Published in final edited form as:

Semin Diagn Pathol. 2017 January ; 34(1): 60–75. doi:10.1053/j.semdp.2016.11.003.

Cutaneous EBV-related lymphoproliferative disorders

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Abstract

This article will focus on the cutaneous lymphoproliferative disorders associated with EBV, with an emphasis on the upcoming changes in the revised 4th Edition of the WHO classification of tumors of the hematopoietic system, many of which deal with cutaneous disorders derived from NK-cells or T-cells. Extranodal NK/T-cell lymphoma usually presents in the upper aerodigestive tract, but can involve the skin secondarily. EBV-associated T- and NK-cell lymphoproliferative disorders (LPD) in the pediatric age group include the systemic diseases, chronic active EBV infection (CAEBV) and systemic EBV+ T-cell lymphoma of childhood. Hydroa vacciniforme (HV)-like LPD is a primarily cutaneous form of CAEBV and encompasses the lesions previously referred to as HV and HV-like lymphoma (HVLL). All the T/NK-cell-EBV-associated diseases occur with higher frequency in Asians, and indigenous populations from Central and South America and Mexico. Among the B-cell EBV-associated LPD two major changes have been introduced in the WHO. The previously designated EBV-positive diffuse large B-cell lymphoma (EBVDLBCL) of the elderly, has been changed to EBV-DLBCL with ‘not otherwise specified’ as a modifier (NOS). A new addition to the WHO system is the more recently identified EBV+ mucocutaneous ulcer, which involves skin and mucosal-associated sites.

Keywords

Extranodal NK/T-cell lymphoma; EBV+ mucocutaneous ulcer; Hydroa vacciniforme; Chronic active EBV infection

Introduction

The Epstein Barr Virus (EBV) is a ubiquitous lymphotropic herpesvirus that infects >90% of the world population,¹ efficiently transforms human B-cells in vitro, and is highly associated with a variety of B-cell lymphomas.² EBV also plays an important role in other malignancies worldwide, such as nasopharyngeal carcinoma (NPC)³, gastric cancer (GC)⁴ and mature T-cell and NK-cell lymphomas (MTNKL)⁵. The global burden of EBV-attributable cancer deaths is substantial, with ~200,000 new cases of EBV-associated malignancies and ~143,000 cancer deaths annually^{6,7}. These observations have led the National Institute of Health (NIH) to identify EBV as an important vaccine target for cancer

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prevention, with a high public health and economic impact¹. The establishment of collaborative networks to discover predictive markers and immune correlates in EBV-related malignancies was identified as a high priority¹.

EBV is a highly adaptable tumor virus that can transform different cell types through constitutive activation of NF- κ B, inhibition of apoptosis, activation of *MYC*, *BCL2*, and *NOTCH1*, and induction of extensive DNA methylation and genomic instability in the host cell⁸. These effects are mediated by 12–15 EBV latent proteins that function as transcriptional coactivators (EBNAs), signaling molecules (LMP-1, 2A), and epigenetic modifiers (EBNAs, LMP-1), affecting thousands of transcriptional programs and pathways in the host cell⁹. Furthermore, the immediate early (IE) gene BZLF1, which activates EBV's lytic cycle, directly promotes lymphomagenesis¹⁰. The expression of BZLF1's activator XBP1 is associated with poor outcomes in B-cell lymphoma^{11,12}. Finally, EBV promotes tumor evasion in the microenvironment by increasing IL-10 and inducing the expression of PD-L1 on infected cells¹³.

