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ORIGINAL PAPER

Update from the 4th Edition of the World Health Organization Classification of Head and Neck Tumours: Hematolymphoid Tumours

Noah A. Brown[1] · **Kojo S. J. Elenitoba-Johnson**[2]

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Abstract In 2017, the latest revision to the WHO Classification of Head and Neck Tumours will be released. Similar to the 2005 WHO, the codification of hematopoietic and lymphoid neoplasms of the head and neck is included within chapters pertaining to the nasal cavity and paranasal sinuses, the nasopharynx, the larynx, the oral cavity and oropharynx, the neck and the salivary glands. Herein, we describe both changes to the classification of hematolymphoid neoplasms of the head and neck since the 2005 WHO, as well as recent advances in our understanding of the underlying pathogenesis and molecular pathology of these neoplasms.

Keywords WHO · 2017 · Revision · Edition · Hematolymphoid · Hematopoietic · Lymphoma

Introduction

This section applies to hematopoietic and lymphoid neoplasms of the head and neck including the nasal cavity and paranasal sinuses, the nasopharynx, the larynx, the oral cavity and oropharynx, the neck and the salivary glands. While there have been relatively few changes to the classification of hematolymphoid neoplasms of the head and neck since the 2005 WHO classification of Head and Neck Tumours, there have been significant advances in our understanding of the underlying pathogenesis and molecular pathology of these neoplasms (See Table 1).

CD30-Positive T-Cell Lymphoproliferative Disorder

CD30-positive T-cell lymphoproliferative disorder (TLPD) encompasses a clinicopathologic spectrum that typically occurs in the oral cavity or occasionally other mucosal sites in the head and neck. This entity was not formally codified in the 2005 WHO classification of Head and Neck Tumours, but has since been added to the current edition. These tumors are analogous to the clinicopathologic spectrum observed in primary cutaneous CD30-positive TLPD. Primarily affecting older adults, these lesions typically present as a mass, often with ulceration [1]. Lesions show sheets of large and atypical neoplastic cells with pleomorphic nuclei, often within a mixed inflammatory background [2–4]. Neoplastic cells show strong uniform CD30, by definition, express CD4 more often than CD8, frequently express cytotoxic markers and are negative for CD56, ALK and EBV [4]. Recently, rearrangements involving *DUSP22* on 6p25.3 have been identified in these lesions, similar to those observed in primary cutaneous TLPD and ALK-negative anaplastic large cell lymphoma [3]. Importantly, most cases of CD30-positive TLPD show complete resolution with local therapy alone [3–5].

Special Issue: World Health Organization Classification Update

✉ Kojo S. J. Elenitoba-Johnson
Kojo.Elenitoba-Johnson@uphs.upenn.edu

[1] Department of Pathology, University of Michigan Health System, Ann Arbor, MI, USA

[2] Department of Pathology, Perelman School of Medicine at University of Pennsylvania, 609A Stellar Chance Laboratories, 420 Curie Boulevard, Philadelphia, PA 1904, USA

Table 1 Summary of histologic, immunophenotypic, pathogenic and prognostic features of head and neck hematolymphoid neoplasms

Diagnosis	Histologic features	Immunophenotype	Molecular/pathogenesis	Prognosis
CD30-positive T-cell lymphoproliferative disorder	Analagous to primary cutaneous CD30-positive T-cell lymphoproliferative disorder. Sheets of large, atypical cells with mixed inflammatory background	Strong, uniform CD30. CD4 more often than CD8. Cytoxic marker expression. Negative for CD56, ALK, EBER	Some cases with rearrangements of *DUSP22* on 6p25.3	Most cases resolve with local therapy alone
Extranodal NK/T-cell lymphoma	Angiocentric/angiodestructive with variably atypical T-cells and geographic necrosis	T-cell antigens, cytotoxic markers, EBER and CD56	EBV infection with downregulation of MiR-146a and MiR-15a. Mutation of tumor supressor genes *TP53, DDX3X* and genes in region of 6q21-23 *(PRDM1, ATG5, AIM1, HACE1* and *FOXO3*). Activating mutations of *JAK3, STAT3, PTPRK*	Aggressive behavior with variable prognosis. Invasion of bone or skin, high circulating EBV DNA and EBV + cells in the bone marrow associated with worse prognosis
Extraosseous plasmacytoma	Sheets of variably atypical plasma cells. Extranodal marginal zone lymphoma and plasmablastic lymphoma are important differential diagnoses	CD138, CD38, MUM1/IRF4. Variable CD79A. CD20 and PAX5 negative	Similar genetic features as plasma cell myeloma with some differences in *IGH* translocation partners	Most cases eradicated by local radiation. Recurrence in ~25%. Progression to plasma cell myeloma in ~15%
Diffuse large B-cell lymphoma (DLBCL)	Sheets of large cells with centroblastic, immunoblastic or anaplastic cytology	Expression of B-cell markers	Germinal center B-cell: alterations of *BCL6, BCL2* translocations, *EZH2* mutations, *GNA13* mutations. Activated B-cell: mutations activating BCR/TLR and NFκB pathways (*MYD88, CD79A, CARD11, TNFAIP3*)	Aggressive behavior with variable prognosis. Bone marrow involvement, concurrent MYC and BCL2 and/or BCL6 rearrangements and MYC and BCL2 co-expression associated with poor prognosis
EBV + mucocutaneous ulcer	Circumscribed ulcer with polymorphous infiltrate containing large, atypical B-cells often resembling Reed–Sternberg cells	Expression of B-cell markers, EBER positivity	EBV infection with waining immune defense due to age or iatrogenic immunosuppression	Spontaneous regression or relapsing-remitting course requiring only conservative management
Classical Hodgkin lymphoma (CHL)	Mixed inflammatory background with mononuclear Hodgkin cells and/or multi-nucleated Reed–Sternberg cells	CD30 positive, CD15 positive in most cases. Weak positivity for PAX5. Negative or weakly positive for CD20 and CD79A	Crippled B-cell expression program. Constitutive activation of NFκB. EBV in many cases	Curable in most cases with chemotherapy and radiation
Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)	Nodules comprised predominantly of small T-cells, studded with large cells with lobulated nuclei (LP cells)	LP cells express B-cell antigens and are negative for CD30 and CD15. LP cells rosetted by cells with T follicular helper cell immunophenotype. CD21 highlights folllicular dendritic meshwork with nodules	Frequent *BCL6* rearrangements. Somatic hypermutation in *PAX5, PIM1, RHOH* and *MYC*. No EBV	Slow progression with excellent prognosis for low-stage disease. Progression to DLBCL in 3–5% of cases

