

Head and neck hematolymphoid proliferations: what is new?

Silvia Varricchio¹, Rosaria Cappiello¹, Francesca Magnoli², Daniela Russo¹, Giovanna Motta³, Clara Bertuzzi³, Elena Sabattini³, Gennaro Ilardi¹, Mariarosaria Cervasio¹, Claudia Giordano⁴, Alessandro Severino⁴, Marco Picardi⁴, Massimo Mascolo¹

¹ Department of Advanced Biomedical Sciences, Pathology Section, University of Naples Federico II, Naples, Italy; ² Unit of Oral Medicine and Pathology, Dental Clinic, Azienda Socio-Sanitaria Territoriale dei Sette Laghi, Varese, Italy; ³ Haematopathology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; ⁴ Department of Clinical Medicine and Surgery, Hematology Section, University of Naples Federico II, Naples, Italy

Summary

In 2024, the World Health Organization published its 5th edition of tumor classification, which comprises several updates and modifications in the “blue book” focused on head and neck tumors. These changes feature a systematized and expanded discussion on haematolymphoid proliferations using a multi-parameter approach that comprises clinical features, morphology, immunophenotype, and genetic data, with the latter becoming an essential characteristic for classification. Moreover, for the first time, the World Health Organization has included non-neoplastic diseases, such as reactive lymphoid proliferations, alongside several recognized independent disorders, including Epstein-Barr Virus positive mucocutaneous ulcers and IgG4-related diseases. Also, various neoplastic diseases, such as paediatric-type follicular lymphoma and large B-cell lymphoma with IRF4 rearrangement, are recognized as independent entities. Finally, the focus has expanded to include different types of histiocytic neoplasms. This review examines and illustrates the main changes and updates on hematolymphoid proliferation and neoplasia in the Head and Neck chapter of the 5th Edition of the Head and Neck WHO classification.

Key words: head and neck, World Health Organization, hematolymphoid proliferations and non-neoplastic conditions

Introduction

In 2024, the World Health Organization (WHO) published the 5th edition of Head and Neck (H&N) tumor classification, which includes several important differences with respect to the previous version of the “blue book”. For the first time, the WHO has included non-neoplastic conditions, such as reactive lymphoid proliferations, alongside several entities, such as Epstein-Barr Virus-positive mucocutaneous ulcers (EBV-MCU), IgG4 disorders, pediatric-type follicular lymphoma (PFL), large B-cell lymphoma with IRF4 rearrangement (LBCL-IRF4) and various types of histiocytic neoplasms recognized as independent.

This review examines the clinical features, morphology, immunophenotype, and genetic data, focusing on the main changes in hematolymphoid proliferation and neoplasia.

As in previous editions, the WHO classification of H&N tumors describes the non-neoplastic and neoplastic lymphoid disorders affecting the nasal cavity and paranasal sinuses, nasopharynx, larynx, oral cavity, oropharynx, neck, and salivary glands ¹. Lymphomas are the second most common malignancy in this region, following squamous cell carcinoma ². They

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Correspondence

Daniela Russo
E-mail: daniela.russo@unina.it

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represent 5% of all malignancies in the H&N region ³. Lymphomas are generally divided into Hodgkin's lymphomas (HL) and non-Hodgkin's lymphomas (NHL). HL mainly has a nodal origin; only approximately 5% arise in extranodal sites. NHL is frequently extranodal until 30% of cases ⁴, representing the second site of involvement for their onset after the gastrointestinal tract ⁵. Thirty-five to 65% of all these lymphomas occur in Waldeyer's ring ⁶, which is not specifically a nodal site, although, for staging purposes, it is assumed as such, ^{2,7} and 6-25% in salivary glands ⁸. Other affecting sites are the sinonasal region, the larynx, the oral cavity, the tongue and, infrequently, the odontogenic region and maxillofacial bones ^{2,8}.

This review aims to examine the current state of knowledge about H&N lymphoproliferative disorders highlight the recently introduced or modified entities, such as PFL, LBCL-IRF4, and extranodal NK/T-cell lymphoma ⁹. Furthermore, there will be a concise discussion on histiocytic and dendritic cell diseases.

Discussion

This review focuses on the main changes introduced in the WHO Classification of H&N Hematolymphoid Proliferation and Neoplasia, 5th Edition (Tab. I).

Due to the large number of lymph nodes and other structures, lymphoid and not, the H&N region is exposed to infections and autoimmune diseases. For this reason, it is crucial to have guidelines that can help to differentiate a benign disease, such as reactive lymphoid hyperplasia, from a neoplastic one, such as lymphoma. Among infectious agents, there are viruses (Epstein-Barr virus, cytomegalovirus, herpes simplex virus, human immunodeficiency virus), bacteria (Bartonella henselae, pyogenic bacteria), and mycobacteria; among autoimmune diseases, there is systemic erythematous lupus (LES), rheumatoid arthritis, and Sjogren syndrome. Otherwise, there are disorders of unknown etiology, such as IgG4-related disease, histiocytic necrotizing lymphadenitis, Kawasaki disease, Kimura disease, and atypical marginal zone hyperplasia of mucosa-associated lymphoid tissue ⁹⁻¹¹. As a basic rule, in reactive lymphoid hyperplasia, the general lymphoid architecture is preserved with the possibility to distinguish lymphoid follicles (with intact B-cell) from interfollicular and paracortical areas (with

Table I. Comparison of the Fourth and Fifth Editions of the WHO Classification of Hematolymphoid Tumors in the Head and Neck Region: this table highlights the key differences between the 4th and 5th editions of the WHO classification of hematolymphoid tumors affecting the head and neck region. The new entities are highlighted in bold.