The classification of the various lymphoproliferative disorders is based on the lineage of the target cells, i.e., T, B, and NK-cells (Table 1). This article will focus on the cutaneous lymphoproliferative disorders associated with EBV, with an emphasis on the upcoming changes in the revised 4th Edition of the WHO classification of tumors of the hematopoietic system¹⁴, many of which deal with cutaneous disorders derived from NK-cells or T-cells. Extranodal NK/T-cell lymphoma usually presents in the upper aerodigestive tract, but can involve the skin secondarily. EBV-associated T- and NK-cell lymphoproliferative disorders (LPD) in the pediatric age group include the systemic diseases, chronic active EBV infection (CAEBV) and systemic EBV+ T-cell lymphoma of childhood. Hydroa vacciniforme (HV)-like LPD is a primarily cutaneous form of CAEBV and encompasses the lesions previously referred to as HV and HV-like lymphoma (HVLL). All of the T/NK-cell-EBV-associated diseases occur with higher frequency in Asians, and indigenous populations from Central and South America and Mexico.

Among the B-cell EBV-associated LPD two major changes have been introduced in the WHO¹⁴. The previously designated EBV-positive diffuse large B-cell lymphoma (EBV-DLBCL) of the elderly, has been changed to EBV-DLBCL with 'not otherwise specified' as a modifier (NOS). This reflects the fact that some cases can occur in younger individuals¹⁵. A new addition to the WHO system is the more recently identified EBV+ mucocutaneous ulcer, which involves skin and mucosal-associated sites¹⁶. This condition is closely associated with immune deficiency and defective immune surveillance for EBV. Other entities with cutaneous manifestations in the B-cell group include lymphomatoid granulomatosis, which can show direct skin involvement or manifest as a 'paraneoplastic' lymphohistiocytic panniculitis. Other EBV-driven LPD that can involve the skin include plasmablastic lymphoma, which can present as a form of post-transplant LPD and in the setting of HIV.

While some examples of systemic peripheral T-cell lymphoma have frequent skin involvement, such as angioimmunoblastic T-cell lymphoma and peripheral T-cell lymphoma

NOS, those entities will not be discussed here as EBV, when present, is nearly always confined to B-cells, as an epiphenomenon of reactivation.

Extranodal NK/T-cell lymphoma, nasal type (ENKTL)

Extranodal NK/T-cell lymphoma, nasal type, is a mature form of T/NK-cell lymphoma with extranodal (frequently upper aero-digestive) infiltration by EBV-infected cytotoxic lymphocytes with associated angioinvasion and angioneclerosis¹⁷. As the name implies, some cases appear to arise from EBV-infected T-cells, while most are of NK-cell derivation. In the United States, ENKTL is very rare, accounting for fewer than 1% of non-Hodgkin's lymphoma (NHL). The disease is much more prevalent in areas of Mexico, South and Central America, and Asia where it represents nearly 6% of all NHL, and in certain particular areas, up to 22–44% of all NHL^{18,19}. It is the most common type of nasal lymphoma in Asia and central America^{20,21}.

ENKTL shows an invariably strong association with EBV infection, irrespective of the patient's origin, which supports a direct pathogenic role of the virus in lymphomagenesis. The EBV is present in a clonal episomal form. It commonly shows a 30 base pair deletion in the gene encoding LMP-1²², and likely unrelated to the deletion, LMP-1 is often not expressed. Most studies show that EBV is typically subtype A in Asia and subtype B in Western countries^{23,24}.

Clinically the disease presents in extranodal sites, mostly in the upper aerodigestive tract, including the nasal cavity (by far the most frequent site), orbital soft tissue, paranasal sinuses, and palate (Fig. 1). Some cases can also present in an extranasal location, although lymph node involvement is uncommon. Most patients present with signs of local tumor infiltration. Ulceration, perforation of the nasal septum (in the past, many of these cases were called midline lethal granuloma²⁵), and symptoms of mass lesion (epistaxis) are frequently seen¹⁷. B-symptoms, such as fever, weight loss, malaise and night sweats occur in a significant proportion of patients. ENKTL can also be associated with hemophagocytosis and those patients have a worse prognosis²⁶. Dissemination to the skin, gastrointestinal tract, testis or cervical lymph nodes can also be present, while bone marrow involvement is relatively uncommon (10–16% of cases). Skin involvement is present in 10% of cases of ENKTL and manifests as nodules that ulcerate and often have a necrotic center, erythematous maculopapular lesions, cellulitis, and abscess-like swelling. Skin lesions are typically found on the legs and trunk).

