BENIGN LYMPHOPROLIFERATIVE DISORDERS IN THE IMMUNOSUPPRESSED PATIENT: AN UPDATE

Lymphoproliferative disorders and immunosuppression

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Abstract

Immunosuppressed patients may be affected by a wide range of lymphoproliferative disorders (LPDs) ranging from self-limiting benign disorders to malignant monoclonal lymphoid proliferations. These LPDs may be associated with systemic immune disorders, develop following organ transplantation or occur in the background of other forms of iatrogenic immunosuppression. Lymphotropic viruses, including Epstein-Barr virus (EBV) and Human Herpesvirus-8 (HHV8), have been associated with the pathogenesis of distinct LPDs. The resulting classification of this group of disorders is very complex and inconsistent, with several new and emerging entities. Consequently, the diagnosis of a LPD, especially in an immunosuppressed patient, and their subsequent clinical management usually represents an important pitfall during daily clinical and pathology work. Therefore, the aim of this review was to use the available literature to describe the clinicopathological features of the most important benign LPDs that may be diagnosed in the head and neck region of immunosuppressed patients. Original clinical and microscopic images were used to illustrate some of these entities.

Keywords: Lymphoproliferative disorder; EBV; HHV8; HIV; immunosuppressed.

1. Introduction

Lymphoproliferative disorders (LPDs) in the immunosuppressed patient range from benign polyclonal to malignant monoclonal lymphoid proliferations, usually of B-cell derivation.[1-2] The World Health Organization (WHO) classification recognises 4 types of immunosuppression-associated LPDs: (1) LPDs associated with primary immune disorders, (2) human immunodeficiency virus (HIV)-associated LPDs, (3) post-transplant lymphoproliferative disorders (PTLDs), and (4) other iatrogenic immunosuppression-associated LPDs.[3] Novel types of immunosuppression-associated LPDs that have emerged due to newer therapeutic agents and other less-recognised immunosuppression settings have not been included in the current classification.[2] Viruses, in particular lymphotropic subtypes such as Epstein-Barr virus (EBV) and Human Herpesvirus-8 (HHV8), have long been associated with the pathogenesis of distinct LPDs, especially in immunosuppressed patients.[4-5]

This review will discuss benign lymphoproliferative disorders in the immunosuppressed patient, with an emphasis on entities commonly affecting the head and neck region. This review article is part of a special issue published by the *Journal of Oral Pathology and Medicine* covering the most important aspects of haematolymphoid lesions and neoplasms affecting the oral cavity and neighbouring structures.

2. Classification of immunosuppression-associated lymphoproliferative disorders

The spectrum of immunosuppression-associated LPDs has culminated in a cumbersome terminology that has resulted in confusion and inconsistent disease definitions.[2] In 2015, the Society for Hematopathology and the European Association for Haematopathology conducted a workshop where a working vocabulary was

proposed for all immunosuppression-association LPDs. The proposed 3-part unifying nomenclature includes the name of the lesion or closest approximation to the latest WHO terminology, the associated virus (if any), and the specific immunosuppression background.[6] This proposed standardisation allows for a simplified approach to group diseases with similar morphologic, immunophenotypic and genetic features.[2]

3.LYMPHOPROLIFERATIVE DISORDERS ASSOCIATED WITH PRIMARY IMMUNE DISORDERS

Some LPDs may arise in a background of immunosuppression due to primary immune disorders (PIDs).[3,7] Currently, there are over 60 different PIDs with variable clinical features and pathological findings.[1,3] Those most commonly associated with LPDs include ataxia-telangiectasia, Wiskott-Aldrich syndrome, common variable immunodeficiency, severe combined immunodeficiency, X-linked lymphoproliferative syndrome, autoimmune lymphoproliferative syndrome and Nijmegen breakage syndrome.[3,7] Similar to other immunosuppression states, LPDs in patients with PIDs include hyperplasias (discussed later), polymorphous lymphoid infiltrates and lymphomas.[3] EBV-infection is associated with the development of LPDs in most patients and, in rare instances, may result in fatal infectious mononucleosis.[1,7] LPDs occurring in the background of PIDs often occur in extranodal sites, with head and neck lesions being exceedingly rare.[1,3]

4. HIV-ASSOCIATED LYMPHOPROLIFERATIVE DISORDERS

HIV has profound immunological effects, including cellular and tissue manifestations throughout the lymphoreticular system.[1] Strictly speaking, not all immunological manifestations of HIV should be considered as LPDs. However, a

range of LPDs do arise in the context of HIV-associated immunosuppression, most of which following viral infection. These will be discussed under the appropriate viral-associated LPD.

