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REVIEW AND PERSPECTIVES

# Lymphomas of the head and neck region: an update

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## Abstract

The field of haematopathology is rapidly evolving and for the non-specialized pathologist receiving a specimen with the possibility of a lymphoid malignancy may be a daunting experience. The coincidence of the publication, in 2017, of the WHO monographies on head and neck and haematopoietic and lymphoid tumours prompted us to write this review. Although not substantially different from lymphomas elsewhere, lymphomas presenting in this region pose some specific problems and these are central to the review. In addition, differences in subtype frequency and morphological variations within the same entity are discussed. The difficulty in diagnosis related to some specimens led us to briefly mention common subtypes of systemic lymphomas presenting in the head and neck region.

**Keywords** Head and neck · Lymphomas · Classification

## Introduction

Lymphomas constitute the second most common group of malignancies in the head and neck only inferior to cancers of epithelial origin. For the non-specialized pathologist, the evaluation of a potential lymphoma in the head and neck may be challenging due to the numerous subtypes found in this region, including entities exclusive for the head and neck. The introduction of new subtypes and reclassification of previously established entities by the latest WHO lymphoma classification [1], and reflected in the fourth edition of the WHO Classification of Head and Neck Tumours [2], made this field even more challenging. This prompted us to provide an easy overview of diagnosis of head and neck lymphomas, most of them in extranodal locations. One main consideration should be made with regard to the term "extranodal" in the head and

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neck, as Waldeyer's ring (base of tongue, tonsils and adenoids) is the most common anatomical site for extranodal lymphoma in this region (35–65% of all head and neck lymphomas) [3]. Nevertheless, for staging purposes, this is considered as nodal location [4] and will only be mentioned in the context of the specific difficulties this location poses in the diagnostic work-up, mostly due to the small amount of tissue obtained for examination.

The anatomical distribution of head and neck lymphomas varies tremendously in the literature but involves in descending order the sinonasal tract, larynx, oral cavity and tongue [2]. Haematolymphoid tumours in odontogenic and maxillofacial bones are exceedingly rare and virtually only solitary plasmacytoma has been described [5]. Salivary gland lymphomas account for only 1–6% of all salivary gland tumours but as much as 6–25% of extranodal lymphomas in the head and neck [6]. The large variation in the proportions of salivary gland extranodal lymphoma in the literature is a result of the definition of extranodal being a lymphoma arising outside a lymphoid organ. In the parotid gland, this is complex as a significant proportion is likely to represent a nodal lymphoma arising in an intra- and/or periparotid lymph node with subsequent spread into the salivary gland parenchyma or even regional involvement by systemic disease.

In the following overview on the most relevant and characteristic lymphomas encountered in the head and neck region, the characteristic features and advances in diagnosis and treatment will be highlighted.

Table 1 summarizes the most relevant information for each entity.

## Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue

### General features

Extranodal marginal zone lymphoma (EMZL) of mucosa-associated lymphoid tissue (MALT lymphoma) most frequently occurs in the stomach (60–70%) but is also relatively common in the head and neck region. EMZL is an antigen-driven neoplasm characterized by an indolent clinical course and, in the head and neck, is preferentially associated with autoimmune disorders [7], arising within pre-existing chronic inflammation. Progression to diffuse large B cell lymphoma is rarely seen [8, 9].

Irrespective of site, EMZL has similar histological features. In most cases, the picture is quite monotonous dominated by monocytoid or centrocytoid tumour cells (Fig. 1). By definition, EMZL is a proliferation predominantly consisting of small- to intermediate-sized lymphocytes with variable morphology (Fig. 1c). Transformed large cells may be present, but the formation of sheets of large cells should lead to the diagnosis of diffuse large B cell lymphoma (DLBCL). Quite often, there is plasma cell differentiation at the periphery of the lesion, and this may predominate causing difficulties in the differential diagnosis with lymphoplasmacytic lymphoma. Detection of the *MYD88* L265P mutation, present in almost all lymphoplasmacytic lymphoma, is also detected in 6–9% of EMZL [10, 11]. Its reasonable negative predictive value may prove useful in separating EMZL from lymphoplasmacytic lymphoma. Characteristic Dutcher bodies may be present within the tumour cells. Reactive lymphoid follicles with germinal centres are common, sometimes colonized by the tumour. The tumour cells may invade glands, resulting in so-called lymphoepithelial lesions [12]. Although these are not pathognomonic of EMZL, their presence combined with clonality studies will assist in the differential diagnosis of reactive conditions. Neoplastic cells do not have a specific immunophenotype and express pan B cell antigens, like CD20, CD79a and PAX5, BCL2 and are monotypically positive for IgM or less frequently IgA or IgG. In addition, EMZL is negative for CD5, BCL6, CD10, CD23 and cyclin D1 and lack or have a weak expression of IgD. Follicular dendritic cell markers may reveal an expanded meshwork that corresponds to colonized follicles. Cases with predominant nodular pattern and overt follicular colonization may be difficult to distinguish from follicular lymphomas. Negativity for germinal centre markers like CD10 or BCL6 supports the diagnosis of EMZL. Cases with abundant reactive follicles should be considered in the differential diagnosis with lymphoid hyperplasia and other differential diagnoses including sarcoidosis, granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis) or chronic infection. Monotypic light chain restriction should support the diagnosis of EMZL but atypical marginal zone hyperplasia described in the tonsil [13] and lymph nodes [14], a polyclonal but monotypic proliferation, may create special difficulties. The expression of CD43 by the lymphoma cells is, by some, used for the diagnosis in cases where the light chain stains are not interpretable. However, this must be used with care, as atypical marginal zone hyperplasia is also CD43 positive [13]. In EMZL, chromosomal translocations and genetic aberrations are heterogeneous but have in common the activation of the NF-κB pathway [15–17]. Gains of chromosome 3/3q and of chromosome 18/18q are observed in 20–40% of cases, but all these are non-specific. Translocations involving t(11;18)(*BIRC3-MALT1*) and t(14;18)(*IGH-MALT1*) are found in salivary gland and ocular adnexal EMZL. The t(3;14)(*IGH-FOXP1*) is recurrently found in EMZL affecting thyroid and ocular adnexal but is not found in salivary gland EMZL [18, 19].