Historically, the prognosis is generally poor, although initial response to therapy is variable. Some patients respond to therapy and can achieve complete remission whereas others die of disseminated disease despite aggressive therapy. The survival rate is 30–40%^{27,28} but in recent years it has improved with more intensive therapy including upfront radiotherapy and the SMILE regimen²⁹. Unfavorable prognostic factors include advanced stage (III or IV), bone marrow (BM) or skin involvement, and high levels of EBV DNA in the serum^{27,30}. Cases with extranasal presentations have a more aggressive clinical behavior, compared to the nasal ones³¹, and those with primary skin disease (and without systemic dissemination) appear to have a better prognosis^{27,28,30}.

Higher EBV viral load correlates with a worse outcome and disease activity^{32,33}.

Histological features of ENKTL are similar irrespective of the site of involvement and characteristically include an angiocentric and angiodestructive growth pattern with coagulative necrosis, admixed apoptotic bodies, and fibrinoid change in blood vessels, even in the absence of angioinvasion^{34,35} (Figs. 2–4). In cutaneous or mucosal sites, pseudoepitheliomatous changes can be seen. The tumor cells can exhibit a marked range in cell size. The nuclei can be round or folded, have coarse or vesicular chromatin, and small inconspicuous nucleoli. Mitotic figures are frequently seen, in addition to apoptosis and karyorrhectic debris. Cytoplasmic granules are seen in some cases. Areas of geographic necrosis can also be present. Background inflammatory cells are variable, and may include plasma cells, histiocytes, and neutrophils. In the skin, focal epidermotropism can sometimes be seen, more typically with ‘tagging’ of cells along the dermal-epidermal junction, but in the absence of pagetoid upward migration or the formation of Pautrier microabscesses. A perivascular, periadnexal and interstitial character of the infiltrate is present, with or without extension into the adipose tissue. When the adipose tissue is affected, necrosis and rimming of the adipocytes by the malignant cells is noted, which can mimic the findings present in primary cutaneous gamma-delta T-cell lymphoma and subcutaneous panniculitis-like T-cell lymphoma. Permeation of the tumor cells into the skeletal muscle fibers with associated myonecrosis can also be observed^{17,36}. The importance of cytologic grading of ENKTL is a matter of debate^{26,37–39}. The International Peripheral T-cell Lymphoma Project revealed that the presence of more than 40% of transformed large cells was associated with a worse prognosis in the nasal cases, but not in the extranasal sites⁴⁰. Others have not been able to reproduce these findings²⁸. Similar to the presence of large cells, a high proliferation index, as measured by Ki67 (>60–70% or >50%) can be predictive of a worse prognosis^{31,41–43}.

ENKTL can be of T or NK-cell origin^{44–47}. ENKTL nearly always has a cytotoxic phenotype, with expression of cytotoxic granules (granzyme B, TIA-1, and perforin). Most cases are derived from NK cells, are CD56-positive, and are negative for surface CD3 expression yet positive for cytoplasmic CD3 subunits including CD3ε and CD3ζ. As such, ENKTL will be positive for CD3 when using polyclonal anti-CD3 antibodies in immunohistochemistry (IHC). However, irrespective of cell lineage, most cases are positive for CD2, CD43, CD45RO, HLA-DR, CD25, CD7 and FAS (CD95) and negative for CD4, CD5, CD8, TCRγ, βF1, CD16, and CD57^{22,48}. *In-situ* hybridization studies for EBV-encoded RNA (EBER) are routinely used in clinical practice to confirm EBV infection, as LMP-1 is typically negative. Rare cases can exhibit expression of CD4, CD8, TCRδ, βF1, as well as CD20. CD30 is positive in 20–40% of cases, particularly in cases with a rich large cell component. The Ki67 proliferation index is typically very high (>50%), even in the presence of small cell-predominant tumors. All cases of ENKTL are invariably EBV-positive. Caution is advised in reviewing cases with extensive necrosis, as EBV mRNA *in-situ* hybridization (EBER) requires intact RNA (Fig. 5). The PD-1/PD-L1 axis is upregulated in virally induced lymphomas (as a mechanism for the virus to evade the immune system), and overexpression of such markers is noted in cases of ENKTL^{49–51}.