	Fifth edition	Fourth edition
Reactive haematolymphoid and related lesions	-Reactive lymphoid hyperplasia -EBV+ mucocutaneous ulcer -IgG4-related disease	Not previously included
Myeloid tumors	Extramedullary myeloid sarcoma	Extramedullary myeloid sarcoma
B cell lymphomas	-Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue -Mantle cell lymphoma -Follicular lymphoma -Paediatric-type follicular lymphoma -Large B-cell lymphoma with IRF4 rearrangement -Diffuse large B-cell lymphoma -Burkitt lymphoma -Plasmacytoma -Plasmablastic lymphoma	-Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue -Mantle cell lymphoma -Follicular lymphoma -Diffuse large B-cell lymphoma -Burkitt lymphoma -Plasmacytoma -Plasmablastic lymphoma
T/NK cell tumors	-T-lymphoblastic leukaemia/lymphoma -Primary mucosal CD30-positive T-cell lymphoproliferative disorder -Extranodal NK/T-cell lymphoma (molecular classification: TSIM-subtype; MB-subtype; HEA-subtype)	-T-lymphoblastic leukaemia/lymphoma -Primary mucosal CD30-positive T-cell lymphoproliferative disorder -Extranodal NK/T-cell lymphoma
Hodgkin Lymphoma	Hodgkin lymphoma	Hodgkin lymphoma
Histiocytic and dendritic cell tumors	-Juvenile xanthogranuloma -Erdheim Chester disease -Rosai-Dorfman disease -Langerhans cell histiocytosis -Follicular dendritic cell sarcoma	-Langerhans cell histiocytosis -Follicular dendritic cell sarcoma

intact T cells). However, when morphology is insufficient, an immunohistochemistry panel can be useful in challenging cases. The most helpful marker is Bcl2, negative in germinal centers in reactive follicles, and polytypic light chain staining. Close clinical correlation (the presence/absence of a mass lesion¹⁰ and information about the autoimmune state, general medical history, and laboratory dates) between clinical and pathological information is mandatory.

Most lymphomas affecting the H&N area show clinical and histological features like those of their nodal counterparts. These include extranodal marginal zone lymphoma (EMZL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), plasmacytoma and myeloma, as well as T-lymphoblastic leukemia/lymphoma (T-LBL/L) and primary mucosal CD30-positive T-cell lymphoproliferative disorder (CD30-TCLD).

Given the wide range of diseases to describe, we will highlight the clinical pathological features of newly introduced entities.

EBV Mucocutaneous Ulcer (EBV-MCU)

EBV-MCU is a self-limited lymphoproliferative disease characterized by a polymorphous lymphoid infiltrate, which comprises small and large B and T lymphocytes, plasma cells, immunoblasts, and Hodgkin-like cells. Many patients have immunodeficiency, often due to iatrogenic immunosuppression from drugs such as methotrexate, azathioprine, cyclophosphamide, and TNF-alpha inhibitors¹²⁻¹³. Literature has shown

that iatrogenic immunodeficiency occurs in 66.1% of cases; the remaining cases are associated with immunosenescence, primary immunodeficiencies, and HIV/AIDS status¹⁴.

An EBV-MCU commonly presents as a single, well-defined ulcer in mucocutaneous regions¹⁴. These sites typically comprise the oropharyngeal mucosa, which accounts for up to 69.3% of cases, the oral cavity, and the pharynx. Less frequently, these ulcers can also affect the skin and gastrointestinal tract¹⁵. Histology shows a polymorphous lymphoid infiltrate of plasma cells and small and large B and T lymphocytes, often arranged in a peripheral line. Also, the infiltrate comprises histiocytes and granulocytes. Notably, there is a population of atypical cells, some exhibiting features characteristic of Reed-Sternberg cells associated with HL. The large cells typically are CD30+, CD15+/-, PAX5+, MUM1+, with a variable expression of B-cell associated markers (CD20, CD79a, OCT2, BOB1) and CD45, and negativity for CD3, CD10, Bcl6, CD56, and granzyme B/cytotoxic markers. The overlying epithelium shows ulceration, accompanied by acanthosis and pseudoepitheliomatous modifications in the surrounding epidermis or mucosa (Fig. 1).

Based solely on established pathological criteria, EBV-MCU can sometimes be misdiagnosed as EBV-positive diffuse large B-cell lymphoma (EBV-DLBCL), which shows a significantly different prognosis.

In fact, it more commonly occurs in lymph nodes and exhibits a rapidly progressive clinical course¹³.