### Ocular adnexa

Fifty percent of ocular adnexal lymphomas are EMZL [20] and *Chlamydia psittaci* has been implicated as an aetiologic

**Table 1** General features of head and neck lymphomas

| Entity | Morphology | Immunophenotype | Genetic abnormalities | Treatment | Prognosis |
|---|---|---|---|---|---|
| **EMZL** | Small B lymphocytes, centrocyte-like, monocytoid or plasmacytoid morphology<br>Nodular architecture with marginal zone expansion<br>Lymphoepithelial lesions | +CD20/CD79a/PAX5/BCL2<br>**+CD43**<br>**−CD5/CD10/cyclin D1 cytokeratin for LELs** | Activation of NF-κB pathway<br>Gains 3/3q and 18/18q t(11;18) & t(14;18) in salivary/ocular adnexal t(3;14) in thyroid. MYD88 L286P in 6–9% | XRT antibiotics, under evaluation | Favourable |
| **FL** | Small irregular B lymphocytes (centrocytes)<br>Nodular architecture with neoplastic follicles lacking polarization<br>Expanded, serpiginous follicles with high Ki67 index (> 30%) in paediatric FL | +CD20/CD79a/PAX5<br>**+CD10/BCL6**<br>**−CD5/cyclin D1** | BCL2 negative in paediatric FL<br>mutations in TNFRSF14 and MAP2K1 in paediatric FL | Surgical in paediatric FL | Favourable |
| **LBCL w/ IRF4** | Mid to large lymphocytes<br>Follicular and diffuse growth patterns | +CD20/CD79a/PAx5<br>**+IRF4/MUM1 high Ki67**<br>+/−BCL6/ BCL2<br>−CD10 | Cryptic rearrangement of IRF4 with IGH | Immunochemotherapy XRT | Favourable with treatment |
| **PCN** | Proliferations of mature terminally differentiated B cells or plasma cells with typical to plasmablastic morphology | **+CD138/38/IRF4/MUM1**<br>**−CD19/CD20/CD79a**<br>**+/−EMA and CD56** | 14q31 breaks or t(4;14) | XRT alone<br>Surgical + XRT | Generally favourable 25% recur 15% progress to systemic myeloma with poor prognosis |
| **PBL** | Large cells with immunoblastic to plasmablastic morphology<br>Diffuse architecture<br>Oral cavity in HIV+ or immunosuppressed | **+CD138/38/IRF4/MUM1/EMA**<br>**−CD19/CD20/CD79a High Ki67**<br>**+EBER (EBV) in 75%** | MYC translocations (50%)<br>Complex karyotype | ChemoXRT | Poor |
| **ENKTL** | Polymorphic lymphoid infiltration<br>Irregular nuclear contours, vascular damage, necrosis<br>Nasal cavity/nasopharynx assoc. w/ EBV<br>Increased prevalence in Asians and Native Americans | **+CD2/cytoplasmic CD3ε+/CD56**<br>**−CD3/CD4/CD5/CD8/CD57/CD16**<br>**+Cytotoxic markers TIA-1/granzyme B/perforin**<br>**High Ki67**<br>**+EBER** | Mutations in *DDX3X*, *JAK3*, *STAT3*, *STAT5B* and *TP53* | ChemoXRT | Poor |
| **CD30PTCLD** | Atypical large lymphocytes with "hallmark cells) in a mixed inflammatory background<br>Diffuse pattern<br>Oral cavity location | **T cell phenotype, with loss of lineage markers (often −CD7) generally CD4+**<br>**−B cell and NK cell markers**<br>**−ALK-1 and EBER** | | Surgery +/− XRT | Indolent |
| **CLL/SLL** | Small monotonous B lymphocytes<br>Nodular architecture with proliferation centres of prolymphocytes | +CD20/CD79a/PAX5<br>**+CD5/LEF1**<br>**−CD10/BCL6/cyclin D1** | | | Indolent |
| **MCL** | Small B lymphocytes<br>Nodular architecture | +CD20/CD79a/PAX5<br>**+CD5/cyclin D1/SOX11**<br>**−CD10/BCL6** | t(11;14)(q13;q32) cyclin D1 IGH | Chemotherapy | Poor |
| **DLBCL** | Large atypical B lymphocytes | | | Chemotherapy | Intermediate |

**Table 1** (continued)

| Entity | Morphology | Immunophenotype | Genetic abnormalities | Treatment | Prognosis |
|---|---|---|---|---|---|
| | Diffuse infiltrate | +CD20/CD79a/PAX5 **CD10, BCL6, BCL2, MUM1/IRF, FOXP1** to assess germinal centre versus activated B cell types | translocations involving *BCL2*, *BCL6* and *MYC* | | |
| **EBVPMCU** | Scattered large immunoblastic or Hodgkin-like cells in a mixed inflammatory background<br>Solitary oropharyngeal ulcer in immunosuppressed patient | +CD45/CD20/CD79a/PAX5<br>**+CD30, +/−CD15**<br>**+EBER** | | Reduction of iatrogenic immunosuppression<br>Anti-CD20/CD30 immunotherapy | Indolent |
| **EBL** | Monomorphic intermediate-sized lymphocytes, scant basophilic cytoplasm, fine chromatin "starry-sky" pattern with tingible body macrophages | +CD20/CD79a/PAX5<br>**+CD10/BCL6**<br>**−BCL2**<br>**High Ki67**<br>**+EBER** | *IG/MYC* translocations as t(8;14) | Chemotherapy | Aggressive |

On separate lines or in bold are the most helpful immunophenotypic features

*EMZL* extranodal marginal zone lymphoma, *FL* follicular lymphoma, *LBCL w/ IRF4* large B cell lymphoma with IRF4 rearrangement, *PCN* plasma cell neoplasms, *PBL* plasmablastic lymphoma, *ENKTL* extranodal NK/T cell lymphoma, nasal type, *CD30PTCLD* CD30-positive T cell lymphoproliferative disorders, *CLL/SLL* chronic lymphocytic leukaemia/small lymphocytic lymphoma, *MCL* mantle cell lymphoma, *LBCL* large B cell lymphoma, *EBVPMCU* Epstein-Barr virus-positive mucocutaneous ulcer, *EBL* endemic Burkitt lymphoma, *XRT* radiation therapy. Bold type denotes the most discriminating markers




**Fig. 1** Extranodal marginal zone lymphoma of the conjunctiva in a 77-year-old male. **a** Characteristic fleshy, salmon-colored and highly vascularized appearance of the lesion. **b** Computerized tomography demonstrating localized involvement of the lateral and superficial ocular adnexa, consistent with disease localized to the conjunctiva. The patient was subsequently treated with brachytherapy. **c** Monocytoid appearance of the infiltrate. Cells have a small nucleus with pale cytoplasm. H&E stained. ×100 original magnification

agent. This is not confirmed by all groups and the association may have a greater influence in some geographical regions

[21–25]. Patients with eyelid EMZL typically present with swelling of the eyelid, whereas conjunctival lymphoma characteristically presents early as a salmon-coloured tumour mass of the conjunctiva (Fig. 1a, b) [26, 27]. The clinical course of EMZL is usually indolent and the disease tends to remain localized.