The T-cell receptor (TCR) and immunoglobulin heavy chain (IGH) genes are in germline configuration in ENKTL derived from NK cells. Clonal rearrangements of the TCR genes

are detected in 10–40% of cases, indicative of a cytotoxic T-cell origin in some cases^{52,53}. It is estimated that approximately 85% of nasal ENKTL are of NK-cell origin, while only 50% of the extranasal ones are derived from NK cells. In addition to TCR gene rearrangement studies, the addition of immunohistochemistry for BF1 and TCR γ can be used to distinguish neoplasms of NK or T-cell origin. Recent studies have demonstrated activation of the JAK-STAT signaling pathway in ENKTL¹⁷. Activating mutations of *JAK3* are present in 21–35% of cases^{54–57}. Irrespective of the mutation, phosphorylation of JAK3 is present in up to 87% of cases. STAT3 phosphorylation (activation) is noted in 90% of cases^{58–60}, while its mutation is only seen in 3% of cases^{56,57}. Underexpression of PTPRK, located in the 6q21 region, due to deletion (50%) or promoter hypermethylation, can lead to overactivation of STAT3⁶¹. Other mutations that have been found in ENKTL include *TP53* (20–60%)^{62–64}, *PRDM1*^{58,65–67}, *FOXO3*⁶⁶, *RAS/KRAS/HRAS* (<5%)^{63,68}, *ATG5*⁶⁵, *FAS* (50–60%)^{69,70}, *KIT* (5–71% in China vs 22% Japan)^{63,71}, *CTNMB1* (16–30%)^{63,68}, and perforin (12.5%)⁷². Promoter hypermethylation is extraordinary common across viral-induced malignancies, and also for ENKTL. Some of the genes that can be affected include *BCL2*, *DAPK1*, *PTPN6*, *TET2*, *SOCS6*, *ASNS*, *PRDM*, *AIM*, *HACE1*, *MLH1*, *RARB*, *ATG5*, *TP73*, *CDKN2A/2B/1A*, etc^{73–75}. An extraordinary degree of genomic instability is also proven by the frequent aberrations seen by cytogenetics in ENKTL. In addition to the 6q21 deletion, 1q21-q44 gains (50%), 2q13-q14 (25–30%), 2q31-q32 (20–42%), 6p25-p11 (25–40%), 7q11-q34 (20–50%), 7q35-q36 (40–60%), 17q21 (20–50%), and 20q11 gains are noted (30–50%). 11q23 (13–30%), 11q24-q25 (20–30%), 13q14 (15–60%), 17p13 (20–40%) losses are also seen^{58,65,76–79}.

The differential diagnosis of ENKTL in the skin includes other aggressive types of cutaneous lymphoma. Primary cutaneous $\gamma\delta$ T-cell lymphoma (PCGDL) is also often CD56 +, and usually lacks expression of CD5, CD4 and CD8. As opposed to ENKTL, epidermotropism is more frequently found, and the lesions show strong expression of TCR γ . Rare cases can be also double positive for β F1, and some cases of PCGDL can be TCR silent. EBER is only rarely expressed (<5% of cases)⁸⁰. Mycosis fungoides can rarely be CD56+^{81,82}, and, as opposed to ENKTL, shows more prominent epidermotropism and frequent formation of Pautrier micro-abscesses. Most cases of MF are positive for β F1, and more typically CD4 positive. Other entities included in the differential diagnosis are other EBV-associated T-cell or NK-cell lymphoproliferative disorders such as EBV+ peripheral T cell lymphoma, not otherwise specified (PTCL, NOS), chronic active EBV + infection, systemic EBV T-cell lymphoproliferative disease of childhood, and hydroavacciniforme-like lymphoproliferative disorder, which also occurs predominantly in children. Aggressive NK-cell leukemia can also be included in the differential diagnosis, and shares similar immunophenotypic features to ENKTL. However, skin involvement is relatively uncommon in the disease, allowing in the clinical distinction.