Table 1 (continued)

Diagnosis	Histologic features	Immunophenotype	Molecular/pathogenesis	Prognosis
Burkitt lymphoma BL	Monomorphic medium-sized cells with squared-off borders, mitotic figures and scattered tingible body macrophages	Expression of B-cell antigens and germal center markers. Negative for TdT and negative or weakly positive for BCL2. 100% proliferative index (Ki-67). May be EBER positive, particularly endemic variant	*MYC* rearrangements in 90%, most commonly *IGH*, less frequently *IGK* or *IGL*. *MYC* negative lymphomas resembling Burkitt with 11q aberration recognized as separate provisional entity in 2016 Heme WHO. Endemic cases frequently show EBV, cytomegalovirus and HHV8 infection, expression of EBV lytic genes and recurrent alterations of *ARID1A, CCNF* and *RHOA*. Sporadic cases frequently show alterations of *MYC, ID3, TCF3* and *TP53*	Highly aggressive but intensive chemotherapy regimens result in cure in up 90%
Follicular lymphoma (FL)	Follicular and/or diffuse patern with centrocytes and centroblasts. Follicles are closely packed with absent or attenuated mantles and lack of polarization or tingible body macrophages. FL in children and young adults (particularly in the tonsil) shows high-grade features i.e. prominent centroblasts or blastoid follicular cells	Expression of B-cell antigens and germal center markers. Follicles show staining for follicular dendritic cells (CD21, CD23)	Most cases demonstrate a t(14;18). Tonsillar FL in children and young adults typically lack t(14;18) and *BCL6* or *MYC* rearrangements and instead carry *MUM1/IRF4* rearrangements in 50%	Low-grade FL (grade 1–2) is indolent and not usually curable. The majority of grade 3 FL show an aggressive clinical course. However, FL in children and young adults - tonsillar in particular - shows a more localized, indolent clinical behavior than conventional grade 3 FL
Mantle cell lymphoma (MCL)	Small to intermediate-sized, monomorphic cells arranged in a vaguely nodular, diffuse, mantle zone or rarely follicular pattern. No proliferation centers. May have hyalinized vessels and/or epithelioid histiocytes	Expression of B-cell markers, CD5 and cyclin D1. SOX11 in rare cyclin D1-negative MCL	Most cases demonstrate t(11;14) *CCND1-IGH*. Cyclin D1-negative MCL may have rearrangements of *CCND2* or *CCND3*. Mutations of ATM and TP53 common	More aggressive than other small B-cell lymphomas with median survival of 3–5 years. Most cases cannot be cured
T-lymphoblastic leukemia/lymphoma (T-LBL/L)	Small to intermediate-sized cells with fine chromatin, variably prominent nucleoli and scant cytoplasm	Most positive for cytoplasmic CD3, TdT, CD7 and CD1a; variably positive for CD10; either double-positive or double-negative for CD4 and CD8. Early T precursor (ETP) lymphoblastic leukemia/lymphoma is CD7 positive without CD1a or CD8 and positive for one or more myeloid/stem cell markers	Frequent rearrangements involving the T-cell receptor genes. Activation of Notch signalling and loss of CDKN2A common. ETP with frequent mutations of myeloid-associated genes	Aggressive disease often with more high-risk features than B-LBL/L. Indolent T-lymphoblastic proliferation is a non-neoplastic entity that can mimic T-LBL/L and frequently involves lymphoid tissue of the head and neck

Table 1 (continued)