4.1. HIV-associated lymphadenopathy

Persistent generalised lymphadenopathy is a common manifestation within a HIV-related symptom complex. This condition is defined as lymphadenopathy of at least 3 months duration involving two or more noncontiguous sites, in the absence of intercurrent illness or the use of drugs associated with lymphadenopathy.[8] This lymphoid hyperplasia often affects the nasopharynx and Waldeyer's ring.[8-9] Clinically, patients may present with airway obstruction due to a nasopharyngeal or tonsillar mass lesion.[9]

The histological appearance of reactive lymphadenopathy in HIV-infection varies with the duration of the disease.[1,8-9] Early phases of HIV-infection usually present with florid follicular hyperplasia with giant geographic follicles composed predominantly of centroblasts **(Figure 1)**.[1,8-9] There may be accompanying intrafollicular haemorrhage **(Figure 1A)** and multinucleated giant cells (termed polykaryocytes), occasionally resembling Warthin-Finkeldey giant cells seen in measles **(Figure 1B)**.[1,8-9] The enlarged follicles often lack a discernable mantle zone, making identification difficult.[1,9] Paracortical hyperplasia is also seen, with plasmacytosis, as well as an increase in high endothelial venules.[8] In addition to the sinus histiocytosis, there are often aggregates of monocytoid B-cells with accompanying neutrophils, mimicking toxoplasma lymphadenitis.[8] The late stage of HIV-associated lymphadenopathy is dominated by follicular involution and lymphoid depletion **(Figure 2A)**. Follicle depletion results in a relative or pseudo-paracortical

expansion and increased overall vascularity.[8] During all stages, demonstration of HIV-infection within FDCs is possible by IHC staining for the p24-gat protein of HIV **(Figure 2B)**.[1,9]

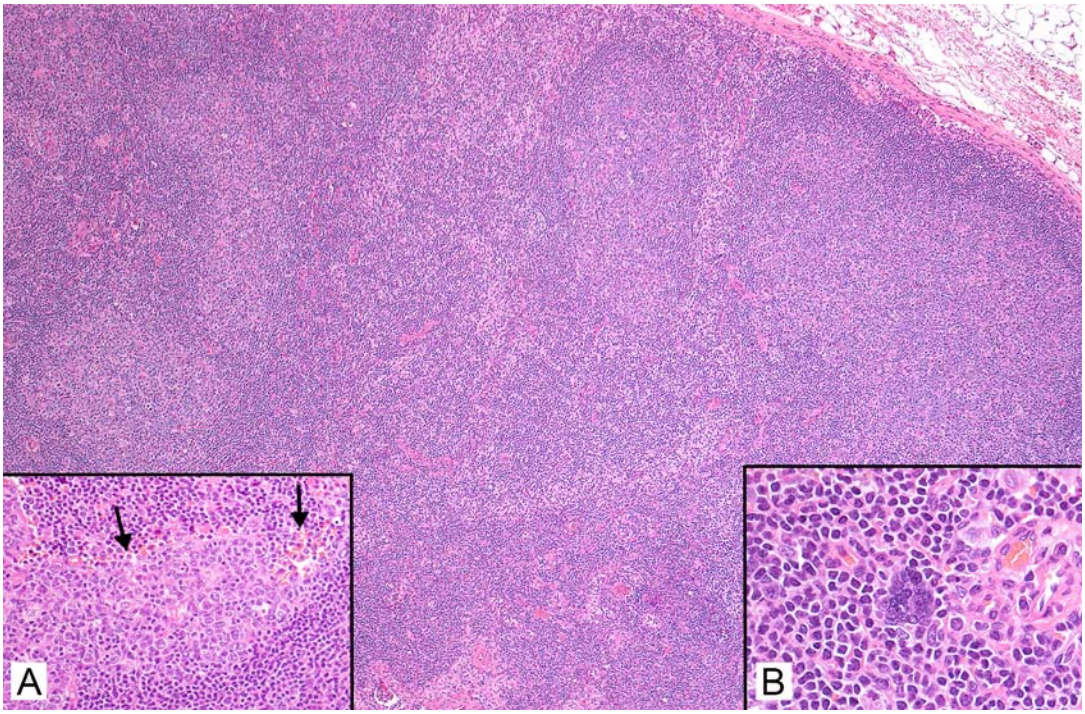

Figure 1. hotomicrograph of early HIV-associated lymphadenopathy characterised by florid follicular hyperplasia with giant follicles (H&E; original magnification × 40). (A) Mild intrafollicular haemorrhage (arrows) (H&E; original magnification × 200). (B) Scattered multinucleated giant cells (H&E; original magnification × 200)