The distinction of PTCL, NOS from ENKL is typically based on the EBV status, following the recommendations of the WHO classification. ENKL are invariably EBV +, while PTCL, NOS in the setting of CD56 expression is EBV-. However, a recent study reported 7 cases of EBV-negative aggressive NK-cell leukemia, 3 of which had cutaneous involvement at presentation⁸³. The EBV-negative cases had an aggressive clinical course, similar to that of EBV-positive aggressive NK-cell leukemia. A recent study has shown no significant

differences in survival when comparing primary cutaneous ENKTL vs CD56+ PC PTCL⁸⁴. Blastic plasmacytoid dendritic cell neoplasms (BPDCN) also are CD56 +. Morphologically BPDCNs are composed of medium sized cells, with fine nuclear chromatin, and blastic appearance. These lesions typically lack the angiotropism and angiodestruction present in ENKTL. Immunophenotypically, they are positive for CD123, BDCA2, TCL-1, CD4, and show variable TdT expression, while negative for CD3 and EBV. All those markers are negative in ENKTL. Lymphomatoid granulomatosis (LyG), when it involves the skin, is usually in the form of a paraneoplastic lymphohistiocytic panniculitis⁸⁵. However, larger lesions may contain EBV + B-cells with necrosis and vascular damage. LyG involves the lungs and kidneys, The neoplastic cells are EBV + B-cells, but are associated with a rich background of reactive T-cells.

Systemic chronic active EBV infection of T-cell or NK-cell type

This is a rare systemic EBV + polyclonal, oligoclonal or monoclonal T-cell or NK-cell LPD that has a range in severity. It was originally defined as a severe illness lasting more than 6 months, after primary EBV infection, showing continued high titers to EBV and evidence of major organ involvement (pneumonia, bone marrow aplasia, uveitis, lymphadenitis, hepatitis, splenomegaly). More recently EBER ISH expression has been used to document EBV in affected tissues⁸⁶. The more recent criteria also allow the diagnosis in the presence of symptoms that last for longer than 3 months, and have high levels of EBV viremia^{14,17,87}. While the affected cells are typically T or NK-cells, rare cases of B-cell derivation can occur⁸⁸.

The disease has a strong racial predilection for individuals of Asian or South American descent, and most notably occurs in children and adolescents^{89–92}. More infrequently, CAEBV can occur in middle age or older adults. Patients typically present with prolonged fevers, hepatosplenomegaly, anemia and thrombocytopenia, lymphadenopathy and cutaneous manifestations. The latter are typically in the form of mosquito bite allergy (33%), rash (26%), and HV-like manifestations. Most patients have high antibody titers (EBV VCA IgG, EBNA), as well as high EBV viremia^{87,88,91–93}.

The cutaneous findings will be discussed with the HV-like and mosquito bite allergy diseases. In other organs, such as lymph nodes, CAEBV shows paracortical hyperplasia, a polymorphous infiltrate, and a rich background of inflammatory cells, that include plasma cells and sometimes granulomas. Some cases can have associated hemophagocytic lymphohistiocytosis (HLH), best demonstrated in bone marrow, lymph node and liver biopsies^{91,94}. Numerous EBV+ cells are seen. When monotonous sheets of EBV+ tumor cells are noted, such cases are best classified as systemic EBV+ T-cell lymphoma of childhood, ENKTL, or aggressive NK-cell leukemia (ANKL).