Several key characteristics must be remembered when considering the differential diagnosis. An EBV-

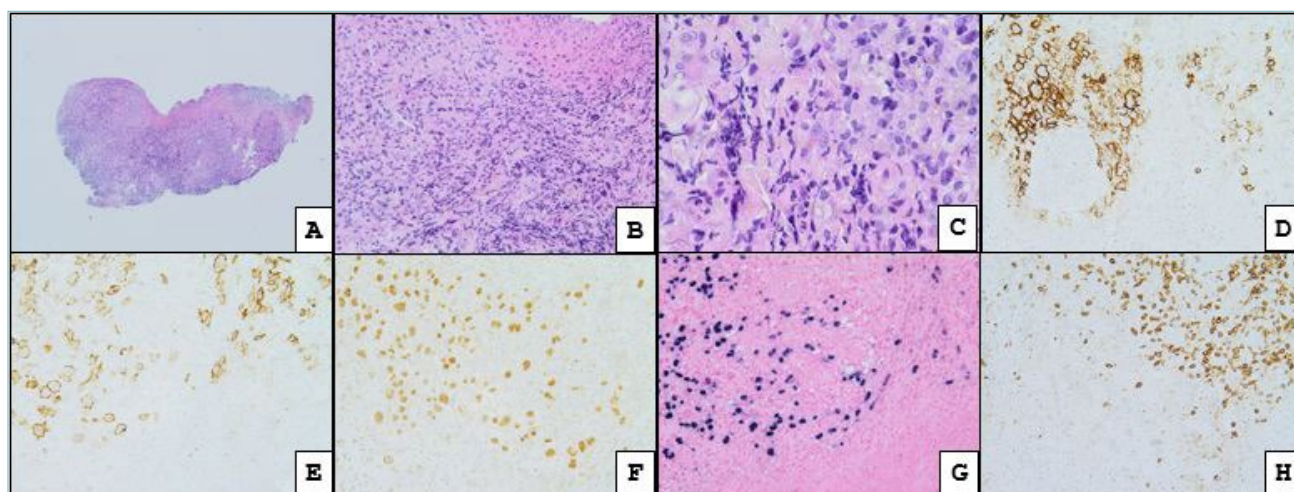


Figure 1. EBV mucocutaneous ulcer: (A) Hematoxylin and eosin staining, 40x magnification. (B) Hematoxylin and eosin staining, 200x magnification. (C) Hematoxylin and eosin staining, 600x magnification. (D) Immunostaining for CD20, 200x magnification. (E) Immunostaining for CD30, 200x magnification. (F) Immunostaining for PAX5, 200x magnification. (G) Immunostaining for EBV, 200x magnification. (H) Immunostaining for CD3, 200x magnification.

MCU typically presents as mucocutaneous ulcers characterized by isolated, well-demarcated lesions in younger and immunodeficient patients; conversely, EBV-DLBCL usually affects older patients and presents as a mass lesion. Histologically, both are associated with a mixed inflammatory background, but EBV-positive cells in EBV-MCU are found in various cell types while they are mostly restricted to the large, atypical cells in EBV-DLBCL.

Finally, EBV-MCU is generally self-limiting and has a favorable prognosis. Conversely EBV-DLBCL is aggressive and is usually associated with a poor biological behavior.

Classical HL must be distinguished from EBV-MCU by the presence of Reed-Sternberg cells and a more common B-cell negative immunophenotype. Clinically, a mucocutaneous localization of cHL is often associated with systemic B-symptoms and advanced stage with extranodal primary onset being exceedingly rare¹³. Extranodal NK/T-cell lymphoma exhibits an angiocentric and angiodestructive growth pattern with massive necrosis. Unlike EBV-MCU, this lymphoma consists of NK or T cells typically expressing CD2 and CD56 and lacking CD5, with possible expression of CD30. It primarily affects extranodal sites, particularly the nasal cavity and skin¹⁶. Also, lymphomatoid granulomatosis (LG) exhibits an angiocentric and angiodestructive lesion pattern. However, LG primarily consists of B cells and often expresses CD30. Clinically, it is associated with pulmonary nodules, skin lesions, and systemic B symptoms¹⁶.

Finally, EBV-positive polymorphic lymphoproliferative disorder (EBV-PLPD) shares some features with EBV-MCU but is often associated with immunosuppressive conditions. EBV-PLPD usually presents systemic symptoms, including fever, weight loss, and swollen lymph nodes (lymphadenopathy). It typically affects multiple sites, primarily the lymph nodes, spleen, and liver. Histologically, it is represented by a heterogeneous lymphoid population, which includes B cells, T cells, and plasma cells. Occasionally, Reed-Sternberg-like cells may be seen, but their presence is not definitive. Immunophenotypically, EBV-PLPD resembles EBV-MCU, with B cells often expressing EBV latent membrane proteins (EBER, LMP1, and EBNA2) in various cellular morphologies. Additionally, monoclonal or oligoclonal immunoglobulin gene rearrangements are frequently observed¹⁶.

Given the overlapping features among these diseases, a close correlation between morphological and phenotypical features and clinical and imaging data is crucial for proper diagnosis and correct management.

IgG4-Related Disease

IgG4-related disease is a chronic autoimmune disorder characterized by storiform fibrosis and a rich infiltrate of lymphocytes and IgG4+ plasma cells in serum and several tissues¹⁷.

Patients typically present with a painless mass due to the enlargement of exocrine glands. The most affected glands are in the H&N region, particularly the salivary glands (especially the submandibular gland) and the lacrimal/orbital glands. However, other exocrine glands and additional sites, such as the pancreas, retroperitoneum, mediastinum, lungs, and kidneys, can also be involved.