Treatment with surgery, systemic therapy or local radiotherapy, depending of clinical status and stage of the disease, is preferred in these patients [28]. In the context of variable association between *C. psittaci* and ocular adnexal EMZL, some groups use an antibiotic therapy with doxycycline. However, the causative association between ocular adnexal EMZL and *C. psittaci* has not been firmly established and the use of doxycycline in the primary care should closely monitored [24, 25, 29, 30]. In low-stage ocular adnexal EMZL, the preferred treatment is radiotherapy applying 24–25 Gy in conventional daily fractions [31]. The prognosis is good with approximately 90% ten-year overall survival [32].

### Salivary glands

EMZL is often associated with Sjögren's syndrome, a systemic autoimmune disorder with lymphoepithelial sialadenitis as a hallmark feature [33, 34]. Epimyoepithelial islands composed mainly of proliferating epithelial cells should not be confused with lymphoepithelial lesions (Fig. 2). Similarly, chronic IgG4-related sclerosing sialadenitis (Küttner tumour), a localized inflammatory disorder, has also been implicated in salivary gland EMZL [34]. Like in ocular adnexa, the clinical course of salivary EMZL is usually indolent, and it tends to remain as a localized disease. In a large retrospective international study of 248 patients with salivary gland EMZL, there was no difference between patients who received local or systemic therapy in first-line management, and hence, radiotherapy is the treatment of choice for salivary gland EMZL [31]. The median progression-free survival and overall survival were 9.3 and 18.3 years, respectively [35, 36]. Patients aged < 60 years with low to intermediate International Prognostic Index (IPI) score and associated Sjögren disease had improved overall survival [37].

## Head and neck nodal predominant lymphoproliferative disorders, affecting young patients

### Paediatric nodal marginal zone lymphoma

Paediatric nodal marginal zone lymphoma (PNMZL) is similar to a classic adult nodal marginal zone lymphoma that typically affects head and neck lymph nodes. This neoplasm occurs with isolated lymphadenopathy, usually in cervical region, submental zone, around major salivary glands and in rare cases in tonsils. It is described in young patients (2–27 years old) and there is a striking male predominance (male-to-female ratio of 7:1 to 20:1) [38–40].

Histologically, PNMZL shows a nodular pattern, with large follicles, composed of small- to medium-sized cells, often with centrocyte-like appearance. The cells of the mantle zone can extend into the nodules, mimicking progressive transformation of germinal centres (PTGC). Other histological features, such as marginal zone differentiation, plasma cell differentiation and scattered large immunoblastic cells, are similar to those observed in classic nodal marginal zone lymphoma [38–40].

Phenotypically, the tumour cells are positive for the B cell markers CD20, CD79a and PAX5 and can co-express CD43. These markers also show that tumour population usually extends outside the nodules reaching the interfollicular area. BCL2 is positive in half of cases. IgD is variably positive

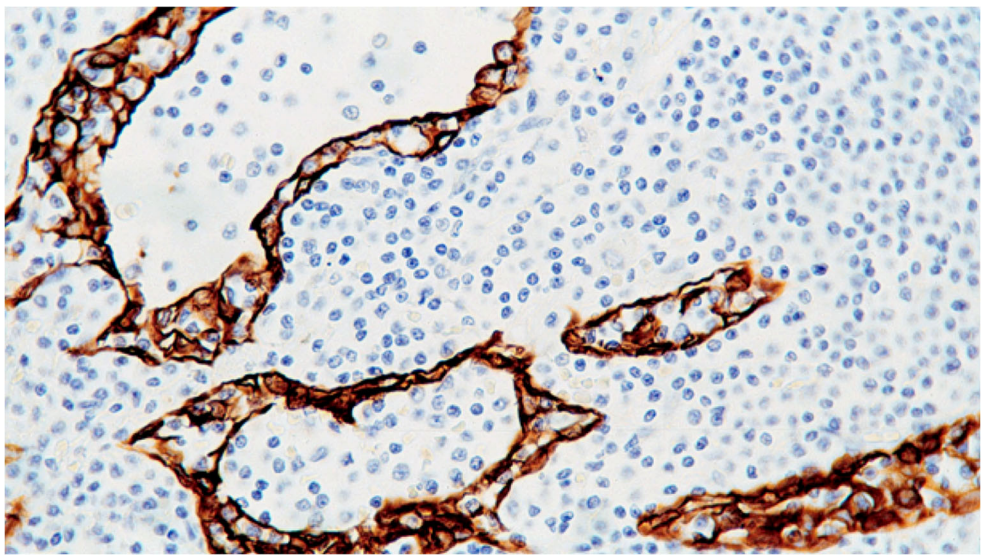

**Fig. 2** Extranodal marginal zone lymphoma in the parotid: typical lymphoepithelial lesions. The epithelium is distorted by the presence of infiltrating lymphoma cells immunostained with an anti-keratin antibody (CAM5.2). ×100 original magnification

and highlights the PTGC-like changes [38–40]. Germinal centre markers BCL6 and CD10 are negative. Numerous T-follicular helper PD1-positive cells are identified within the nodules [39]. Marginal zone hyperplasia in children must be considered in the differential diagnosis [13, 14] and B cell receptor clonality studies may be required for the diagnosis. In most cases, clonal rearrangements of the IGHV region are detected. Trisomy 18 and rarely trisomy 3 can be found in this neoplasm [40].

PNMZL like paediatric-type follicular lymphoma (PTFL) has a very good prognosis. In a retrospective study, complete resection and observation seem to be enough [41].

### Paediatric-type follicular lymphoma

PTFL is a form of follicular lymphoma, involving lymph nodes of the head and neck and Waldeyer's ring.

Clinically, this neoplasm occurs mainly in young men (5–25 years; male-to-female ratio of 10:1). It presents usually as an isolated enlarged lymph node in head and neck region or with involvement of the Waldeyer's ring. Less frequently, involvement of other anatomical sites, such as testes, inguinal or femoral lymph nodes, is reported. There are no risk factors associated with the development of this neoplasm [42].

Morphologically, PTFL shows a partial or total effacement of the affected lymphoid tissue. The atypical lymphoid proliferation presents a follicular pattern, with large follicles, prominent germinal centres, often with a serpiginous configuration, starry-sky pattern and attenuated or absent mantle zones (Fig. 3). In some cases, marginal zone differentiation can be found. The tumour cells are monotonous, in some cases with centroblastic features and in others with medium cells and blastoid morphology, mimicking usual follicular lymphoma grade 3A or 3B. Mitoses are frequent. Areas of diffuse large cell lymphoma should not be present. In that case, the diagnosis of PTFL is excluded [1, 42].