The prognosis of CAEBV is variable, with some patients experiencing a relatively indolent clinical course, while others succumb to the disease. An adverse prognostic feature is HLH. The median survival is approximately 70–78 months, and adverse markers of clinical outcome include late onset (>8 years of age), thrombocytopenia, and T-cell infection (5-year

survival is 59% for T-cell disease and 87% for NK-cell disease)^{87,88,94}. A positive clonal result can sometimes be associated with a more aggressive clinical course⁹¹.

Severe mosquito bite allergy

This is a cutaneous manifestation of chronic active EBV infection precipitated by mosquito bites or vaccination^{95,96}. Severe mosquito bite allergy (SMBA) is very uncommon, and most cases arise in individuals from Asia and Mexico^{97–105}. This is not an allergic disease, but rather a cutaneous manifestation of CAEBV of NK-cell lineage, with oligoclonal or monoclonal populations of NK-cells¹⁰⁶.

Most patients are <20 years of age, with a median age of 6.7¹⁰⁶. The cutaneous manifestations include erythematous papules, macules and plaques which can subsequently develop into bullae, ulcerate and eventually heal with scarring. Systemic symptoms are also common, and include fever, lymphadenopathy, and liver dysfunction^{107,108}. When patients recover from the systemic symptoms they become disease free until the next mosquito bite. Vaccinations can also sometimes elicit a similar reaction¹⁰⁹. In SMBA patients show high levels of IgE, high EBV viremia and NK-cell lymphocytosis (80%)⁹⁵. Histologically, the skin shows epidermal necrosis and ulcer formation. Marked dermal edema and infiltration by neutrophils and a dense lymphoid infiltrate is noted. Vasculitis is present in the center with karyorrhectic debris, and extravasated red blood cells in the dermis. The lymphoid infiltrate is composed of a mixture of CD4 +, CD8 + T-cells and NK-cells. EBV-positive cells represent a minority of the infiltrate (<10%).

The prognosis is variable: some patients behave in an indolent fashion, with a chronic protracted course of cutaneous manifestations, while others can develop fulminant HLH or progress to frank lymphoma, such as ANKL¹⁰⁹.

Hydroa vacciniforme-like lymphoproliferative disease (HV-LPD)

This is a chronic EBV+ LPD of childhood with risk of progression to systemic lymphoma¹⁷. Classic HV is a rare, intermittent ultraviolet (UV) light-induced vesiculopapular and scarring eruption, that typically remits after adolescence^{110–112}. Systemic symptoms are not usually present in this disease. The estimated prevalence of HV is approximately 0.34 cases/100,000¹¹⁰. In some cases, the lesions can occur in non-sun exposed areas. Later studies have shown the association between HV and clonal proliferations of T-cells, and the term HV-like lymphoma (HVLL) was introduced in the WHO classification in 2008¹¹³. However, because of the inability to predict which patients will behave in an indolent fashion, and which ones will develop overt lymphoma, the term HV-LPD has been proposed and introduced for the upcoming edition of the WHO monograph¹⁴. Other terms that have been used to describe HVLL in the past included edematous scarring vasculitic panniculitis, angiocentric cutaneous T-cell lymphoma of childhood, hydroa-like cutaneous T-cell lymphoma and severe HV. It has been proposed that certain populations (e.g. Asian and south American) can have a particular risk for development of lymphoma, while in others (North American and European) the disease has a very indolent course^{110,114}. Recent clinical studies suggest that HV-LPD can be successfully treated with immunomodulators

(thalidomide¹¹⁵, antivirals¹¹⁶, interferon¹¹⁷, etc) rather than systemic chemotherapy, as the latter has been associated with a higher mortality among these patients¹¹⁸.