Diagnosis	Histologic features	Immunophenotype	Molecular/pathogenesis	Prognosis
Extranodal marginal zone lymphoma (MALT lymphoma)	Heterogeneous mixture of B-cells including marginal zone (centrocyte-like) cells, monocytoid B-cells, small lymphocytes, plasma cells and scattered immunoblasts and centroblast-like cells. Neoplastic cells typically infiltrate the epithelium forming lymphoepithelial lesions	Expression of B-cell antigens. Negative for CD5, CD10, BCL6 and cyclin D1	In salivary glands, lymphoepithelial sialadenitis is a precursor lesion. Monoclonal B cells present in more than half of salivary lesions from Sjögren patients and acquisition of mutations such as in TNFAIP3 associated with lymphoma development. Translocations involving MALT1 including t(14;18) (IGH-MALT1), t(11;18) (API2-MALT1) are uncommon in head and neck MALT lymphomas. Hepatitis C is another predisposing factor. Anecdotal evidence of MALT lymphoma arising in the setting of IgG4-related disease	Variable clinical course. Advance stage, high circulating EBV DNA associated with inferior prognosis
Follicular dendritic cell (FDC) sarcoma	Mass with pushing border, often arranged in fascicular, whorled or storiform patterns with admixed small lymphocytes. Cells may be spindled, ovoid or epithelioid cells with eosinophilic cytoplasm, indistinct cell borders and finely dispersed chromatin. Nuclear pseudoinclusions, and binucleated or multinucleated cells are common. A subset of cases are associated with hyaline-vascular Castleman disease	Positivity for FDC-associated antigens including CD21, CD23, CD35, clusterin, CXCL13 and podoplanin	Unknown	Surgery is potentially curable in early disease, but late recurrence and metastasis can occur. Large tumor size, disseminated disease, extensive necrosis, high mitotic rate and nuclear atypia associated with worse prognosis
Plasmablastic lymphoma (PBL)	Sheets of large cells resembling immunoblasts	Expression of plasmacytic markers including CD138, CD38 and IRF4/MUM1. Negative or only weakly positive for CD45, CD20 and PAX5. EBER positive in >80%. Negative for HHV8	Most frequently in the setting of HIV-related immunosuppression. Associated with EBV infection, and MYC dysregulation with *MYC* translocation or gains in half of cases	Very aggressive with most patients dying within a year
Langerhans cell histiocytosis (LCH)	A mixture of inflammatory cells, including eosinophils, and neoplastic Langerhans cells with folded or grooved nuclei and moderate to abundant cytoplasm	Positivity for S100, CD1a and CD207 (langerin)	Activation of MAPK pathway with *BRAF* V600E in 50% *and MAP2K1* mutations in 25%	Highly dependent on staging with >99% survival for unifocal disease and ~33% for multisystem involvement
Extramedullary myeloid sarcoma	Effacement of tissue architecture by myeloblasts with or without promyelocytic or neutrophilic maturation	CD68 positivity most common followed by MPO, CD117, lysozyme, CD34 and TdT	Variety of chromosomal aberrations including monosomy 7, trisomy 8, inv(16) and t(8;21)-particularly in pediatric patients. NPM1 mutations are also found in 16% of cases	Variably but often unfavorable

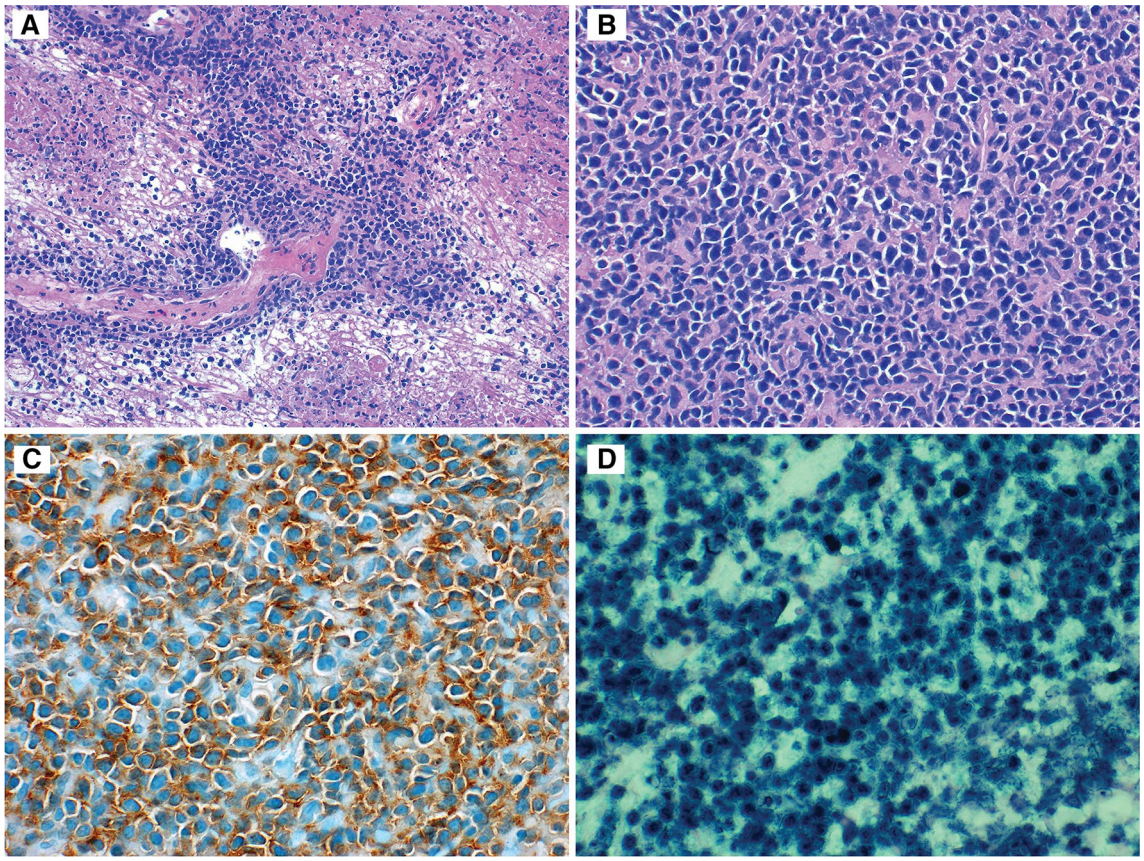

Fig. 1 Extranodal NK/T-cell lymphoma **a** Angiocentric growth with surrounding necrosis. **b** Monotonous, intermediate-sized atypical lymphocytes. **c** CD56 positivity. **d** Positivity for EBV in-situ hybridization (EBER)

