disease express increased levels of interleukin-4, interleukin-5, eotaxin and RANTES. *Clin Exp Allergy*. 2002;32:1787–93.
- Senel MF, Van Buren CT, Etheridge WB, Barcenas C, Jammal C, Kahan BD. Effects of cyclosporine, azathioprine and prednisone on Kimura's disease and focal segmental glomerulosclerosis in renal transplant patients. *Clin Nephrol*. 1996;45:18–21.
- Katagiri K, Itami S, Hatano Y, Yamaguchi T, Takayasu S. In vivo expression of IL-4, IL-5, IL-13 and IFN-gamma mRNAs in peripheral blood mononuclear cells and effect of cyclosporin A in a patient with Kimura's disease. *Br J Dermatol*. 1997;137:972–7.
- Shanti RM, Aziz SR. HIV-associated salivary gland disease. *Oral Maxillofac Surg Clin North Am*. 2009;21:339–43.
- Schioldt M. HIV-associated salivary gland disease: a review. *Oral Surg Oral Med Oral Pathol*. 1992;73:164–7.

27. Harris NL. Lymphoid proliferations of the salivary glands. *Am J Clin Pathol.* 1999;111:S94–103.
28. Vargas PA, Mauad T, Bohm GM, Saldiva PH, Almeida OP. Parotid gland involvement in advanced AIDS. *Oral Dis.* 2003; 9:55–61.
29. Bernier JL, Bhaskar SN. Lymphoepithelial lesions of salivary glands; histogenesis and classification based on 186 cases. *Cancer.* 1958;11:1156–79.
30. Morris MR, Moore DW, Shearer GL. Bilateral multiple benign lymphoepithelial cysts of the parotid gland. *Otolaryngol Head Neck Surg.* 1987;97:87–90.
31. Ihrler S, Zietz C, Riederer A, Diebold J, Lohrs U. HIV-related parotid lymphoepithelial cysts. Immunohistochemistry and 3-D reconstruction of surgical and autopsy material with special reference to formal pathogenesis. *Virchows Arch.* 1996;429:139–47.
32. Dave SP, Pernas FG, Roy S. The benign lymphoepithelial cyst and a classification system for lymphocytic parotid gland enlargement in the pediatric HIV population. *Laryngoscope.* 2007;117:106–13.
33. Morales-Aguirre JJ, Patino-Nino JA, Mendoza-Azpiri M, et al. Parotid cysts in children infected with human immunodeficiency virus: report of 4 cases. *Arch Otolaryngol Head Neck Surg.* 2005;131:353–5.
34. DiGiuseppe JA, Corio RL, Westra WH. Lymphoid infiltrates of the salivary glands: pathology, biology and clinical significance. *Curr Opin Oncol.* 1996;8:232–7.
35. Ulirsch RC, Jaffe ES. Sjogren's syndrome-like illness associated with the acquired immunodeficiency syndrome-related complex. *Hum Pathol.* 1987;18:1063–8.
36. Maiorano E, Favia G, Viale G. Lymphoepithelial cysts of salivary glands: an immunohistochemical study of HIV-related and HIV-unrelated lesions. *Hum Pathol.* 1998;29:260–5.
37. Vicandi B, Jimenez-Heffernan JA, Lopez-Ferrer P, et al. HIV-1 (p24)-positive multinucleated giant cells in HIV-associated lymphoepithelial lesion of the parotid gland. A report of two cases. *Acta Cytol.* 1999;43:247–51.
38. Itescu S, Brancato LJ, Winchester R. A sicca syndrome in HIV infection: association with HLA-DR5 and CD8 lymphocytosis. *Lancet.* 1989;2:466–8.
39. Elliott JN, Oertel YC. Lymphoepithelial cysts of the salivary glands. Histologic and cytologic features. *Am J Clin Pathol.* 1990; 93:39–43.
40. Patton LL, van der Horst C. Oral infections and other manifestations of HIV disease. *Infect Dis Clin North Am.* 1999;13: 879–900.
41. Terry JH, Loree TR, Thomas MD, Marti JR. Major salivary gland lymphoepithelial lesions and the acquired immunodeficiency syndrome. *Am J Surg.* 1991;162:324–9.
42. Finfer MD, Gallo L, Perchick A, Schinella RA, Burstein DE. Fine needle aspiration biopsy of cystic benign lymphoepithelial lesion of the parotid gland in patients at risk for the acquired immune deficiency syndrome. *Acta Cytol.* 1990;34:821–6.
43. Wu L, Cheng J, Maruyama S, et al. Lymphoepithelial cyst of the parotid gland: its possible histopathogenesis based on clinicopathologic analysis of 64 cases. *Hum Pathol.* 2009;40:683–92.