Several reactive morphologic patterns can be identified, including the multicentric Castleman disease-like pattern, which can be differentiated by the presence of atrophic follicles in Castleman disease, as opposed to the normal-sized or hyperplastic follicles found in IgG-related Castleman-like diseases. The other patterns include follicular hyperplasia, interfollicular expansion, progressive transformation of germinal centers, inflammatory pseudotumor-like, mononucleosis-like, and Rosai-Dorfman-like patterns.

Histologically, the disease presents with a dense infiltrate of lymphocytes and plasma cells, with an increased number of IgG4-positive plasma cells (more than 100 per high-power field) and a higher ratio of IgG4 to IgG-positive cells (greater than 40%). Eosinophils are almost always present. Other notable features are storiform fibrosis, obliterative phlebitis, and phlebitis, which do not result in luminal obliteration¹⁸. Diagnosis of IgG4-related disease is established through clinical symptoms, signs, and radiological, serological, and histopathological findings. It is crucial to meticulously rule out a differential diagnosis of malignancy, a step that cannot be overstated in the diagnostic process (Fig. 2).

The primary differential diagnoses include mucosa associated lymphoid tissue (MALT) lymphoma, plasma cell neoplasia, infections, lesions such as inflammatory myofibroblastic tumors, and inflammatory/autoimmune disorders like Sjogren syndrome, chronic sialadenitis NOS, Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, sarcoidosis, multicentric Castleman disease, among others¹⁹.

Pediatric Follicular Lymphoma (PFL)

PFL represents an uncommon type of follicular lymphoma. This entity, described since 2008 due to its unique clinical pathology and molecular genetic characteristics, has been recognized as a distinct entity

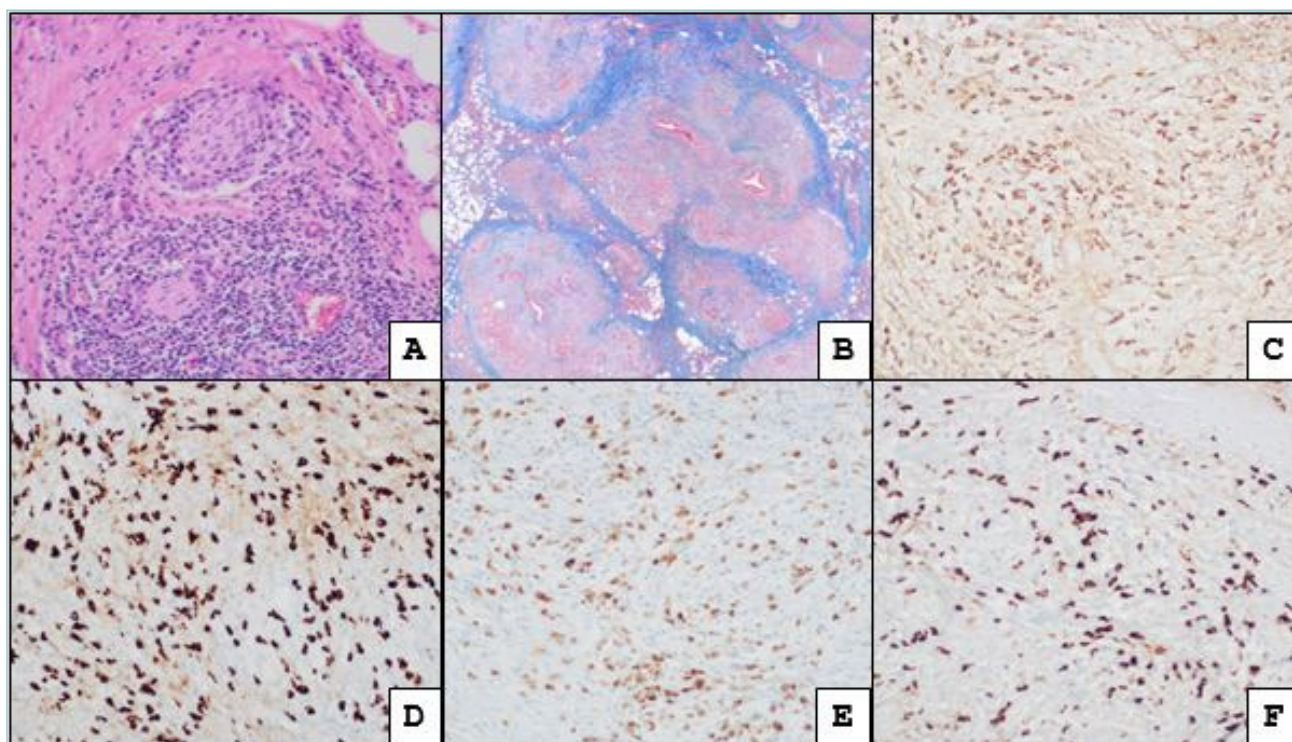


Figure 2. IgG4-related disease. (A) Hematoxylin and eosin staining, 200x magnification. (B) Trichrome Masson staining, 20x magnification. (C) Immunostaining for IgG, 200x magnification. (D) Immunostaining for IgG4, 200x magnification. (E) Immunostaining for kappa, 200x magnification. (F) Immunostaining for lambda, 200x magnification.