The neoplastic cells are positive for CD20, CD79a and PAX5 and express the germinal centre markers BCL6 and CD10. Nevertheless, BCL2 is usually negative. With CD21 and CD23, the dendritic follicular cell network shows a nodular pattern. A high proliferation index is found with KI67 (> 30%). IRF4/MUM1 is negative. In cases with diffuse and strong positivity for IRF4/MUM1, lymphomas with IRF4 rearrangements should be excluded [1, 42].

Genetically, PTFL usually presents a clonal immunoglobulin gene rearrangement; however, mutations affecting BCL2, BCL6 or IRF4/MUM1 are not detected. The most common genetic aberrations observed in this entity include mutations affecting TNFRSF14 and MAP2K1 [1, 42–44].

This neoplasm has an excellent prognosis, usually with localized disease, without evidence of progression or relapse, and it can be treated with excision alone [45].

### Large B cell lymphoma with IRF4 rearrangement

Large B cell lymphoma with IRF4 rearrangement represents only 0.05% of diffuse large B cell lymphomas, which predominantly affects children and young adults. Waldeyer's ring and head and neck lymph nodes are the most commonly involved anatomical sites. Gastrointestinal tract has also been reported. Clinically, patients present an early-stage disease with isolated tonsillar or lymph node swelling [46, 47].

Morphologically, the tumour is composed of medium- to large-sized cells, with vesicular chromatin and small basophilic nucleoli. The growth pattern is follicular and diffuse. In the follicular pattern, large neoplastic follicles can be seen, without starry-sky pattern and with attenuated or absent mantle zones.

The tumour cells have a B cell mature immunophenotype, with expression of CD79a, CD20 and PAX5. The antibody for IRF4/MUM1 is strongly positive. BCL6 and BCL2 may also be expressed. CD10 and BLIMP1 are usually negative. The proliferation index is high. These tumours are associated with a cytogenetically cryptic rearrangement of IRF4 with an IGH locus [47, 48]. Strong IRF/MUM1 expression with co-expression of BCL-6 and a high proliferation index is an indication for confirmatory IRF-4 FISH. Patients have a favourable prognosis with combination of immunochemotherapy and radiation [47].

## Plasma cell neoplasms

Plasma cell neoplasms are clonal proliferations of plasma cells or mature lymphocytes (terminally differentiated B cells) that produce a single class of immunoglobulin. This group of neoplasms includes non-IgM monoclonal gammopathy of undetermined significance (non-IgM MGUS), plasma cell myeloma, plasmacytoma, monoclonal immunoglobulin deposition diseases and plasma cell neoplasms with associated paraneoplastic syndrome.

Extraosseous (extramedullary) plasmacytomas (EP) are localized plasma cell tumours that arise in tissues outside of the bone marrow and represent up to 3% of all plasma cell tumours. EP occurs in the upper aerodigestive tract in more than 80% of cases, most often in the nasal cavity, paranasal sinuses, nasopharynx, tonsils and larynx, with regional lymph nodes involved in less than 10% [49]. Clinically, they present as solitary tumours without bone marrow involvement and are more frequent in male adults [50, 51].

EP is usually composed of plasma cells indistinguishable from normal plasma cells. Multinucleated and pleomorphic cells may be prominent in some cases. Depending on the amount of plasmablasts, the term plasmablastic plasmacytoma can be used [52]. Low-grade or high-grade lymphoproliferative disorders with extensive plasmacytic differentiation such as EMZL, plasmablastic lymphoma (PBL) or lymphoplasmacytic lymphoma must be excluded. Inflammatory or reactive lesions

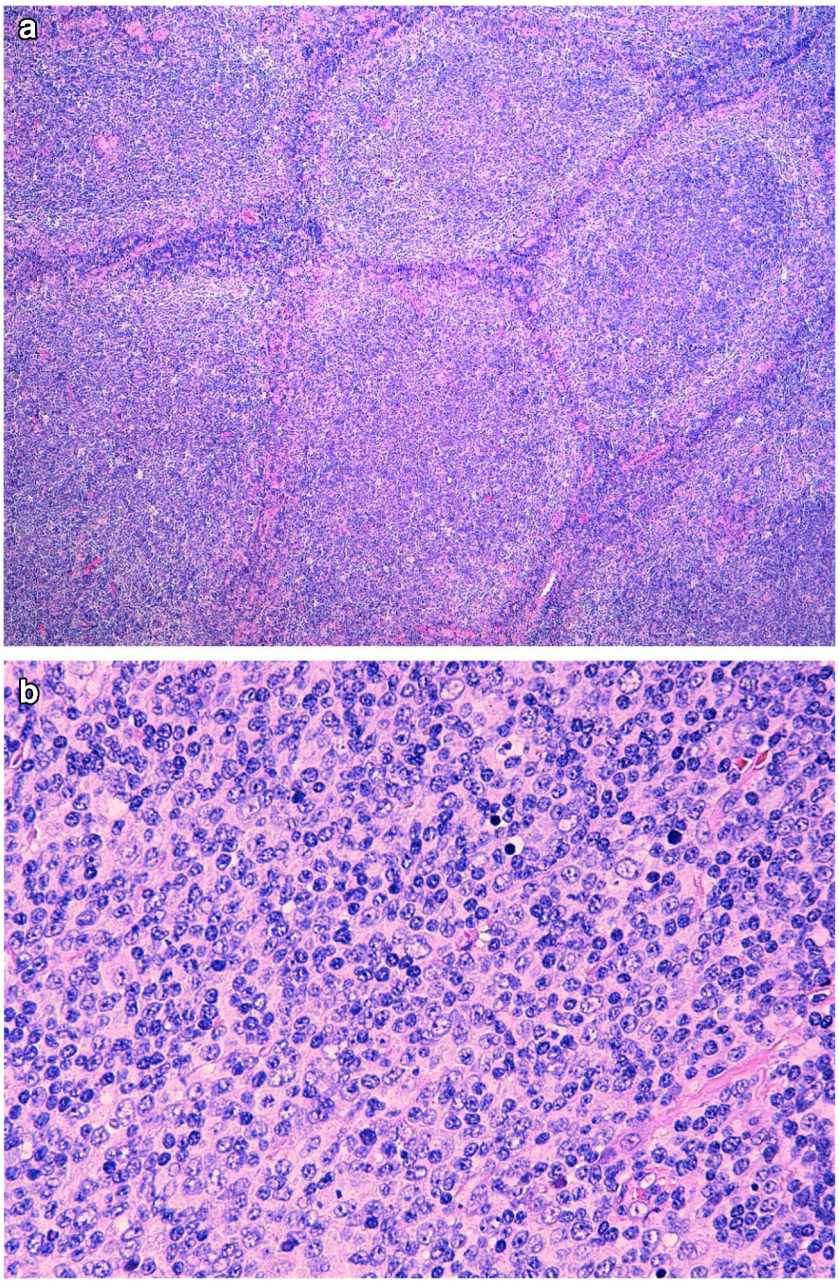


**Fig. 3** Paediatric follicular lymphoma. **a** Low-power view of large confluent follicles (original magnification ×40). **b** High-power view of large cells with centroblast-like appearance. (Original magnification ×400) H&E stained

with numerous plasma cells sometimes may be difficult to distinguish from a plasmacytoma. Immunoglobulin light chain expression should be enough to differentiate these cases.