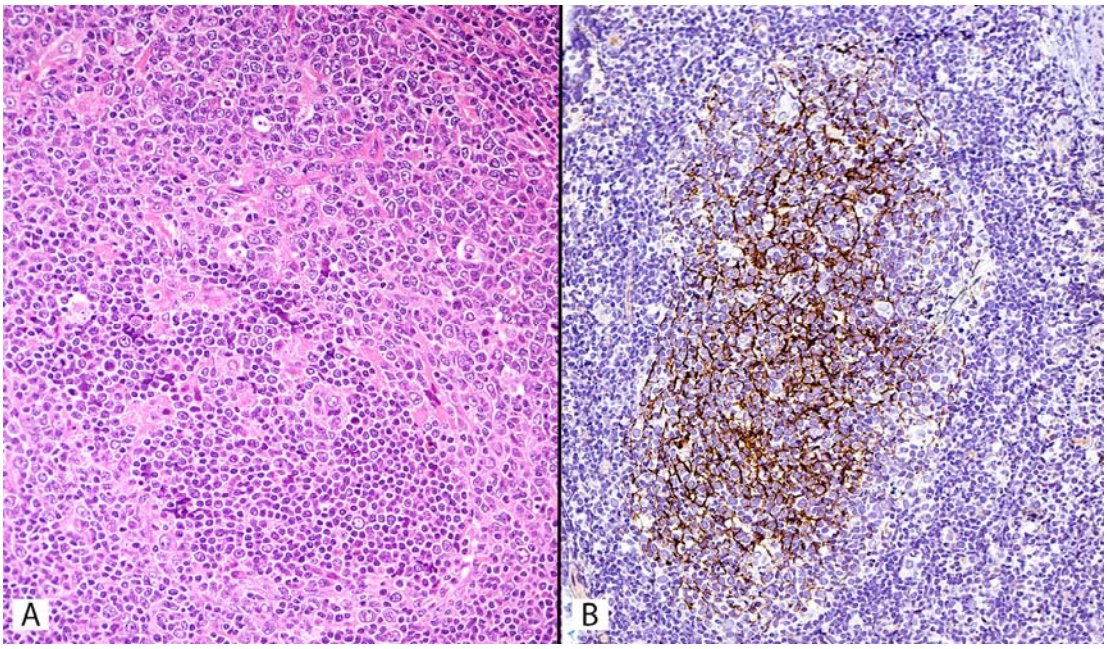

Figure 2. (A) Photomicrograph of late HIV-associated lymphadenopathy with extensive follicle involution (H&E; original magnification × 200). (B) p24 IHC stain highlighting HIV infection within FDCs (original magnification × 100)

4.2. Diffuse infiltrative lymphocytosis syndrome

Diffuse infiltrative lymphocytosis syndrome (DILS) is a rare multisystemic disease first described in 1989 in 12 HIV-infected patients.[10-11] The disorder is characterised by CD8+ T-cell lymphocytosis accompanied by lymphocytic infiltration of multiple organs. DILS affects approximately 3%-8% of HIV-infected patients.[11-12] Early HIV-infection is initially characterised by a transient CD8+ T-cell expansion, which eventually declines parallel to CD4+ T-cell depletion.[11] However, in some cases, CD8+ T-cell expansion persists, leading to tissue and organ infiltration.[11]

Common clinical features include salivary gland enlargement and sicca signs.[11-12] In general, painless swelling of glandular organs occurs bilaterally with associated cervical lymphadenopathy **(Figure 3A)**.[11-12] Unilateral parotid gland enlargement has rarely been reported. DILS, however, remains a multisystemic

disease with involvement of multiple organs including the lungs, peripheral nervous system, kidneys, liver and digestive tract.[10-11] DILS should be differentiated from other conditions presenting with parotid gland enlargements. This includes Sjögren's syndrome (SS), but also HIV-associated lymphoepithelial lesions, bacterial and viral infections, sarcoidosis and several B-cell lymphomas. The disorder shares many clinical features with SS and IgG4-related disease, and should be distinguished via clinical work-up, serology and HLA-associations **(Table 1)**.[10-12] DILS also requires distinction from B-cell lymphoma, which usually presents with unilateral parotid enlargement.[11]