in the revised 4th edition of the WHO classification. The 5th edition describes it in a separate paragraph from the “classical follicular lymphoma”^{12,20}. As suggested by the name, PFL usually occurs in children and young adults (aged from 5 to 25 years old) with an elevated prevalence among males (M:F = 10:1), most often involving H&N lymph nodes and less often inguinal and axillary ones^{9,21}, in all case at very limited stage. The histology of PFL is characterized by a replacement of normal lymphoid tissue with a proliferation of large and irregular follicles occupied by medium-sized blastoid cells and less frequently centroblasts, a loss of polarity in germinal centers which gain a starry sky appearance. Moreover, an attenuated mantle zone is found. Until now, extracapsular extension has not been described. Sometimes, some reactive follicles can be found at the lymph nodes’ periphery in the “node within a node” pattern²¹. Neoplastic cells are CD10+, CD19+, CD20+ and BCL6+, CD5-, and BCL2-. The most frequent genetic mutations occur in the MAPK pathway (about 50%), TNFRSF14 (about 50%), and IRF8 (about 15%), and, in contrast to “adult-type follicular lymphoma,” PFL lacks rearrangements of BCL2, Bcl6, MYC and IRF4^{12,22}

(Fig. 3). It is essential to distinguish PFL from “adult type” follicular lymphoma, considering that the former has an excellent prognosis with patients that require only surgical excision and a watch-and-wait follow-up²³. Another differential diagnosis to keep in mind is with the pediatric marginal zone lymphoma (PMZL), although in some cases features of both categories can be observed in the same node. In these cases, the differential diagnosis can be highly challenging, but both do show excellent outcome. PMZL is negative for germinal center associated markers (including LLT-1 and STMN-1) and shows florid follicular hyperplasia, which lacks FOXP-1 expression²¹.

Large B-Cell Lymphoma with IRF4 rearrangement (LBCL-IRF4)

LBCL-IRF4 is a rare and biologically distinct subtype of LBCL, characterized by recurrent chromosomal translocations involving the IRF4 gene. It was initially classified as a provisional entity in the 2016 revised 4th edition of the WHO classification within the FL group, LBCL-IRF4 is now recognized as a distinct and

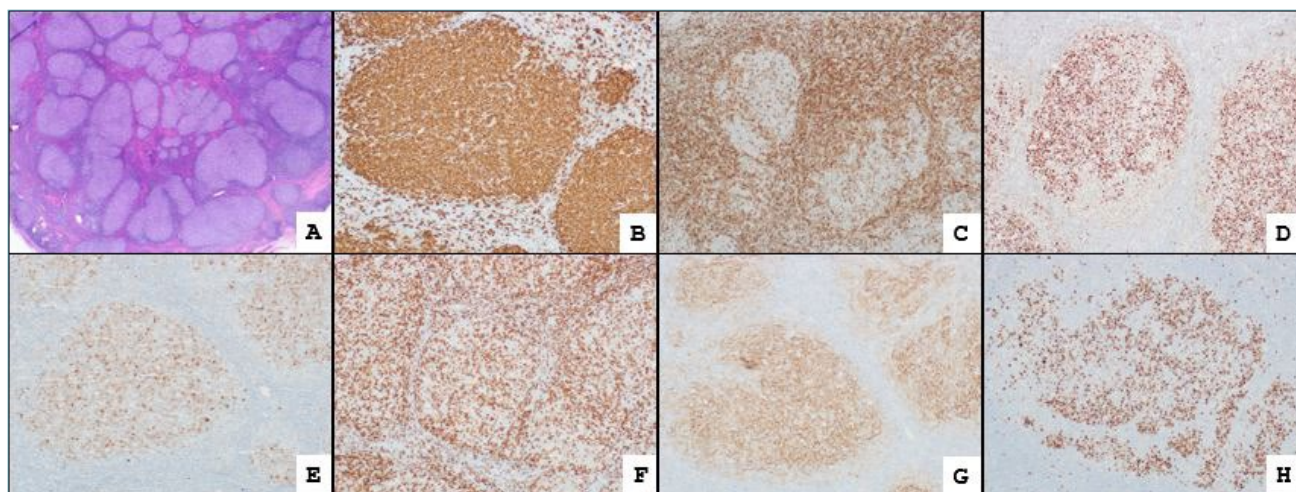


Figure 3. Pediatric follicular lymphoma (PFL): (A) Hematoxylin and eosin staining, 20x magnification. (B) Immunostaining for CD20, 100x magnification. (C) Immunostaining for BCL2, 100x magnification. (D) Immunostaining for BCL6, 100x magnification. (E) Immunostaining for CD10, 100x magnification. (F) Immunostaining for CD3. (G) Immunostaining for CD23, 100x magnification. (H) Immunostaining for MIB/Ki67, 100x magnification.

definitive entity in this latest edition ²⁴. This lymphoma commonly occurs in the H&N, particularly in Walden's ring and cervical lymph nodes. It primarily affects young individuals, with a median age of 12 years (ranging from 4 to 79), and has an equal distribution among genders. Patients typically present with enlarged tonsils or isolated lymph nodes, which appear as solid and fleshy masses upon examination of the cut surface.