Like plasma cell myeloma, EP shows immunoglobulin light chain restriction. This may be assessed via immunohistochemistry, in situ hybridization, flow cytometry or PCR. EP is associated with a plasma cell phenotype, with strong expression of CD138, CD38 and IRF4/MUM1. B cell markers CD19, CD20 and CD79 are negative or weakly positive. Epithelial membrane antigen (EMA) is expressed in some cases. CD56 is positive in approximately 80% of plasma cell myelomas and a similar proportion of extramedullary plasmacytomas maintain CD56 expression. Negativity for CD56 has been associated with aggressive behaviour and primary or secondary plasma cell leukaemia [53]. In contrast to plasma cell myeloma, cyclin D1 is usually negative in EP [52, 54, 55]. Epstein-Barr positivity has been observed in occasional plasmacytomas of the head and neck in immunocompetent individuals [56].

These lesions have breaks in the 14q31 (IGH), similar to plasma cell myeloma. Some cases present *IGH/FGFR3* fusion corresponding to a t(4;14)(p16;q32). On the other hand, t(11;14)(q13;q32), t(14;16)(q32;q23) or t(8;14)(q24;q32) is absent [57].

The treatment of these tumours is surgical, usually accompanied with radiotherapy or with radiotherapy alone due to the radiosensitivity of the disease. Regional recurrences develop

in 25% of patients with EP and the prognosis is determined by progression to multiple myeloma, which occurs in approximately 15% of patients [53, 55]. The behaviour of extramedullary plasmacytomas without progression to medullary plasma cell myeloma is good, usually with an indolent course. On the contrary, extramedullary spread of a medullary plasma cell myeloma is associated with poor prognosis [58].

## Plasmablastic lymphoma

PBL is a highly aggressive B cell tumour composed by large neoplastic cells with immunoblastic or plasmablastic features and plasma cell phenotype. Clinically, PBL usually occurs in the oral cavity of adult males in association with an immunodeficiency status like HIV infection, in the context of iatrogenic immunosuppression or in elderly patients who are more commonly HIV-negative [52, 59, 60]. Plasmablastic lymphoma rarely occurs in children, frequently in HIV-infected individuals. In the head and neck region, PBL commonly presents as an asymptomatic swelling in extranodal sites, particularly in the oral cavity with gingiva as the most frequently involved site, although the nasal cavity and paranasal sinuses may be also involved.

Histologically, PBL is composed of diffuse, cohesive proliferations with a morphology ranging from immunoblasts to cells with plasmacytic differentiation indistinguishable from plasmablasts in plasmablastic plasma cell myeloma [52] (Fig. 4). High mitotic activity and apoptotic bodies are frequent. Immunohistochemical features are consistent with plasma cell differentiation with positivity for IRF4/MUM1, CD38, CD138 and EMA. CD79a and immunoglobulins are variably expressed. B cell antigens like PAX5 and CD20 are negative. Ki67 proliferation index is high. Some cases express the T cell-associated markers CD43 and CD45RO [61]. The differential diagnosis with plasmacytoma is not always possible. Epstein-Barr virus (EBV) is positive in 75% of cases. Genetic alterations usually involve *MYC* translocations, which have been identified in approximately 50%, usually in the context of complex karyotypes [62–64].

Plasmablastic lymphoma is usually treated with chemotherapy, radiotherapy (with or without surgical excision) or combinations of these modalities. The prognosis is generally poor with approximately 60% of tumours relapsed in the first year after treatment and a median survival of less than 6 months and overall survival at 2 and 5 years of 42.4% and 33.5%, respectively. In recent reports, the use of bortezomib, alone or in combination with other systemic drugs, seems to improve response rates and prognosis [65]. EBV positivity, presence of B symptoms and the use of chemotherapy alone were identified as determinants of poor prognosis [60, 61].

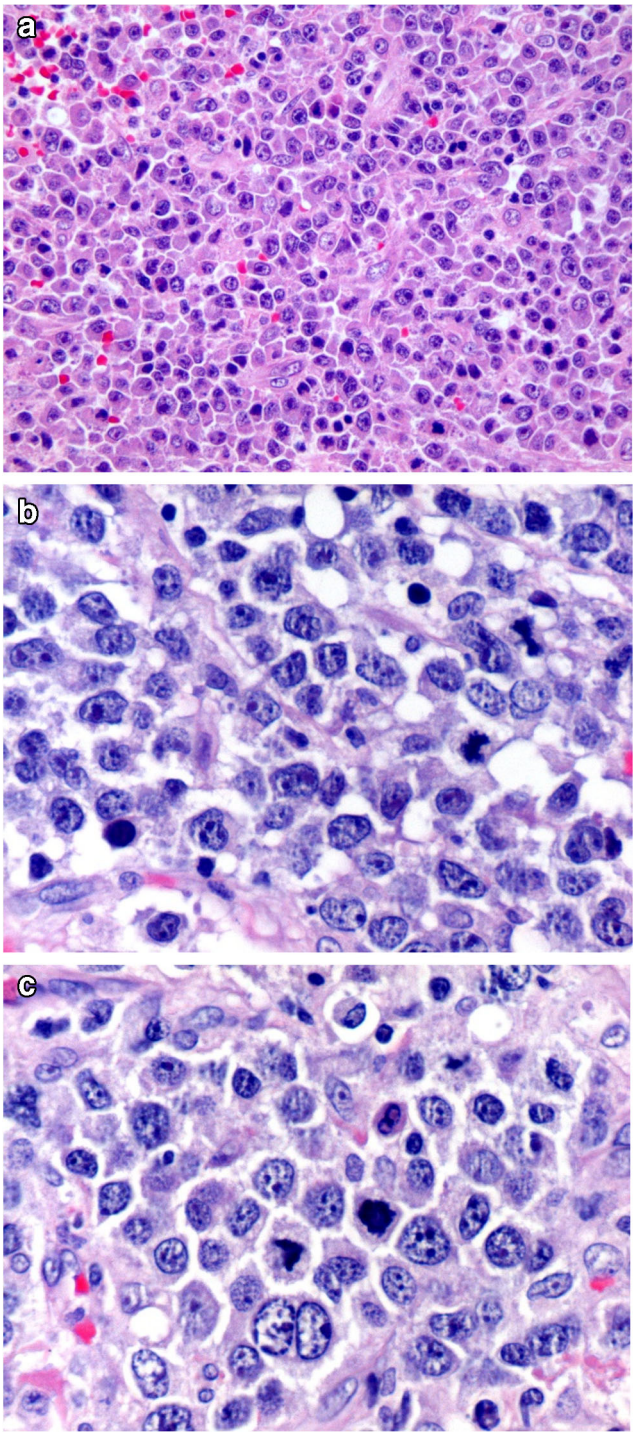


**Fig. 4** Plasmablastic lymphoma: diffuse sheets (**a**; original magnification ×100) of a large cell with pleomorphic features and plasmablastic morphology (original magnifications are ×400 (**b**) and ×600 (**c**)). H&E stained