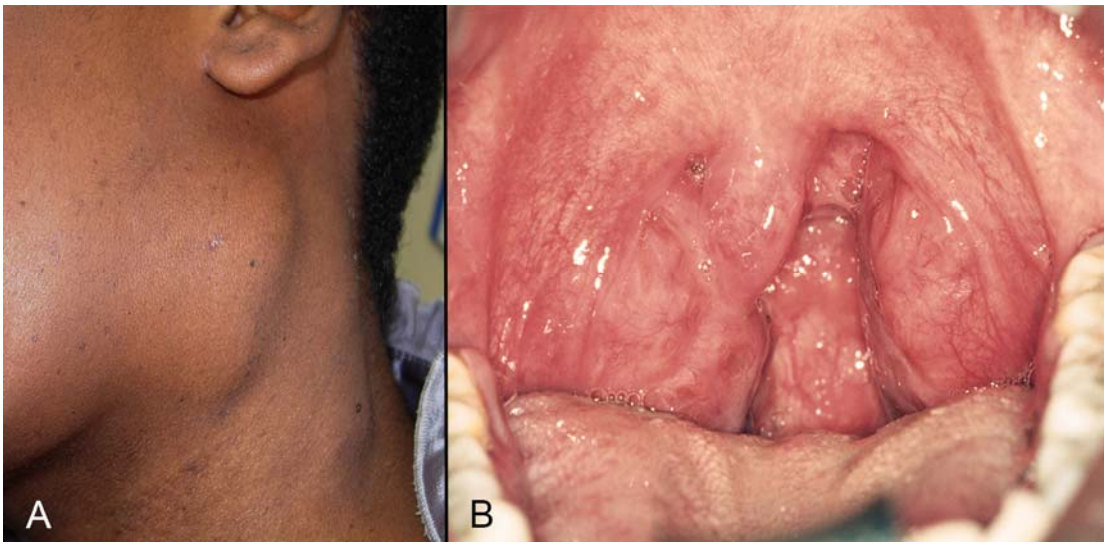

Figure 3. (A) HIV-positive male patient with parotid gland enlargement and cervical lymphadenopathy suggestive of DILS. (B) HIV-positive patient with lymphoid hyperplasia of Waldeyer's ring

Salivary gland enlargement by DILS may show a spectrum of histopathological features ranging from complete preservation to massive destruction of the glandular structures with diffuse fibrous replacement. A labial salivary gland biopsy is usually diagnostic.[11] The affected glands are characteristically infiltrated by CD8+ T-cells, causing a benign lymphoepithelial lesion that may be solid or cystic. IHC is an essential tool required to delineate the different T-cell subtypes. However, a

final diagnosis of DILS should only be considered in the presence of chronic HIV-infection, bilateral salivary gland enlargement or xerostomia present for greater than 6-months, evidence of organ-infiltration and a blood CD4+/CD8+ T-cell ratio less than 1.[11-12] Other autoimmune diseases need to be excluded, as well as coinfection with viruses such as Hepatitis C and EBV.[11-12]

TABLE 1. Comparison of DILS, Sjögren's Syndrome (SS) and IgG4-related salivary gland (SG) disease

	DILS	**SS**	**IgG4-Related SG Disease**
CLINICAL			
Age	Mainly adults	Mainly adults (5^{th}–7^{th} decades)	Mainly adults (6^{th}–7^{th} decades)
Gender	Mainly males	Mainly females	Slight male predominance
Immune status	HIV-positive	Autoimmune-mediated disease	Autoimmune-mediated disease
Gland involvement	Mainly salivary glands	Salivary and lacrimal glands	Salivary glands, pancreas and lacrimal glands
Extraglandular involvement	Lungs, lymph nodes, peripheral nervous system, kidneys, liver, gastrointestinal tract	Rare: Lymph nodes, lungs, kidneys, liver	Lymph nodes, gallbladder, liver, thyroid, lungs, kidneys
Salivary gland enlargement	Mainly bilateral	Mainly bilateral	Mainly bilateral
Sicca symptoms	Yes	Yes	Yes
SEROLOGY	CD8+ T-cell lymphocytosis	Positive anti-SSA (RO) &/or anti-SSB (LA) RF positive in 95% ESR usually elevated	Serum IgG4, IgG and IgG4/IgG ratio elevated
HLA ASSOCIATION	HLA-DR5 HLA-DR6	HLA-DR3 HLA-DR15 (Restricted to autoantibody-positive patients)	Inconclusive

DILS is a benign LPD with a good overall prognosis. Since the introduction of highly active antiretroviral treatment (HAART), the prevalence of DILS has significantly decreased, confirming that DILS is indeed an HIV-driven immune response.[12] First-line treatment is HAART, but steroids may be required in symptomatic patients.[11]

5.EBV-ASSOCIATED LYMPHOPROLIFERATIVE DISORDERS IN IMMUNOSUPPRESSED PATIENTS

EBV affects 90% of the population and has a predilection for B-cells.[13-15] The virus has been identified as the primary cause of infectious mononucleosis (IM), which is typically self-limiting among immunocompetent patients.[16] In most cases, B-cell LPDs are EBV-positive and show a spectrum of lesions, including hyperplasias, polymorphic LPDs, aggressive lymphomas, and, rarely, indolent lymphomas.[2,13-14] Uncommonly, EBV can infect T- or NK-cells to cause a unique group of LPDs.[8] In rare instances, EBV can also cause chronic active Epstein-Barr virus (CAEBV) infection.[3,16-17] The disease typically affects immunocompetent children and for the purpose of this review is not discussed further.