Extranodal NK/T-Cell Lymphoma

Extranodal NK/T-cell lymphoma (ENKTL), nasal type is an extranodal lymphoma with a cytotoxic phenotype, associated with EBV. While this entity was recognized in the 2005 WHO, there have been significant advances in our understanding its underlying pathogenesis. This lymphoma most commonly occurs in the upper aerodigestive tract and is more prevalent among East Asians [6] and the indigenous populations of Mexico and Central and South America [7]. Commonly presenting as nasal obstruction and/or epistaxis, ENKTL frequently shows an angiocentric/angiodestructive pattern leading to geographic necrosis. The tumor cells express T cell antigens, cytotoxic markers (TIA1, granzyme B or perforin), EBV RNA (EBER) and frequently CD56 [8] (Fig. 1).

Since the 2005 WHO, our understanding of the molecular pathogenesis of ENKTL has expanded. Several tumor suppressor genes within the commonly deleted region at 6q21-23 have recently been identified including *PRDM1, ATG5, AIM1, HACE1*, and *FOXO3* [9–11]. In addition to *TP53* [12], *DDX3X* was recently identified as another commonly mutated tumor suppressor gene [13]. The JAK/STAT pathway is activated in most cases with frequent genetic alterations of *JAK3, STAT3* or *PTPRK* [14–17]. While EBV has long been implicated in the pathogenesis of ENKTL, recent studies have shown that EBV infection downregulated host microRNA and that downregulation of MiR-146a [18] and miR-15a promotes cell proliferation and is associated with a poor prognosis [19]. Recent studies have also highlighted the role of quantitative EBV DNA assay in plasma and PET findings in risk stratification [20].

Extraosseous Plasmacytoma

Extraosseous (extramedullary) plasmacytoma is a mass-forming proliferation of clonal plasma cells in the absence of underlying plasma cell myeloma, as described in the previous WHO. Important differential diagnoses to exclude include plasmablastic lymphoma and extranodal marginal zone lymphoma with extensive plasmacytic differentiation. These tumors frequently involve the upper respiratory tract and appear as sheets of plasma cells expressing markers of plasmacytic differentiation including CD138, CD38 and MUM1/IRF4 (Fig. 2). CD79A is variably expressed

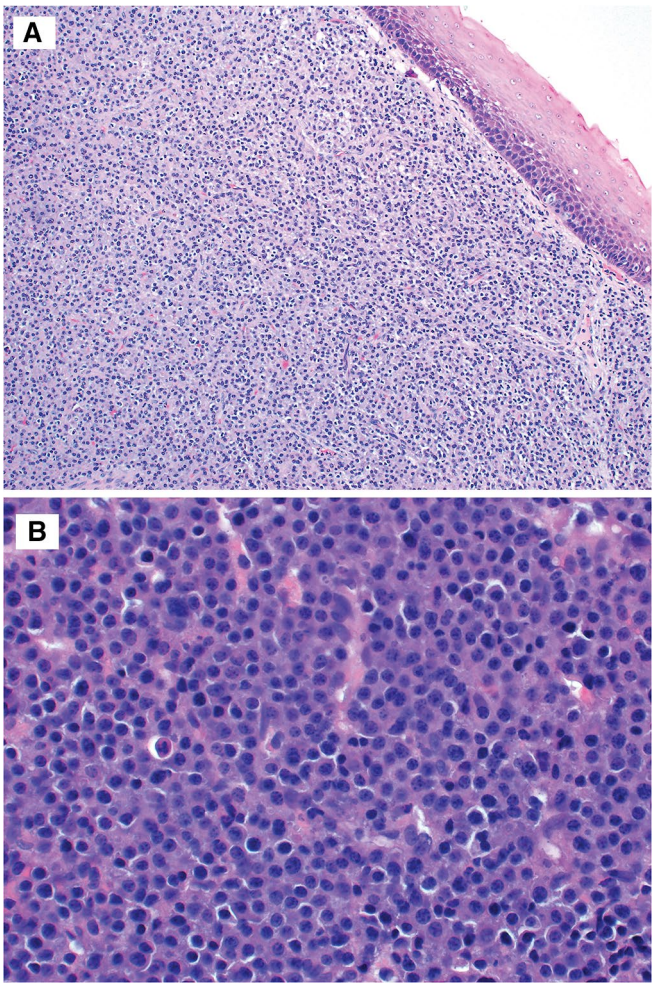

Fig. 2 Extraosseous (extramedullary) plasmacytoma. **a** A mass formed by monotonous cells with abundant cytoplasm underlying squamous epithelium. **b** Sheets of plasma cells with clumped chromatin and abundant eosinophilic cytoplasm

while CD20 and PAX5 are typically negative. Plasmablastic lymphoma should be considered in the setting of EBV positivity.

Studies have shown similar genetic features between plasma cell myeloma and extraosseous plasmacytoma though differences in *IGH* translocation partners have been reported [21].

Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is a diffuse infiltration by intermediate to large-sized B cells with variable cytological features including centroblastic, immunoblastic and anaplastic. DLBCL can occur at any site in the head and neck region. The 2017 Head and Neck WHO does not specifically address the recent advances made in understanding of DLBCL or the separate classifications of DLBCL recognized in the 2016 WHO classification of hematopoietic and lymphoid tumors [22]. In particular, the importance of classifying DLBCL based on cell of origin—activated B-cell (ABC) or germinal center B-cell (GCB)—is widely accepted based on differences in clinical outcome, gene expression, chromosomal alterations and somatic mutations [23, 24]. Recent next-generation sequencing studies have shown that both GCB and ABC DLBCL frequently have inactivating mutations of *TP53* and immunosurveillance genes, alterations of epigenetic regulators and oncogenic activation of BCL6. GCB DLBCL have frequent alterations *EZH2* and *BCL2* translocations similar to follicular lymphoma as well as mutations in the cell motility regulator *GNA13*. In contrast, ABC DLBCL have frequent mutations in genes activating BCR/TLR and NFκB pathways (e.g. *MYD88, CD79A, CARD11, TNFAIP3*). Additional important categories include high grade B-cell lymphoma (HGBL) with rearrangements of *MYC* and *BCL2* and/or *BCL6* which is associated with a poor prognosis [17, 19, 25]. Recent studies have also suggested that "double-expressor lymphomas" (i.e. MYC and BCL2) may also have a worse outcome [26].

EBV + DLBCL, NOS is also recognized as a distinct entity by the 2016 WHO classification of hematopoietic and lymphoid tumors [17, 27, 28]. The "NOS" designation is intended to exclude other entities with neoplastic

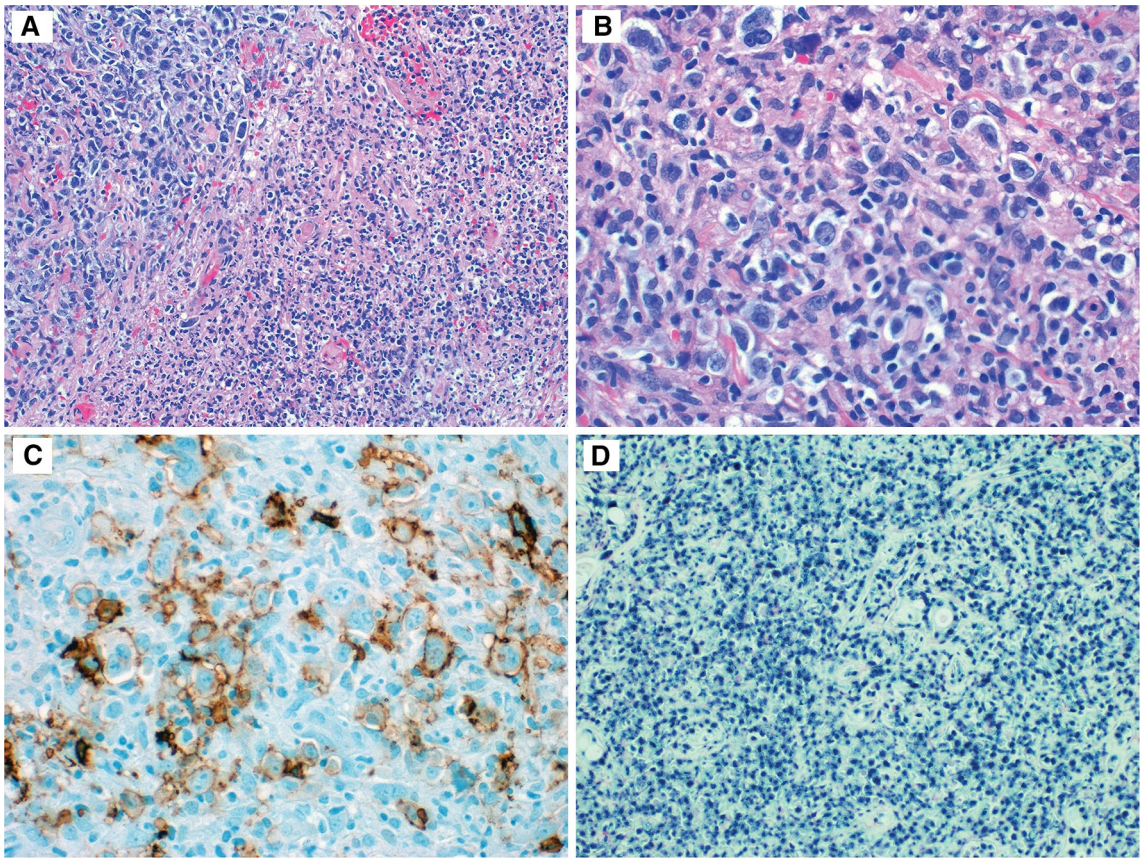

Fig. 3 EBV+ mucocutaneous ulcer. **a** Ulcerated mandibular gingiva with underlying infiltrate of large atypical cells. **b** Polymophous infiltrate of large, markedly atypical cells resembling Reed–Sternberg cells. **c** CD20 positivity consistent with a B-cell process. **d** Uniform positivity for EBV in-situ hybridization (EBER)

EBV+ B-cells such as lymphomatoid granulomatosis. However, in the head and neck region, it is important to consider a EBV+ mucocutaneous ulcer, an indolent condition codified as a provisional entity in the 2016 WHO classification of hematopoietic and lymphoid tumors [17]. These lesions frequently appear as circumscribed oral ulcers in immunocompromised or elderly patients and are characterized by a polymorphous infiltrate with atypical large B-cells often resembling Reed–Sternberg cells [29] (Fig. 3). These ulcers may regress spontaneously or have a relapsing-remitting course, generally requiring only conservative management [24, 30].