## Extranodal NK/T cell lymphoma, nasal type

Extranodal NK/T cell lymphoma, nasal type is an aggressive neoplasm composed of natural killer (NK cell) and T cells with cytotoxic features, typically associated with Epstein-Barr virus

infection and is characterized by the presence of vascular damage and prominent necrosis. Together with other conditions that affect the central region of the face (i.e. Wegener's granulomatosis, tegumentary leishmaniasis), it was also known as lethal midline granuloma. This tumour affects mostly male adults and is more prevalent among Asians and Native Americans [66, 67].

The lymphoma commonly involves the nasal cavity and nasopharynx, producing non-specific symptoms of upper airway infection and nasal obstruction, rhinorrhoea or nasal bleeding. The lesion is locally invasive, but bone marrow involvement is unusual [68]. Extranodal NK/T cell lymphoma infrequently affects anatomical sites outside the upper aerodigestive tract. These cases are referred to as "extranasal NK/T cell lymphomas" and can involve skin, soft tissue, gastrointestinal tract, lungs and testis and are associated with more advanced disease and inferior outcome [69].

Histologically, extranodal NK/T cell lymphoma is composed of a dense polymorphic lymphoid infiltrate, from small- to large-sized or anaplastic cellular elements, most frequently with medium-sized neoplastic cells with irregular nuclei and pale to clear cytoplasm. An angiocentric or angioinvasive growth pattern is very frequent, with fibrinoid necrosis of blood vessels and coagulative geographic necrosis or ulceration of the affected mucosa (Fig. 5). Mitotic figures and apoptotic bodies are abundant. A prominent mixed inflammatory infiltrate composed of small lymphocytes, plasma cells, histiocytes, eosinophils and neutrophils is present, and can mimic a reactive inflammatory process, especially in the small cell variants. In cases with predominant bone marrow infiltration, aggressive NK cell leukaemia must be considered.

Most of the cases express NK cell, or less frequently T cell, markers and one or more cytotoxic molecules. Tumour cells usually are CD2+, surface CD3− but cytoplasmic CD3ε+. Other common T cell markers, as CD4, CD5, CD8 and TCRαβ or TCRγδ, are usually not expressed. CD56 is positive in most cases, in contrast to the NK markers CD57 and CD16. Cytotoxic molecules as TIA-1, granzyme B or perforin are commonly expressed. CD30 is expressed in up to one third of cases (Fig. 5). The proliferation index with Ki67 is high.

In situ hybridization for EBV-encoded RNA (EBER) is nearly always positive and should be performed even in lesions with a reactive appearance. Cases that lack CD56 expression and EBV infection (EBER negative) should be classified as peripheral T cell lymphomas, not otherwise specified (PTCL-NOS) [66].

In most cases, the T cell receptor and immunoglobulin genes are in germline configuration. Ten to 40% of cases have a clonal rearrangement of the T cell receptors and presumably derived from cytotoxic T cells. Recurrent mutations have been found in *DDX3X*, *JAK3*, *STAT3*, *STAT5B* and *TP53* [70] and may be useful in subtyping of T cell lymphomas.

Extranodal NK/T cell lymphoma involving the nasal region frequently progresses to disseminated disease. Due to rapid and aggressive course of the disease with marked destructive capacity, which is frequently associated with haemophagocytic syndrome (a hyperinflammatory condition, characterized with fever, pancytopenia, coagulation disorders, liver and renal abnormalities), the prognosis is poor with a 5-year survival rate of approximately 50%. Extranasal NK/T cell lymphomas present usually with advanced aggressive disease, poor response to treatment and short survival [71].

For localized disease, treatment consists of high-dose radiotherapy (> 50 Gy), with or without chemotherapy. There is no clear evidence that concomitant radiotherapy/chemotherapy results in improved outcome as compared to adjuvant chemotherapy/radiotherapy [72]. In advanced disease, combination chemotherapy remains the mainstay of treatment although with poor response and dismal outcome [72, 73]. Recently, some L-asparaginase-based chemotherapy regimens and novel immunotherapy options have shown promising results [74, 75]. Although there is limited data available, patients with advanced or relapsed lymphoma in remission can be offered allogeneic stem cell transplantation, preferably in a trial setting. For patients with persistent or residual disease, autologous or allogeneic stem cell transplantation has poor results [76].

## CD30-positive T cell lymphoproliferative disorder

CD30-positive T cell lymphoproliferative disorders include a spectrum of clonal T cell lesions arising usually in the oral cavity and less commonly in other mucosal sites in head and neck region, as nasopharynx and ocular region. This entity is similar to primary cutaneous CD30-positive T cell disorders [77].

Clinically, this affects adults (mean age 54–57 years), predominantly men (male-to-female ratio 1.8–2.8:1) [77, 78]. The oral cavity is the most common site of involvement. A slow-growing lesion with occasional ulceration without spontaneous regression is frequent. Nasopharyngeal, conjunctival and orbital mucosa can be involved in a minority of cases [77–79].

The histopathological findings include a lymphoid infiltration of large atypical cells with irregular nuclei, vesicular chromatin and abundant pale cytoplasm, in a diffuse pattern. Neoplastic large cells with kidney-shaped nuclei, so-called hallmark cells, are usually seen. In the background, a variable number of inflammatory cells is usually present, including small lymphocytes, histiocytes, numerous neutrophils and eosinophils [77–79].

Immunohistochemically, the large cells are, by definition, CD30 positive, with T cell phenotype, more frequently CD4 positive and aberrant loss of lineage markers, usually CD7. In some cases, expression of cytotoxic markers, as for example granzyme B, TIA-1 and perforin, can be seen. B cell markers, NK cell markers, ALK-1 and EBER are negative [77–79].