The architectural pattern of LBCL-IRF4 can be categorized as either follicular, a combination of follicular and diffuse, or entirely diffuse. It features a monomorphic population of neoplastic cells that exhibit open chromatin and small nucleoli, but notably lack a starry-sky background. The neoplastic cells are characterized by the following markers: CD20+, CD3-, CD5 -/+, CD10-/+ , BCL6+, and BCL2+/- . Importantly, there is a strong and diffuse expression of IRF4/MUM1 (Fig. 4).

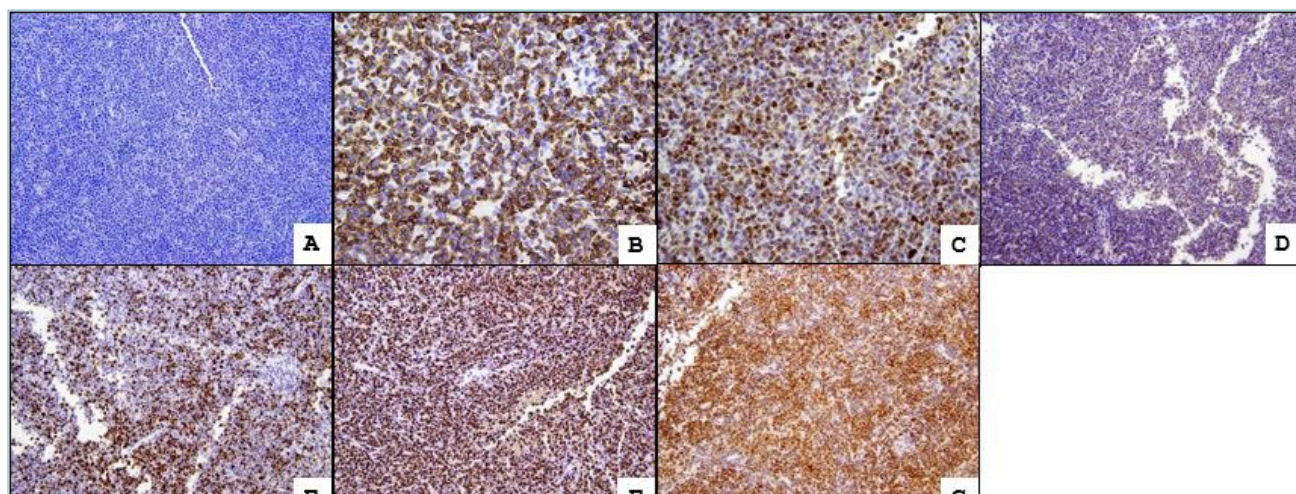


Figure 4. Rearranged IRF BCL: (A) Giemsa staining, 100x magnification. (B) Immunostaining for BCL2, 200x magnification. (C) Immunostaining for BCL6, 200x magnification. (D) Immunostaining for CD10, 100x magnification. (E) Immunostaining for c-MYC, 100x magnification. (F) Immunostaining for Ki-67, 100x magnification (G) Immunostaining for MUM1, 100x magnification.

The molecular profile is characterized by high expression of IRF4/MUM1, which may be due to gene rearrangements or translocations, most commonly involving the IGH genes and, less frequently, immunoglobulin light chain genes. Another significant molecular feature is the unusual co-expression of IRF4/MUM1 and BCL6²⁴.

The primary differential diagnoses for LBCL-IRF4 include the PFL. This tumor usually shows a follicular pattern with a starry-sky appearance characterized by scattered macrophages. In contrast, DLBCL with IRF4 rearrangement is typically more diffuse and does not present a starry-sky appearance, looking definitively malignant. Immunohistochemically, PFL usually shows only Bcl6 positivity and is IRF4 negative, whereas LBCL-IRF4 strongly expresses Bcl6 and IRF4/MUM1. Despite these differences, both types of lymphoma have an excellent prognosis, although LBCL-IRF4 must be chemotreated.

Given the possible follicular growth pattern, FL grade 3B must be excluded; however, despite it can be IRF4 positive at immunohistochemistry, it is mostly CD10 negative and lacks IRF4 rearrangement.

Others B-cell lymphomas with predominant large B-cell composition may pose immunomorphological challenge for the differential diagnosis against LBCL-IRF4, but they never show IRF4 rearrangement as a sole translocation.

These include: DLBCL-NOS (either germinal centre or not germinal centre like phenotype), Primary mediastinal large B-cell lymphoma (it originates in the anterior mediastinum, can phenotypically express IRF4

and Bcl6, but it is predominantly CD10 negative, and more characteristically show CD30 and CD23 positivity), high-grade B-cell lymphoma, NOS (blastoid cytology), Burkitt-like lymphoma with 11q aberration (may exhibits a similar morphology and phenotype to LBCL-IRF4, is MYC-R negative, but harbors 11q aberrations)²⁵.