Most cases of HV-LPD are seen in children and adolescents from Asia, Native Americans from central and south America (Peru, Guatemala and Bolivia), and Mexico^{111,114,118–125}. In Peruvian studies, approximately 50% of cases come from the southern region, correlating with a higher prevalence of early EBV infection in that area. The median age at diagnosis is 8 years. The male to female ratio is increased (2.3:1), and the disease is rare in adults. Males with HV may have a later onset and longer duration than women. Although the disease presents in children, some patients can have persistent symptoms through adulthood.

Clinically, classical HV is characterized by a sporadic, itchy erythematous eruption in sun-exposed areas that occurs shortly (minutes to hours) after sun exposure. The eruption progresses through different stages: papules, vesicles, crusts, and eventually vacciniform (pox-like) scars after several weeks (Fig. 6). Severe forms of the disease can have conjunctival and corneal ulceration and scarring. Marked facial edema is common in the more aggressive forms, associated with unilateral or bilateral eyelid compromise. Periorbital swelling can be the first manifestation of the disease^{110,111,120}. The lesions can become chronic (lasting months to years) and are prone to recurrence, often characterized by temporal heterogeneity, from papules with crusts to well-formed scars in the same area¹¹⁰. When extracutaneous involvement occurs (hepatosplenomegaly, lymphadenopathy, bone marrow infiltration), those cases are best classified as EBV+ T-cell lymphoma of childhood. Fever, weight loss, and asthenia can be present. Elevations of LDH and liver enzymes are noted in one-third of patients^{118,126,127}.

In HV-LPD the lymphoid infiltrate is composed of small to medium-sized hyperchromatic cells centered in the dermis with a perivascular/periadnexal distribution, and with associated epidermal necrosis (Fig. 7). Spongiosis and intraepidermal vesicles are also seen. In the more aggressive forms of the disease the cells can show more atypia, and somewhat similar morphology to ENKTL. Mitotic figures are infrequent. Epidermotropism without Pautrier microabscesses is a common feature. Fully developed lesions show deep extension into the adipose tissue, but without significant rimming of the adipocytes as seen in SPTCL. Angiotropism with or without angionecrosis and fibrinoid changes can be seen^{114,118,121,123,124}.

The EBV-infected cells can be cytotoxic T-cells (CD3+, CD8+, TIA-1+, granzyme B+, perforin+) or NK-cells (CD56+)^{114,118,121,124}. Few can be CD4+ or CD4-/CD8-^{128–130}. CD30 cases can be occasionally positive. LMP-1 is negative. The number of EBV+ cells is variable. The Ki67 is variable and can be very low, or as high as 50%. Expression of CD5, CD7, CD43, and CD25 is variable. CD57 is negative. The T-cells can be positive for either TCR $\alpha\beta$ or TCR $\gamma\delta$. Clonal rearrangements of the T-cell receptor can be demonstrated. Deletion of the long arm of chromosome 6 has been documented¹³¹.

The differential diagnosis includes other NK/T-cell LPD, such as ANKL and ENKTL. In the latter entities diffuse sheets of atypical CD56+, EBER+ cells are noted. Some cases of ANKL can also show skin involvement³⁶. Subcutaneous panniculitis-like T-cell lymphoma

(SPTCL) can have overlap in the immunophenotype, being composed of CD8+ cells. However, SPTCL is negative for CD56, lacks epidermotropism and EBV expression. PCGDL can also be CD56+, but is more typically negative for EBV, presents in older adults, and the location is more typically truncal and in the extremities.

EBV-positive mucocutaneous ulcer (EBV-MCU)

This entity is defined as a solitary, sharply demarcated ulcerative lesion in the skin, oral cavity, or gastrointestinal tract in patients with age-related or iatrogenic immunosuppression, including solid organ transplantation^{16,132–135}. The atypical cells are EBV+ B-cells with a Hodgkin-like phenotype and morphology. A prominent inflammatory background is usually present. Patients generally lack EBV-DNA in the blood, and have a benign clinical course, sometimes with waxing and waning of the lesion without intervention¹⁶. EBV-MCU can be encountered in patients with immunosuppression from azathioprine, cyclosporine, or methotrexate¹³⁶, and also age-related immunosenescence. Its occurrence after solid and allogeneic bone marrow transplantation also has been documented^{137–139}. EBV-MCU appears to be more common in women, with a mean age of 80.