As discussed with follicular lymphoma, it is also important to distinguish DLBLC, NOS from Large B-cell lymphoma with IRF4 rearrangement [17]. This lymphoma which generally occurs in children and young adults most frequently involves the cervical lymph nodes and Waldeyer ring.

Hodgkin Lymphoma

As in the 2005 WHO, classical Hodgkin lymphoma (CHL) is distinct from nodular lymphocyte predominant Hodgkin lymphoma (NLPHL). In CHL, the neoplastic cells (mononuclear Hodgkin cells and multi-nucleated Reed–Sternberg cells) have lost expression of many B-cell specific proteins. They are weakly positive for PAX5 but are typically negative (or only weakly positive) for CD20 and CD79A. CD30 is positive in virtually all cases and CD15 in most. The inflammatory background typically consists of T-cells, plasma cells, histiocytes and eosinophils. In NLPHL, the neoplastic cells have lobulated nuclei, retain B-cell antigen expression are rosetted by T follicular helper cells.

The revision acknowledges that there can be overlap between NLPHL and T-cell histiocyte rich large B-cell lymphoma.

Burkitt Lymphoma

Burkitt lymphoma (BL) is a B-cell lymphoma with an extremely high proliferation rate, often involving extranodal sites, composed of monomorphic medium-sized cells [31]. The current Head and Neck WHO is largely unchanged from the 2005 edition; although the 2016 WHO classification recognizes a new provisional entity. The diagnosis of BL requires integration of morphology, immunophenotype and genetics. Three variants are recognized: endemic (regions where malaria is endemic), sporadic, and immunodeficiency-associated. The characteristic starry-sky pattern is formed by closely packed neoplastic cells with scattered phagocytizing macrophages. Neoplastic cells are positive for CD20, CD10, BCL6 and MYC and are typically negative for BCL2. Ki-67 typically demonstrates a proliferation index of 100% and EBER is frequently positive.

Approximately 90% of cases demonstrate a rearrangement involving *MYC* (8q24), most commonly with *IGH* (14q32) or less frequently to *IGK* (2p12) or *IGL* (22q11) [19, 32, 33]. Some controversy exists over whether cases without MYC rearrangements should be classified as BL. These cases are characterized by 11q alterations including proximal gains and telomeric losses [34, 35]. While these cases resemble BL morphologically, immunophenotypically and by gene expression profiling, they show more complex karyotypes, lower MYC expression and may show more cytological pleomorphism. These cases are classified as BL according to the 2017 Head and Neck WHO while the 2016 WHO classification of hematopoietic and lymphoid tumors recognizes a provisional entity designated "Burkitt-like lymphoma with 11q aberration." [17].

Gene expression profiling studies have shown that endemic and immunodeficiency-associated BL have nearly identical signatures while sporadic cases differ in expression of many genes [36, 37]. Similarly, large-scale sequencing studies have demonstrated differences between endemic and sporadic BL [38, 39]. Endemic cases frequently show both cytomegalovirus and HHV8 infection, expression of EBV lytic genes and recurrent alterations of *ARID1A, CCNF* and *RHOA*. By contrast, sporadic cases more frequently show alterations of *MYC, ID3, TCF3* and *TP53*.

Follicular Lymphoma

Follicular lymphoma (FL) is a lymphoma comprised of centrocytes and centroblasts with at least a partially follicular pattern. This category may include both pediatric and adult FL which are now acknowledged to have important clinicopathologic differences. In the head and neck, cervical lymph nodes are the most common site with Waldeyer ring involvement typically representing secondary tonsillar extension from nodal disease [40]. Isolated oropharyngeal FL is rare, most often occurring in children and young adults. In keeping with a germinal center phenotype, cells are positive for CD10 and BCL6. BCL2 is positive in 85–90% of cases.

The revised WHO acknowledges the differences between FL in the tonsil of children and young adults and other cases of FL. FL in this setting typically shows large expansile follicles, positivity for MUM1/IRF4, a high proliferative index and prominent centroblasts or blastoid follicular center cells rather than classic centrocytes [41, 42]. While most FL cases bear the t(14;18) translocation, MUM1/IRF4-positive FL in children and young adults typically lack the t(14;18) translocation as well as *BCL6* and *MYC* rearrangements and instead carries translocations involving *MUM1/IRF4* in approximately 50% of cases [29, 30]. The 2016 WHO classification of hematopoietic and lymphoid tumors separately classifies these cases as "pediatric-type" follicular lymphoma and avoids classifying these cases as conventional grade 3 FL given the generally localized indolent behavior of these cases [17, 29, 30]. In addition, a separate provision entity designated "large B-cell lymphoma with IRF4 rearrangement" has been designated [17, 29, 43]. This entity most frequently occurs in Waldeyer ring and/or cervical lymph nodes and is meant to include lymphomas with follicular, follicular and diffuse, or pure diffuse growth patterns that would otherwise be designated FL grade 3B or DLBCL. This lymphoma is considered more aggressive than other pediatric-type FL, though patients still seem to respond well to treatment [31]. Additional recent findings include the discovery of recurrent mutations of *CREBBP, KMT2D* and *EZH2* occurring early in the pathogenesis of FL [44–46].

Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is an aggressive B-cell lymphoma of small to medium-sized cells. As described in the 2005 WHO, lymphoma cells usually carry a translocation involving *CCND1* leading to cyclin D1 overexpression. However, the current WHO recognizes cases of cyclin D1-negative MCL. The head and neck region is the second most common extranodal site with MCL accounting for 2.6% of all Waldeyer ring non-Hodgkin lymphomas [47–49]. MCL may show a diffuse, vaguely nodular or mantle-zone pattern and is typically positive for IgD, CD20, CD5 and cyclin D1.