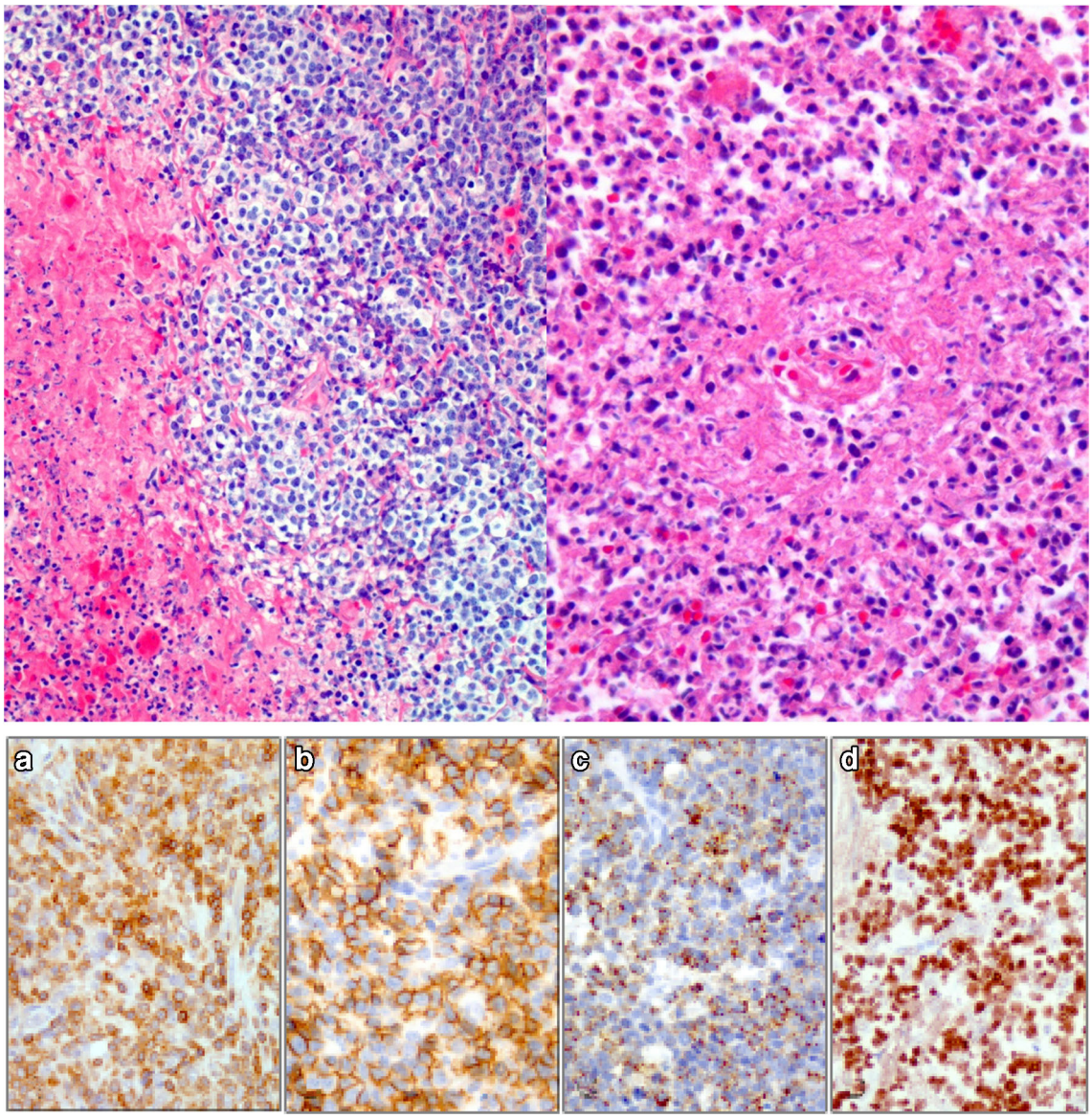


**Fig. 5** Extranodal NK/T cell lymphoma. Upper panels show angiodestructive, necrotic lesion (original magnification ×100). Lower panels display IHC: **a** CD3ε, **b** CD56, **c** TiA1, and **d** EBER. Original magnification ×200

Some cases present rearrangements of *DUSP22-IRF4* locus on chromosome 6p25.3. These findings suggest that this entity could be related to primary cutaneous CD30-positive lymphoproliferative disorders [77].

CD-30-positive T cell lymphoproliferative disorders of the head and neck have an indolent course. Surgical excison, with or without radiotherapy and in some cases combined with systemic chemotherapy, is recommended. Spontaneous regression has been reported [77, 78].

The differential diagnosis includes reactive conditions like traumatic ulcerative granuloma with stromal eosinophilia and lymphoproliferative disorders including chronic active EBV infection in paediatric cases and systemic anaplastic large cell lymphoma.

## Common systemic lymphomas—specific problems in the head and neck region

Although not different from other locations, systemic lymphomas diagnosed in the head and neck may pose some specific problems and those are addressed here.

## Chronic lymphocytic leukaemia/small lymphocytic lymphoma

Although this is the most common leukaemia of adults in western countries, its diagnosis in head and neck samples may be problematic. The differential diagnosis with reactive

conditions is hampered by the quality of the sample with frequent crushing artefact and the usual IHC markers should be used. Including an antibody to lymphoid enhancer-binding factor 1 (LEF1) [80] is useful as it is aberrantly expressed in almost all chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL). All mature normal B lymphocytes and virtually all other B cell lymphomas are negative [80]. In patients with CLL/SLL, the disease will be present in the lymph nodes removed as part of head and neck surgical procedures and coexistence with metastasis is reported [81].

### Mantle cell lymphoma

Mantle cell lymphoma frequently involves extranodal sites, mainly in the gastrointestinal tract. In these locations, the disease has the same histological characteristics as those of the nodal involvement, and the main difficulties in the head and neck region are similar to those encountered in CLL/SLL. MCL is characterized by Cyclin D1 translocation t(11;14)(q13;q32). Staining for Cell Cyclin D1 and SOX11 in CCND1 negative cases, together with CD5 expression by the tumour cells, should clarify the diagnosis. Rarely other cyclins are involved in an immunoglobulin translocation, and this needs to be investigated by FISH.

A recent review [82] expanded an old observation [83] and identified a series of cases, some of which in the head and neck region, mimicking EMZL. According to these authors, "EMCL" may be a subset with preferential involvement of Waldeyer's ring and gastrointestinal tract, mimicking the clinicopathologic features of EMZL. These cases share the morphologic and phenotypic features of the nodal form of MCL and the indolent course of the indolent variant of MCL.

The treatment of common MCL is systemic, and the prognosis is usually poor with a medial overall survival of 3–5 years [28].

## Large B cell lymphomas

Large B cell lymphomas, representing approximately 30% of all lymphomas, are also the most common type of non-Hodgkin lymphoma in the head and neck [84]. This denomination represents a heterogeneous group of neoplasms with many clinicopathologic variants and distinct subtypes. Lymphomas without clinical, morphological and genetic features allowing for subclassification are grouped as DLBCL not otherwise classified (NOS) and represent 80–85% of all cases [1].