5.1. B-cell hyperplasias

Immunosuppression-associated B-cell hyperplasias have a nonspecific morphologic appearance, requiring the presence of EBV for their association with immune suppression to be recognised.[2,6] EBV-positive B-cell hyperplasias have been reported in PTLDs, iatrogenic LPDs, HIV-infection and other rare causes of immunosuppression.[2] B-cell hyperplasias frequently involve lymph nodes, tonsils and adenoids.[6] Most causes of immunosuppression-associated B-cell hyperplasias regress

spontaneously with reduction of immunosuppression. Large obstructive tonsillar masses are often treated via surgical excision with subsequent histopathological evaluation **(Figure 3B)**.[2]

Three subtypes of nondestructive hyperplasias (previously termed early lesions) have been recognised in the WHO 2016 classification: (1) follicular hyperplasia (FH), (2) infectious mononucleosis hyperplasia (IMH) and (3) plasmacytic hyperplasia (PH).[3,6] These nondestructive lesions are classified under post-transplant LPDs in the WHO framework. Criteria for the distinction of these non-destructive PTLDs from other reactive lymphoid infiltrates are not well defined and rest on the extent of proliferation, clinical context, and the presence of EBV.[3]

5.1.1. Follicular hyperplasia

Follicular hyperplasia is an increase in the number and usually the size/shape of secondary lymphoid follicles.[8] In immunosuppressed patients, hypertrophy of adenoids and tonsils has long been recognised. This is usually accompanied by histologic findings of FH, usually presenting as florid follicular hyperplasia.[6] In most instances, the histological features of FH affecting the adenotonsillar region in immunosuppressed and immunocompetent patients cannot be reliably distinguished without the presence of EBV.[6,8] Therefore, a high clinical suspicion is necessary to consider testing for EBV-encoded small RNAs (EBER) in the appropriate clinical context.[3]

5.1.2. Infectious mononucleosis hyperplasia

Infectious mononucleosis hyperplasia is usually diagnosed in biopsies of lymph nodes or tonsils. The histological features are similar to those of infectious

mononucleosis in the normal host, with paracortical expansion by immunoblast-rich infiltrates with a mixed background of small lymphocytes and plasma cells.[3,6,8] Like other hyperplasias, IMH typically forms mass lesions with partial preservation of the lymphoid architecture.[6] The histological features are generally more specific than those of FH or PH, due to the prominent immunoblastic component. This allows for the diagnosis of IMH even in the absence of EBV. Differential diagnostic considerations include other reactive and neoplastic conditions with increased immunoblasts such as infectious mononucleosis and polymorphic B-cell LPDs including mucocutaneous ulcer (discussed later) and EBV-positive CHL.[6]

5.1.3. Plasmacytic hyperplasia

Plasmacytic hyperplasia is characterised by numerous plasma cells expanding the medullary cords and extending into the interfollicular regions.[1,3,6] The plasma cells and their nuclei vary in size, with some showing prominent nucleoli.[1] As in FH and IMH, most cases of PH involve the tonsils and adenoids of younger patients.[3,6] PH is rarely associated with concurrent or subsequent polymorphic LPDs or lymphomas. Similar to FH, the histological features are nonspecific, and the presence of EBV is required for a diagnosis.[6,8]

5.2. EBV-positive mucocutaneous ulcer

EBV-positive mucocutaneous ulcer (EBVMCU) is an indolent form of EBV-driven B-cell LPD first described in 2010. The condition usually occurs in the background of various forms of immunosuppression including medication-related, PIDs, ageing senescence, and more recently in the setting of HIV/AIDS.[7,13,19-20] Adult females with a median age of 62 years are most frequently affected.[7] The condition

usually presents with isolated, shallow and circumscribed mucosal or cutaneous ulcers **(Figure 4)**.[13-14,19-20] EBVMCU can present with lesions involving the oral cavity, gastrointestinal tract and skin.[3,7,13,19-20] The oropharynx is the most commonly involved site, possibly due to its proximity with the lymphoid-rich tissue of Waldeyer's ring.[7,13,15,19] The lymphotropic properties of EBV result in a concentration of latently infected B-cells at this site.[19] Mucosal trauma and persistent antigenic stimulation initiates the activation of these B-cells resulting in uncontrolled B-cell proliferation.[3,15,19] EBVMCU develops in patients who have a sufficient remaining immune response to control systemic infection, but with enough of a level of immune dysregulation for the development of a self-limiting LPD.[18]