44. Kreisel FH, Frater JL, Hassan A, El-Mofty SK. Cystic lymphoid hyperplasia of the parotid gland in HIV-positive and HIV-negative patients: quantitative immunopathology. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2010;109:567–574.
45. Cao D, Begum S, Ali SZ, Westra WH. Expression of p16 in benign and malignant cystic squamous lesions of the neck. *Hum Pathol.* 2010;41:535–539.
46. Syebele K. Regression of both oral mucocoele and parotid swellings, following antiretroviral therapy. *Int J Pediatr Otorhinolaryngol.* 2010;74:89–92.
47. Ellis GL. Lymphoid lesions of salivary glands: malignant and benign. *Med Oral Patol Oral Cir Bucal.* 2007;12:E479–85.
48. Ellis GL APT. Tumors of the Salivary Glands. Atlas of Tumor Pathology. Washington, D. C.: Armed Forces Institute of Pathology. 2007.
49. Hyjek E, Smith WJ, Isaacson PG. Primary B-cell lymphoma of salivary glands and its relationship to myoepithelial sialadenitis. *Hum Pathol.* 1988;19:766–76.
50. Quintana PG, Kapadia SB, Bahler DW, Johnson JT, Swerdlow SH. Salivary gland lymphoid infiltrates associated with lymphoepithelial lesions: a clinicopathologic, immunophenotypic, and genotypic study. *Hum Pathol.* 1997;28:850–61.
51. Carbone A, Gloghini A, Ferlito A. Pathological features of lymphoid proliferations of the salivary glands: lymphoepithelial sialadenitis versus low-grade B-cell lymphoma of the malt type. *Ann Otol Rhinol Laryngol.* 2000;109:1170–5.
52. Bahler DW, Swerdlow SH. Clonal salivary gland infiltrates associated with myoepithelial sialadenitis (Sjogren's syndrome) begin as nonmalignant antigen-selected expansions. *Blood.* 1998; 91:1864–72.
53. Streubel B, Lamprecht A, Dierlamm J, et al. T(14;18)(q32;q21) involving IGH and MALT1 is a frequent chromosomal aberration in MALT lymphoma. *Blood.* 2003;101:2335–9.
54. Thorley-Lawson DA. Epstein-Barr virus: exploiting the immune system. *Nat Rev Immunol.* 2001;1:75–82.
55. Anagnostopoulos I, Hummel M, Kreschel C, Stein H. Morphology, immunophenotype, and distribution of latently and/or productively Epstein-Barr virus-infected cells in acute infectious mononucleosis: implications for the interindividual infection route of Epstein-Barr virus. *Blood.* 1995;85:744–50.
56. Kutok JL, Wang F. Spectrum of Epstein-Barr virus-associated diseases. *Annu Rev Pathol.* 2006;1:375–404.
57. Hurt C, Tammaro D. Diagnostic evaluation of mononucleosis-like illnesses. *Am J Med.* 2007;120 911:e911-918.
58. Balfour HH Jr, Holman CJ, Hokanson KM, et al. A prospective clinical study of Epstein-Barr virus and host interactions during acute infectious mononucleosis. *J Infect Dis.* 2005;192:1505–12.
59. Ebell MH. Epstein-Barr virus infectious mononucleosis. *Am Fam Physician.* 2004;70:1279–87.
60. Wick MJ, Woronzoff-Dashkoff KP, McGlennen RC. The molecular characterization of fatal infectious mononucleosis. *Am J Clin Pathol.* 2002;117:582–8.
61. Straus SE. The chronic mononucleosis syndrome. *J Infect Dis.* 1988;157:405–12.
62. Cohen JI, Kimura H, Nakamura S, Ko YH, Jaffe ES. Epstein-Barr virus-associated lymphoproliferative disease in non-immunocompromised hosts: a status report and summary of an international meeting, 8–9 September 2008. *Ann Oncol.* 2009;20: 1472–82.
63. Ohshima K, Kimura H, Yoshino T, et al. Proposed categorization of pathological states of EBV-associated T/natural killer-cell lymphoproliferative disorder (LPD) in children and young adults: overlap with chronic active EBV infection and infantile fulminant EBV T-LPD. *Pathol Int.* 2008;58:209–17.
64. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon: IARC; 2008.
65. Kojima M, Kashimura M, Itoh H, et al. Epstein-Barr virus-related reactive lymphoproliferative disorders in middle-aged or elderly patients presenting with atypical features. A clinicopathological study of six cases. *Pathol Res Pract.* 2007;203:587–91.
66. Betts RF. Syndromes of cytomegalovirus infection. *Adv Intern Med.* 1980;26:447–66.