In extranodal sites, DLBCL-NOS have variable frequencies depending on the anatomical site. In the ocular region, extranodal DLBCL-NOS account for 10% [20], whereas in other sites, the distribution is as follows: paranasal sinus 75–82%, nasal cavity 29–46%, Waldeyer's ring 80% [85], oral cavity 50% [86], major salivary glands 27% [87] and thyroid gland 50–90% [88, 89]. DLBCL involving Waldeyer's ring usually presents at an early stage with the absence of B symptoms or bone marrow involvement [90, 91]. An association between extranodal DLBCL and EBV infection has been confirmed by demonstration of the EBV-encoded small RNA, in 8–9% of Asian patients and in a much lower proportion (up to 3%) of patients from Western countries [92]. This is not included in DLBCL-NOS [1]. A low-grade lymphoproliferative disorder coexisting with a DLBCL component should be searched in the context of progression of low-grade lymphoma to DLBCL [1].

Histologically, DLBCL-NOS is not different from the nodal samples and is genetically associated with recurrent translocations involving *BCL2*, *BCL6* and *MYC* genes. In Waldeyer's ring, the frequency of *BCL2* translocations is lower than in nodal DLBCL, NOS[90].

Histologically, in this region, especially in small samples, an important differential diagnosis of EBV+ large B cell lymphomas is Epstein-Barr virus-positive mucocutaneous ulcer discussed below.

Lymphoma of the head and neck should be distinguished clinically from systemic lymphoma with secondary extranodal involvement. In order to stage properly, CT or PET-CT scan and bone marrow biopsy must be performed in all cases. As no specific AJCC classification exists for head and neck lymphoma, the Ann Arbor staging manual or the modified Lugano classification should be used [93]. The IPI remains the best available index score in patients with DLBCL [94, 95]. Stage I DLBCL in the ocular adnexa may be treated with high-dose (30–36 Gy) EBRT alone [96]. Standard-of-care frontline therapy with R-CHOP results in 5-year overall survival rates in the range of 60–70%.

## Epstein-Barr virus-positive mucocutaneous ulcer

Due to its possible confusion with a large cell lymphoma, Epstein-Barr virus-positive mucocutaneous ulcer (EBVPMCU) is included here. First described in 2010, EBVPMCU is not in the current WHO classification considered a lymphoma but rather is a lymphoproliferative disorder with mucosal or cutaneous ulceration and signs of EBV infection.

This lesion predominantly affects adults (median age 75 years) with a slight female preference. Patients have history of a slow-growing shallow, sharply circumscribed ulcer that appears as a solitary lesion, involving most commonly the oropharyngeal mucosa but also lip or facial skin. Less frequently, gastrointestinal tract or extra facial skin involvement has been described. Local lymph node enlargement can occur; nevertheless, there is no history of systemic lymphadenopathy, visceromegaly or bone marrow involvement.

Immunosuppression is common in all patients, in the context of HIV infection, iatrogenic immunosuppression (e.g. treatment with cyclosporine, methotrexate, azathioprine or corticosteroids) or age-related immunological senescence [97–99].

Histologically, EBVPMCU is made of scattered large cells, with immunoblastic or Hodgkin/Reed-Sternberg-like features. A variable proportion of apoptotic atypical cells is usually also seen. These cells are intermixed with a polymorphous infiltrate of lymphocytes, plasma cells, histiocytes and eosinophils. A rim of small mature lymphocytes limits the base of the lesion. In some cases, angioinvasion, thrombosis and necrosis are present. Pseudoepitheliomatous hyperplasia in the adjacent squamous epithelium can be present [98, 100].

Phenotypically, the atypical large cells express CD45, PAX5, CD79a and CD20. Further, these cells are strongly positive for CD30. Co-expression of CD15 may be seen in half of the cases. EBER is positive in many small to large pleomorphic B cells. A mixed population of small B lymphocytes, as well as CD4+ and/or CD8+ T cells, is commonly present in the lesion [98, 100].

The differential diagnosis includes lymphoproliferative disorders associated with EBV, as EBV-positive diffuse large B cell lymphoma, lymphomatoid granulomatosis, other immunodeficiency-associated lymphoproliferative disorders, CD30-positive T cell lymphoproliferative disorders and classical Hodgkin lymphoma.

A monoclonal immunoglobulin gene rearrangement is found in approximately one third of cases. A restricted (oligoclonal) or monoclonal T cell receptor gene rearrangement can be detected. This phenomenon might be related to a reduction in the T cell repertoire diversity [101].

This entity follows an indolent, self-limited course. In cases of iatrogenic immunosuppression, a reduction or discontinuation of the drug can lead to a complete remission. However, a minority of cases, in the context of age-related immunosuppression, show relapsing and remitting course that requires CD20- or CD30-directed antibody therapy, chemotherapy, radiotherapy, surgical excision and/or a combination of these to achieve a complete remission [100, 102].

## Endemic Burkitt lymphoma

Burkitt lymphoma (BL) is a highly aggressive B cell lymphoma with rapid proliferation and three clinical variants: endemic, sporadic and immunodeficiency associated. These differ by anatomic site involved and global geographic distribution [1]. Endemic BL is a paediatric malignancy (peak 4–7 years) with a male predominance (2:1) and occurs in the head and neck, typically involving the jaw and facial bones in a mass-forming manner. Symptoms include swelling and distortion of facial bones accompanied by B symptoms of fever, night sweats and weight loss.

Histologically, BL features are similar in the three clinical variants, composed of an infiltrate of rather monomorphic intermediate-sized lymphocytes with scant amphophilic to basophilic cytoplasm and fine nuclear chromatin. There tends to be a "starry-sky" pattern with accompanying tingible body macrophages. BL expresses pan B cell antigens CD19, CD20, CD22, CD79a and CD10, CD38 and BCL6. It is negative for BCL2 and TdT. The Ki-67 proliferation index approaches 100%. EBV is present in most cases, with positive staining for EBER [103].

BL is characterized by *IG/MYC* translocations, commonly t(8;14). Infrequently, t(8;22) or t(8;2) translocations of MYC with kappa or lambda light chain loci may be seen [104].

BL has a rapid, aggressive clinical course and early diagnosis is paramount for effective treatment. It is a highly chemosensitive tumour, treated by combination chemotherapy [104].

## Conclusions

The revisions of the fourth edition of the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues and the fourth edition of the WHO Classification of Head and Neck Tumours, both published in 2017, reflect the recent advances in the field of haematopathology. New approaches are needed to keep up with the new knowledge that led to changes in the classification. This review will help the practicing pathologist in the diagnosis of the specific characteristics of head and neck lymphoma and in the recognition of the regional variations of systemic lymphomas.

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### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest related to this work.

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