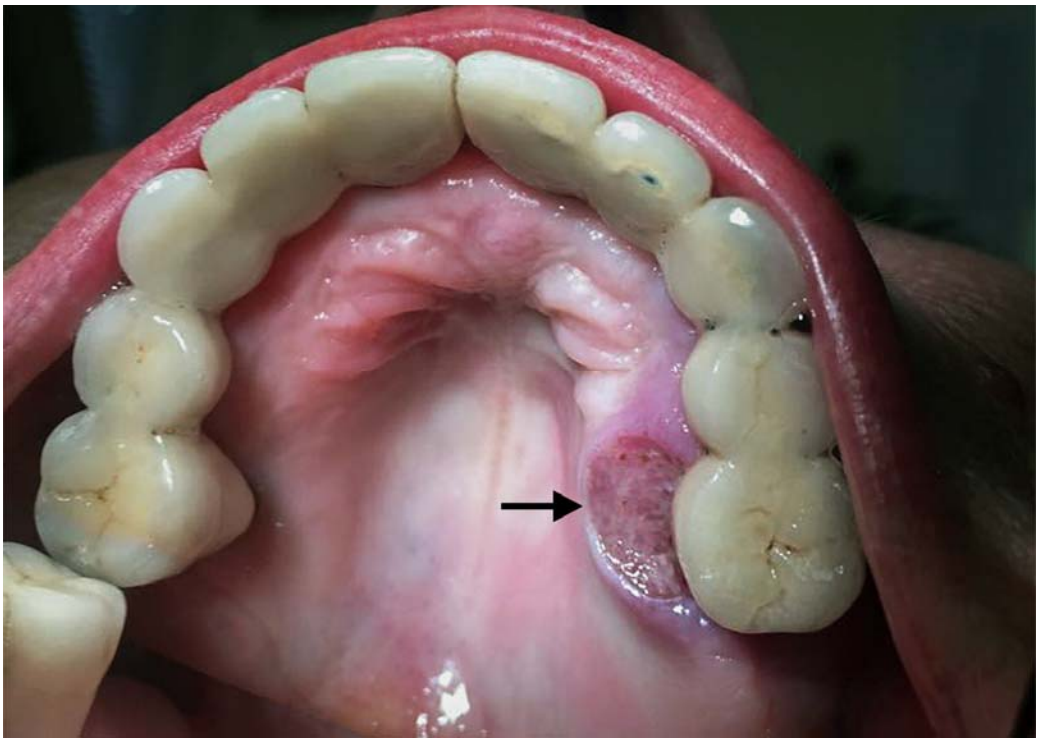

Figure 4. EBVMCU presenting as a shallow, circumscribed ulcer (arrow) of the palatal mucosa

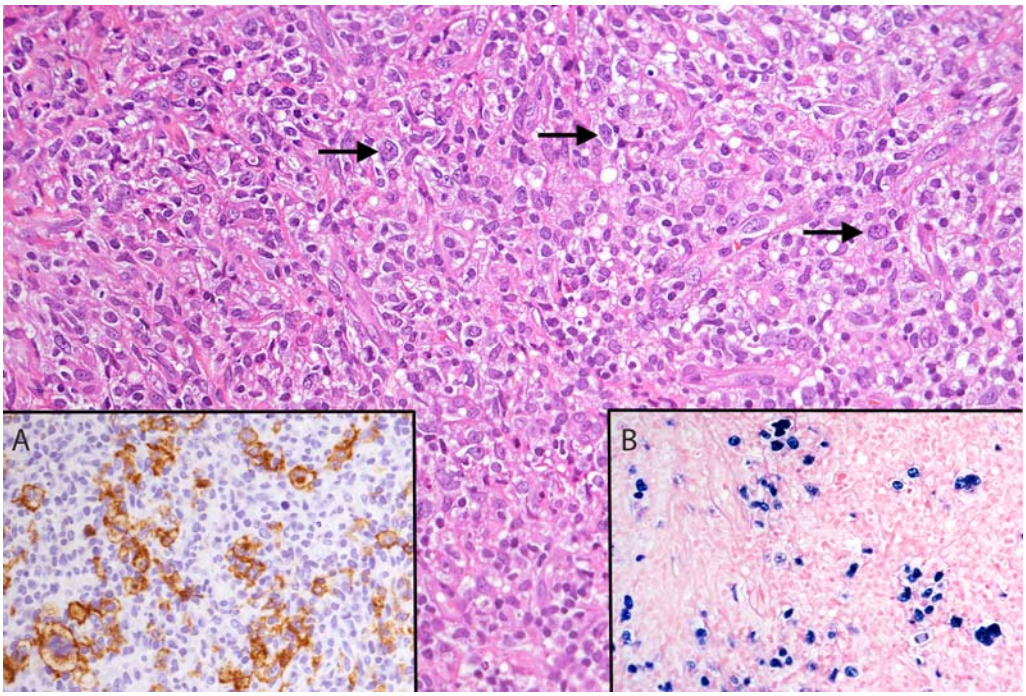

Figure 5. Photomicrograph showing the polymorphous nature of the inflammatory infiltrate with scattered larger cells reminiscent of Reed-Sternberg cells (arrows) (H&E; original magnification × 200). (A) CD30 IHC positivity in the RS-like cells. (original magnification × 200). (B) EBER positivity detected not only in larger immunoblastic cells and the RS-like cells but also in the smaller background lymphocytes (original magnification × 200)