Extranodal NK/T cell lymphoma, nasal type

Extranodal NK/T cell lymphoma comprises natural killer (NK) and T cells with cytotoxic features. It shows an aggressive course and is prevalent in Asia and Latin America (principally in indigenous descendants from Mexico, Guatemala, Peru, and Brazil). The median age is 46-60, and most are males infected by EBV²⁶. The most frequent sites for the arising of extranodal NK/T cell lymphoma are the nasal cavity and nasopharynx, with a clinical presentation as nonspecific sinonasal symptoms like rhinorrhea or nasal obstruction, which often leads to delayed diagnosis²⁷⁻²⁸. Other onset sites are rare yet reported in the literature, including the testis, central nervous system, lungs, skin, soft tissue, and gastrointestinal tract²⁹ which are associated with worse prognosis³⁰. Macroscopic appearance is like an ulcerated, necrotic, and edematous mass; histologically, it is composed of an atypical and dense polymorphic lymphoid proliferation formed by small to large or anaplastic cells organized in an angiocentric or angioinvasive growth pattern. Frequently, fibrinoid

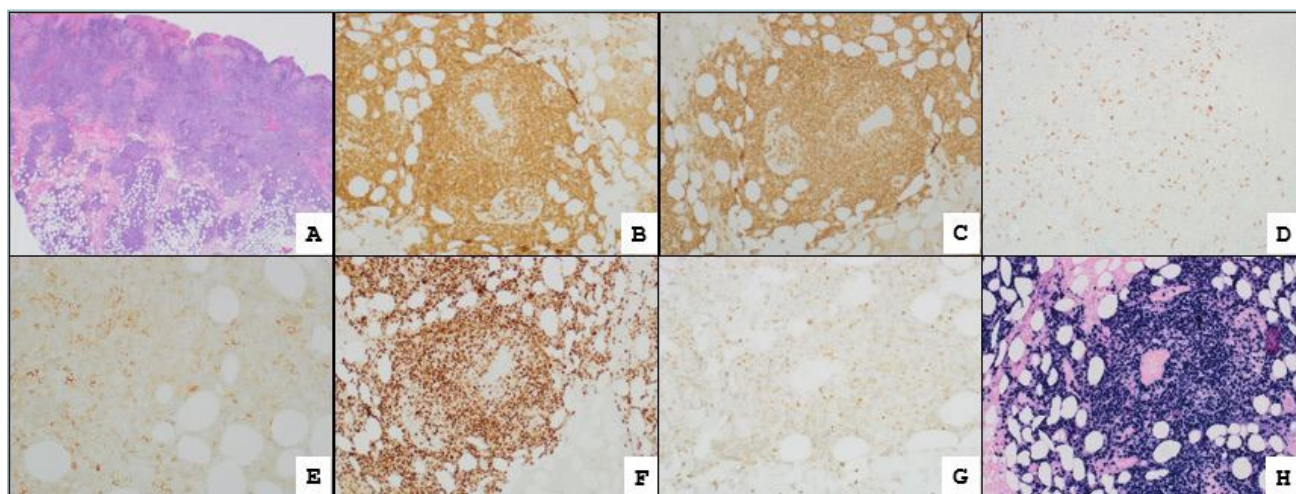


Figure 5. Nasal type T-cell lymphoma TCL: (A) Hematoxylin and eosin staining, 20x magnification. (B) Immunostaining for CD3, 100x magnification. (C) Immunostaining for CD8, 100x magnification. (D) Immunostaining for CD5, 100x magnification. (E) Immunostaining for CD56, 200x magnification. (F) Immunostaining for MIB/Ki67, 100x magnification. (G) Immunostaining for TIA, 200x magnification. (H) Immunostaining for EBV, 100x magnification.

necrosis of blood vessels and coagulative geographic necrosis or ulceration of mucosa can be found ³¹. Neoplastic cells are EBV+ (EBER+), CD2+, CD3+, CD56+, TIA1+, granzyme B and/or perforin, CD4-, CD30 variable, CD5 variable, and CD8 variable ³² (Fig. 5). Although EBER is almost positive, some cases can leak CD56 expression and EBV infection; for these cases, it is appropriate to talk of peripheral T cell lymphomas non-otherwise specified EBV ^{2,33}. In the last edition of WHO, extranodal NK/T cell lymphoma is classified into three molecular subtypes: TSIM-subtype, associated with JAK/STAT activation, NK-origin, and PD-L1 overexpression; MB-subtype shows MYC overexpression and poor outcome.

Epigenetic changes, NF- κ B activation, and T-cell origin ³⁴ characterize the HEA subtype. Therapy is based on radiotherapy and chemotherapy, not comprising conventional anthracycline but founded on L-asparaginase combined with other effective drugs ³⁵. The most recent studies promote the usefulness of immunotherapies ³⁶. However, overall survival at 5 years from diagnosis is between 40-50% ³⁷.

Histiocytic and dendritic cell tumors

For the first time, histiocytic and dendritic cell proliferations are included in the H&N WHO classification. These rare diseases show overlapping clinical and histopathological features and pose considerable diagnostic challenges.

Key differences are seen in their histological patterns, cellular morphology, and the presence of specific immunohistochemical markers, which are crucial in distinguishing between these entities ^{38,39}.

Juvenile xanthogranuloma (JXG) is a benign, non-Langerhans cell histiocytic proliferation, predominantly affecting young children. It typically presents as a solitary, red-brown or yellowish papule or nodule, commonly on the head and neck, and follows a benign course with spontaneous resolution. Histologically, it is characterized by foam cells, histiocytes, and Touton giant cells. JXG is often self-limited, though systemic involvement may require treatment. It shares some histological features with Erdheim-Chester disease (ECD), particularly the presence of foamy histiocytes and Touton giant cells. However, JXG typically lacks BRAF or other MAPK pathway mutations, common in ECD and Langerhans cell histiocytosis (LCH). The clinical context, being localized and usually involving the skin and the absence of systemic involvement, help distinguish JXG from ECD and LCH ^{38,40}.