The revised WHO points out that SOX11 is useful in identifying rare cyclin D1-negative cases of MCL [50, 51]. While most cases have t(11;14) CCND1-IGH translocations, cyclin-D1 negative cases may have rearrangements

of *CCND2* or *CCND3* [52, 53]. Mutations in many other genes including ATM and TP53 are also common [54].

T-Lymphoblastic Leukemia/Lymphoma

T-lymphoblastic leukemia/lymphoma (T-LBL/L) is a neoplasm of lymphoblasts committed to T-cell lineage that rarely occurs in the head and neck region [55]. This entity was recognized in the 2005 WHO, but the current edition points out important diagnostic distinctions and recent molecular discoveries. T-LBL/L consists of small to medium-sized cells with fine chromatin, variably conspicuous nucleoli and scant cytoplasm. Lymphoblasts are typically positive for cytoplasmic CD3, TdT, CD7 and CD1a; variably positive for CD10; and either double-positive or double negative for CD4 and CD8. Early T precursor (ETP) acute lymphoblastic leukemia (ALL) is recognized as a provisional entity in the 2016 WHO classification for hematopoietic and lymphoid tumors [56]. This leukemia is characterized by CD7 without CD1a or CD8 and positivity for one or more myeloid/stem cell markers [57]. A high frequency of mutations in myeloid-associated genes is also associated with ETP ALL [58–60].

Many cases of T-LBL/L have an abnormal karyotype with frequent translocations involving the T-cell receptor genes [61]. Activation of Notch signaling and loss of *CDKN2A* are also common [62].

As the revised WHO points out, it is important to distinguish T-LBL/L from indolent T-lymphoblastic proliferation which is now well recognized as a non-neoplastic entity that can mimic T-LBL/L and frequently involves lymphoid tissue of head and neck [63]. Histologically, these lesions resemble normal thymic cortex without thymic epithelium.

Follicular Dendritic Cell Sarcoma

Follicular dendritic cell (FDC) sarcoma is a rare tumor of nodal and extranodal sites that exhibits phenotypic features similar to FDC. No significant changes have been made in the current classification of this entity. While FDC sarcoma accounts for less than 1% of head and neck tumors, the head and neck is the most common site of involvement for this tumor-most frequently cervical lymph nodes or Waldeyer ring. The tumor displays a pushing border with spindle, ovoid or epithelioid cells, often arranged in fascicular, whorled or storiform growth patterns with admixed small lymphocytes (Fig. 4). The cells have eosinophilic cytoplasm with indistinct cell borders and elongated nuclei with finely dispersed chromatin. Nuclear pseudoinclusions, and binucleated or multinucleated cells are common. A subset of cases are associated with hyaline-vascular Castleman disease. Tumor cells are positive for FDC associated antigens including CD21, CD23, CD35, clusterin, CXCL13 and podoplanin. The pathogenesis of FDC sarcoma remains unknown.

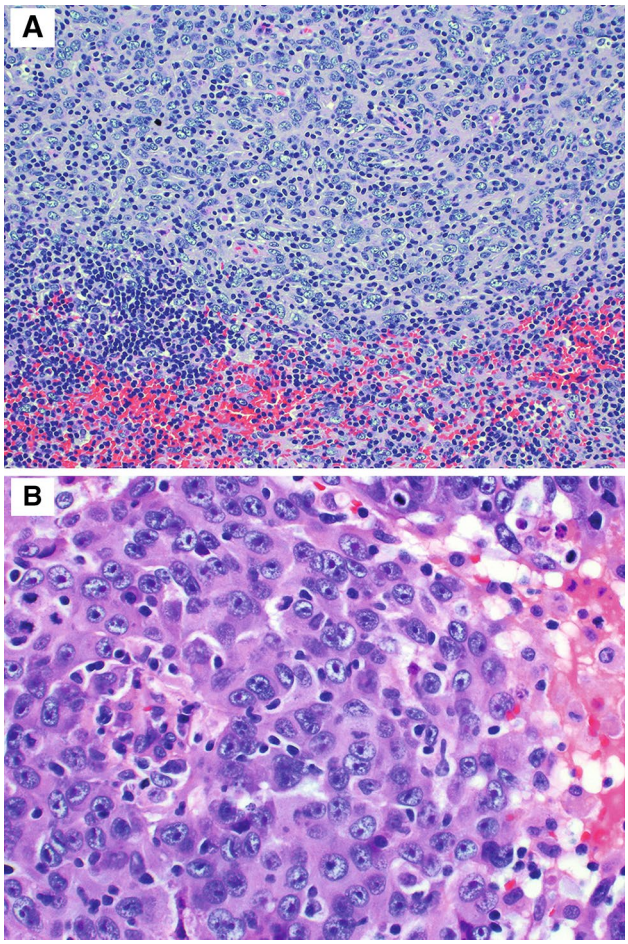

Fig. 4 Follicular dendritic cell sarcoma. **a** Proliferation of spindled to epithelioid cells within a lymph node with a pushing border. **b** Sheets of large, epithelioid cells with prominent nucleoli, abundant eosinophilic cytoplasm and indistinct cell boundaries, lightly infiltrated by small lymphocytes

Extranodal Marginal Zone Lymphoma of Mucosa-Associated Lymphoid Tissue (MALT Lymphoma)