Histologically, EBVMCU usually shows large areas of ulceration, while the adjacent epithelium may show reactive nuclear atypia, often with pseudoepitheliliomatous hyperplasia.[7,13,18-19] The lamina propria contains a dense infiltrate that typically involves the deeper anatomical structures, consisting of small lymphocytes, plasma cells, histiocytes and scattered neutrophils and eosinophils.[3,13,19] Large immunoblastic cells may also be present.[7,13,18-19] Characteristically, there are larger atypical cells scattered throughout resembling Reed-Sternberg cells **(Figure 5)**.[3,7,13,18-19] CD3 and CD20 staining highlights varying degrees of T- and B-cells, proving the polymorphous nature of the infiltrate. Importantly, the larger immunoblastic cells and the RS-like cells are positive for CD45, CD20, PAX5 and

CD30 **(Figure 5A)**. CD15 may be expressed in about half of the cases[3,13,18-19], while CD10 and BCL6 are negative in most cases.[3,7,13] In situ hybridisation for EBER shows abundant staining in the larger immunoblastic cells and the RS-like cells, but also in the smaller lymphocytes **(Figure 5B)**.[7,13,19] There is commonly LMP-1 and EBNA-2 reactivity, consistent with latency patterns II and III respectively.[3,7] Proliferative markers, such as Ki-67, are highly variable.

EBVMCU needs to be distinguished from true neoplastic B-cell proliferations due to differing treatment regimens.[13] These include EBV-associated extranodal Hodgkin lymphoma and EBV-positive diffuse large B-cell lymphoma.[19] Traumatic ulcerative granuloma with stromal eosinophilia (TUGSE), a benign form of chronic oral mucosal ulceration, may also show clinical and histologic resemblance to EBVMCU.[21]

Most cases of EBVMCU have an indolent clinical course with complete recovery or persistent but limited disease.[13,18,20] Current treatment approaches are derived from regimens used in the management of PTLDs (discussed later), and generally include conservative measures.[14-15,20] Reports have suggested favourable outcomes in patients treated by reductions in the dose of immunosuppressant therapy.[13,15,18,20] In age-related cases, most showed spontaneous complete remission.[13] The initiation of HAART in patients with HIV/AIDS appears to be the treatment of choice, allowing for immune function recovery.[19] Patients in which immunosuppression cannot be reversed, have shown responses to rituximab, local radiation and chemotherapy.[3]

6.HHV8-ASSOCIATED LYMPHOPROLIFERATIVE DISORDERS IN IMMUNOSUPPRESSED PATIENTS

In addition to Kaposi sarcoma, HHV8-infection is also associated with a spectrum of LPDs. These include HHV8-positive multicentric Castleman disease, HHV8-positive DLBCL, NOS, and germinotropic lymphoproliferative disorder (GLPD).[3] Except for GLPD, these disorders typically occur in the setting of immunosuppression, particularly HIV-infection.[2-3] Primary effusion lymphoma (PEL) is also considered an HHV8-associated LPD, but is discussed in a separate chapter of the WHO classification. The characteristic benign LPDs associated with HHV-8 involving the head and neck region are described below. It should however be appreciated that there are unusual cases within the spectrum of HHV8- and HHV8/EBV-associated LPDs with overlapping features that do not fulfil the criteria for established entities.[2-3] LPDs characterised by concurrent HHV8- and EBV-infection are rare, with two entities included in the WHO classification: (1) primary effusion lymphoma and (2) germinotropic LPD.[5]

6.1. Multicentric Castleman Disease

This entity is discussed in a separate original article that is also part of this special issue published by the *Journal of Oral Pathology and Medicine*.

6.2. HHV8- and EBV-associated germinotropic lymphoproliferative disorder

GLPD is a rare HHV8-associated LPD first described in 2002 in a series of three patients with localised lymphadenopathy.[22] The entity was included in the 2016 WHO classification together with multicentric Castleman disease and HHV8-positive DLBCL, NOS.[3,7] An analysis of 18 reported cases revealed an adult male

predilection, usually demonstrating HHV8 and EBV co-infection.[4] The pathogenesis and role of both viruses in the development of the disease are not clear. Most cases occur in immunocompetent patients[3,5,7-8], however, four HIV-positive GLPD cases have been reported in the literature.[7,23] Patients present with nodal involvement, with solitary lymphadenopathy often affecting the head and neck region.[5,7]