ECD is a rare systemic disease with frequent bone, retroperitoneum, central nervous system (CNS), and

lung involvement. It is associated with BRAF V600E mutations in over 50% of cases. Microscopically, ECD shows a soft tissue infiltrate of foamy histiocytes and Touton giant cells, often accompanied by fibrosis and a sparse lymphoplasmacytic infiltrate. It may resemble reactive histiocytic proliferations, such as those seen in fat necrosis or post-chemotherapy, which can be challenging to distinguish. However, the clinical presentation (systemic involvement) and immunostaining for BRAF V600E are key diagnostic clues, as they are typically present in ECD but absent in reactive conditions. Foamy histiocytes with abundant cytoplasm and scattered Touton giant cells help further differentiate ECD from other histiocytic proliferations ^{38,41}.

LCH is a clonal proliferation of cells resembling Langerhans cells, typically affecting children. It occurs with bone involvement and often includes eosinophils in the lesions. Histologically, LCH is characterized by cells with irregular, grooved, or folded nuclei with fine chromatin, inconspicuous nucleoli, and abundant pale eosinophilic cytoplasm. These cells are immunohistochemically positive for CD1a and langerin (CD207). LCH should be differentiated from ECD, as LCH histiocytic infiltrates typically do not contain the same foamy cytoplasm and Touton giant cells seen in ECD. Furthermore, LCH's characteristic nuclear grooves and positive CD1a and langerin staining can help distinguish it from ECD and JXG ^{38,42}.

Rosai-Dorfman disease (RDD) is characterized by the accumulation of histiocytes with large, hypochromatic nuclei and abundant eosinophilic cytoplasm. Emperipolesis (the engulfment of intact inflammatory cells) is a key feature. RDD often presents with a prominent lymphoplasmacytic infiltrate, which is more prominent than the fibrosis-dominant infiltrate seen in ECD. Immunohistochemically, RDD histiocytes are positive for S100, which helps distinguish it from other histiocytic disorders. The presence of emperipolesis and the lymphoplasmacytic infiltrate are key features that separate RDD from ECD and other disorders like JXG. Furthermore, RDD histiocytes are frequently associated with alterations in the MAPK/ERK pathway in a third of cases ^{38,43}.

Follicular dendritic cell sarcoma (FDCS) typically presents as a painless mass in nodal and extranodal sites and behaves as a low-grade sarcoma. It is distinguished by the expression of follicular dendritic cell markers and histologically by spindle-shaped cells arranged in fascicular or storiform patterns, often with lymphocytic and eosinophilic infiltrates. FDCS can be differentiated from other histiocytic proliferations by its immunohistochemical profile. The most sensitive markers for FDCS are clusterin, CD21, and CXCL13, while CD21, CD23 and CD35 are most specific. Oth-

er markers that may be expressed include podoplanin, SSTR2a, FDCSP, SRGN, and gascin, as well as PDL1, desmoplakin, EGFR, and vimentin.

Additionally, terminal deoxynucleotidyl transferase (TdT) expression is seen in about 45% of FDCS cases. These immunohistochemical findings help distinguish FDCS from other conditions with similar histological features. In differential diagnosis, LCH must be considered. While FDCS and LCH can exhibit spindle-shaped histiocytes, the absence of characteristic nuclear grooves and the specific immunohistochemical markers of LCH, such as CD1a and langerin, help differentiate these entities^{42,44}.

These disorders differ primarily in clinical presentation, histological characteristics, and systemic involvement. JXG and RDD are more localized and generally self-limited, while ECD, LCH, and FDCS are more systemic, with varying degrees of aggressiveness and prognosis. The differentiation of these disorders is often based on subtle but critical histological features, such as the type of histiocytes (foamy in ECD, Langerhans-like in LCH, and characteristic emperipolesis in RDD), the presence of Touton giant cells (noted in both JXG and ECD), and specific immunohistochemical markers (e.g., CD1a, langerin, S100, BRAF V600E). Carefully integrating clinical features, such as systemic involvement and age of onset, histopathology, phenotype and molecular markers, is crucial for correct diagnosis and an appropriate classification among these histiocytic disorders.

Conclusion

The 5th edition of the H&N Classification of Tumors has included non-neoplastic haematolymphoid diseases, introduced or restructured new diagnostic entities, and expanded to include several types of histiocytic neoplasms. This review summarizes the most important clinical, pathological, phenotypical, and molecular features essential for accurate diagnosis and appropriate classification. For the aim, to improve the management of these patients, hematologists, radiologists, and pathologists must collaborate to implement the most up-to-date diagnostic guidelines into standard clinical practice.

CONFLICTS OF INTEREST STATEMENT

The authors report no conflict of interest.

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AUTHORS' CONTRIBUTIONS

Conceptualization, M.M. and E.S.; investigation, R.C.,

F.M., D.R. G.M, C.B., C.G. and A.S.; date curation, M.P. and E.S.; writing—original draft preparation, D.R., S.V. and R.C.; writing—review and editing, G.I. and M.C.; supervision, M.M. All authors have read and agreed to the published version of the manuscript

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