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) remains largely unchanged in the 2017 WHO. This is an indolent B-cell lymphoma composed of heterogeneous mixture of B-cells including marginal zone (centrocyte-like) cells, monocytoid B-cells, small lymphocytes, plasma cells and scattered immunoblasts and centroblast-like cells [64] (Fig. 5). The neoplastic cells typically infiltrate the epithelium forming

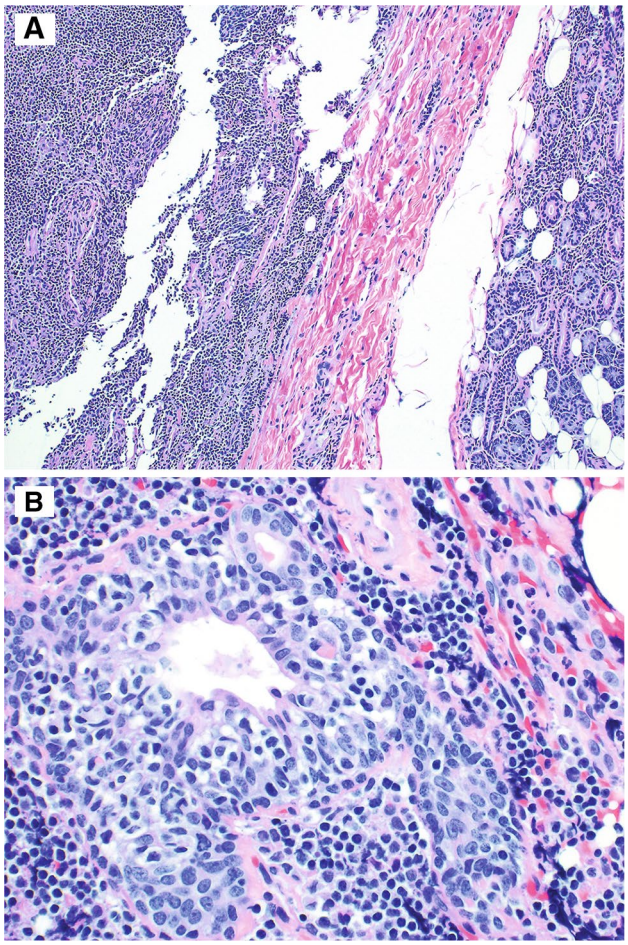

Fig. 5 Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). **a** Parotid gland containing a mass comprised of small lymphocytes. **b** Lymphoepithelial lesions in which glandular tissue is distorted and destroyed by invading neoplastic lymphocytes

lymphoepithelial lesions. The head and neck is the second most frequent site of MALT lymphoma, most frequently involving the ocular adnexa, salivary glands, and less commonly Waldeyer ring [65, 66]. MALT lymphoma cells are positive for B-cell antigens and are typically negative for CD5, CD10, BCL6 and cyclin D1. The revised WHO points out that IRTA1, a marker of marginal zone differentiation is positive in the majority of cases [67]. In salivary glands, lymphoepithelial sialadenitis is a precursor lesion for MALT lymphoma [68]. Monoclonal B cells are present in more than half of salivary lesions from Sjögren syndrome patients and the acquisition of mutations such as in *TNFAIP3* has been associated with lymphoma development [69]. However, translocations involving *MALT1* including t(14;18) (*IGH-MALT1*), t(11;18) (*API2-MALT1*) which are commonly observed in MALT lymphomas of other sites including the stomach, are uncommon in head and neck MALT lymphomas [70]. Hepatitis C is another predisposing factor [71] and there is anecdotal evidence of MALT lymphoma arising in the setting of IgG4-related disease [72, 73].

Plasmablastic Lymphoma

Plasmablastic lymphoma (PBL) is a proliferation of large cells resembling immunoblasts with a plasmacytic immunophenotype. Previously codified as a distinctive form of DLBCL, this neoplasm is now recognized as a completely separate entity. PBL most commonly occurs in the oral cavity but can occur in other extranodal sites including the oropharynx, nasopharynx and sinonasal tract [74, 75]. Lymph nodes are occasionally involved. PBL most frequently occurs in the setting of HIV-related immunosuppression.

PBL is associated with EBV infection and MYC dysregulation with *MYC* translocations or gains occurring in approximately half of cases [20, 76, 77].

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH) is a neoplastic proliferation of Langerhans cells with a peak incidence between 3 and 5 years of age [78]. Similar to other hematolymphoid neoplasms, significant advances in understanding of the pathogenesis of this disease have been made since 2005. Head and neck involvement most commonly affects the skull, orbit, jaw, scalp, periauricular skin, cervical lymph nodes, paranasal sinuses and oral mucosa [79]. Histologically, lesions contain a mixture of inflammatory cells and neoplastic cells with folded or grooved nuclei [80]. These cells express S100, CD1a and CD207 (langerin).

LCH is now known to result from activation of the mitogen activated protein kinase (MAPK) pathway resulting from *BRAF* V600E mutations in approximately half of cases [81] and *MAP2K1* mutations in approximately one quarter [82].

Extramedullary Myeloid Sarcoma

Extramedullary myeloid sarcoma is mass consisting of myeloid blasts occurring outside of the bone marrow. There have not been significant changes in description of this entity since the 2005 WHO. This disease can occur de novo or be associated with acute myeloid leukemia or another myeloid neoplasm [83]. The oral cavity is the most common site, but any head and neck site may be involved [84].

A variety of chromosomal aberrations have been reported including monosomy 7, trisomy 8, inv(16) and t(8;21)—particularly in pediatric patients [28]. *NPM1* mutations are also found in 16% of cases [85].

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