Histologically, affected lymph nodes show a preserved architecture.[3,5,7-8,23] The germinal centers show partial or complete replacement by clusters of plasmablasts, which can have bizarre nuclear features.[3-5,7-8,23] The lymph node background shows florid follicular hyperplasia with prominent plasmacytosis. These plasmablastic cells show varying expression for plasma cell markers CD38, CD138 and MUM1, but are negative for CD10, CD15, CD45 and BCL6.[3-4,7-8,23] The plasmablastic cells are positive for both HHV8 and EBV (EBER).[3,8] LMP-1 and EBNA-2 are typically negative, consistent with latency patterns I and II.[3] Patients usually respond favourably to chemotherapy or radiotherapy, although there have been reported cases that progressed to high-grade lymphoma.[3,8,23]

7. POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS

Post-transplant lymphoproliferative disorder (PTLD) is defined by the WHO as "a lymphoid proliferation or lymphoma that develops as a consequence of immunosuppression in a recipient of solid organ or bone marrow allograft".[3] The WHO classifies PTLD into four categories: non-destructive hyperplasias/early lesions (discussed earlier), polymorphic PTLD, monomorphic PTLD, and classical Hodgkin's lymphoma-type PTLD.[8] Which of these disorders is truly neoplastic is debatable, however, biopsies taken for a suspected PTLD should be handled using a standard "rule out lymphoma" protocol.[8]

There is strong evidence linking PTLD with EBV-infection, with most cases of PTLD occurring as a result of primary or reactivated EBV-infection in an immunosuppressed patient.[24-27] Patients who are EBV-naïve before transplant and acquire EBV-infection in the post-transplant period are at the highest risk for developing PTLD.[18] The incidence of PTLD varies from 1% to 20%, depending on the type of transplanted organ, age of the patient, pre-transplant EBV-status and type and dose of immunosuppression agent.[24-26,28]

PTLD is three to four times more common in children than adult patients.[28] Children are usually EBV-naïve before transplantation and have their primary infection under immunosuppressive therapy.[29] Most cases of PTLD have been described in the gastrointestinal tract, with head and neck manifestations occurring in 25% to 39% of post-transplant patients.[24,28] In the head and neck region, PTLD often presents as adenotonsillar hyperplasia, tonsillitis or cervical lymphadenopathy.[25,27-28] Only 29 cases of PTLD affecting the oral cavity have been described in the literature, with presentations including crater-like defects, gingival hyperplasia, oral ulceration and exophytic tumours.[28,30] EBV-positive mucocutaneous ulcers (discussed earlier) commonly present in the oral cavity, representing a unique B-cell PTLD.

Plasma EBV DNA quantification is crucial in monitoring post-transplant patients for PTLD development. EBV viral load combined with imaging can be sensitive and specific; however, tissue histopathology is the gold standard for diagnosing PTLD.[25]

The immediate management following PTLD suspicion is a reduction in immunosuppression to attempt a balance between immunosuppression and immunosurveillance.[25,27,29] CD20-positive PTLDs beyond early lesions can be treated with rituximab, with the combination of chemotherapy and rituximab reserved for

non-responders.[25-26] Early PTLD is associated with a good prognosis, but more aggressive forms and late-onset disease tend to have a poorer prognosis.[25]

8.OTHER IATROGENIC IMMUNOSUPPRESSION-ASSOCIATED LYMPHOPROLIFERATIVE DISORDERS

Iatrogenic immunosuppression-associated LPDs are lymphoid proliferations that arise in patients treated with immunosuppressant drugs for autoimmune disorders or conditions other than the post-transplant setting.[1,3,7] They range from polymorphic proliferations to cases that fulfill the criteria for lymphoma.[3] Most occur in patients treated with immunosuppressive drugs for rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, psoriasis and other autoimmune disorders. These LPDs were first described in patients treated with methotrexate, but cases have since been reported in those treated with tumour necrosis factor-alpha (TNF-α) antagonists.[1,3,7] The frequency of EBV-infection in these iatrogenic LPDs is variable.[3,8] Most cases occur in an extranodal location, including the gastrointestinal tract, skin, liver, lung, kidney, spleen, CNS, bone marrow, gingiva and soft tissue.[3,8] A significant proportion of patients with iatrogenic LPDs, particularly those related to methotrexate, have shown at least a partial regression following drug withdrawal. Cases not responding to drug withdrawal and relapsing cases may require chemotherapy.[1,3,8]

9. Conclusion

Lymphoproliferative disorders occur at a higher frequency in the background of various forms of immunosuppression and range from benign lymphoid proliferations to full-blown lymphomas. Lymphotropic viruses such as EBV and

HHV8 play an important role in the pathogenesis of distinct LPDs in immunosuppressed patients. This review discussed benign LPDs in the immunosuppressed patient, with an emphasis on entities commonly affecting the head and neck region. The diagnosis of a benign LPD in the setting of immunosuppression requires a high clinical suspicion and strict clinicopathological correlation to avoid overdiagnosis and overtreatment.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest, and all authors have read and approved the final draft.

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