Clinically, the lesions present as a solitary, sharply demarcated ulcers in the oropharyngeal mucosa (buccal mucosa, tongue, tonsils), and less frequently the large bowel and rectum. Skin lesions can also occur, particularly on the lips, arms and trunk. Isolated regional lymphadenopathy can accompany the ulcers, but always in the absence of systemic findings. Spontaneous resolution occurs in 25% of patients¹⁶.

Histologically, the lesions show shallow, mucosal or cutaneous ulcers with adjacent acanthosis of the epidermis or mucosa, and sometimes pseudoepitheliomatous changes. The underlying infiltrate is composed of a mixture of lymphocytes, large immunoblasts, Hodgkin-like cells, plasma cells, histiocytes and eosinophils. The presence of Hodgkin-like, plasmacytoid apoptotic cells and tissue necrosis is characteristic. A rim of small T-lymphocytes at the base of the lesions is noted. The atypical large immunoblasts and Hodgkin-like cells are PAX-5 + (variable dim or strong), OCT2+, MUM1+, BOB1 +, and CD45 +/-. Reduced or absent CD20 expression is present in 33% of cases. The Hodgkin-like cells are typically positive for CD30, with co-expression of CD15 in a significant subset. The reactive small lymphocytes are CD3 + T-cells (Fig. 8). All cases are EBV +. Clonality studies can show rearrangements of the B and T-cell receptor in 39% and 38% of cases, respectively^{16,135,140,141}.

The differential diagnosis of EBV-MCU includes cutaneous involvement by classical Hodgkin lymphoma (CHL), DLBCL, primary cutaneous anaplastic large cell lymphoma (pcALCL), and LyG. CHL never presents primarily in the skin, with cutaneous involvement occurring in rare cases with bulky disease by direct extension. The original cases described as cutaneous CHL are now believed to be examples of cutaneous anaplastic large cell lymphoma, or EBV-MCU. As opposed to CHL, EBV-MCU is more typically CD45 + and positive for other B-cell markers. EBV-DLBCL is also common in older individuals but typically has a more systemic presentation and aggressive clinical course. Isolated cutaneous disease is rare.

EBV-positive diffuse large B-cell lymphoma (EBV-DLBCL)

Originally termed EBV+ DLBCL of the elderly^{142,143}, the updated revision of the WHO has changed the terminology to EBV- DLBCL, NOS to reflect the fact that some cases occur in younger individuals^{14,15}. Immune senescence is thought to play a role in most cases. The disease is more common in certain areas of Asia and Mexico, but less frequent in the US^{143,144}. EBV-DLBCL has a striking predilection for extranodal sites (70%), and particularly the skin, lung, tonsils, and stomach^{140,141,143,144}. It represents 20–30% of all B-cell lymphomas in individuals above the age of 90.

The cutaneous lesions present as plaques, tumors and nodules that are usually non-ulcerated, and with a predilection for the lower extremities^{142,145}. In lymph nodes and other sites two main patterns were reported, polymorphous and monomorphous. However, more frequently a combination of the two is present. Polymorphous lesions are characterized by a mixture of immunoblasts, plasmablasts, centroblasts and Hodgkin-like cells, with abundant inflammatory cells including histiocytes, plasma cells and eosinophils (Fig. 9). It is likely that previously reported polymorphous cases confined to the skin were most likely examples of mucocutaneous ulcer; notably these were associated with a better prognosis¹⁴⁶. The monomorphous type is characterized by sheets of immunoblasts with fewer inflammatory cells. The lymph nodes can show geographic necrosis, a pattern less frequently noted in the skin¹⁴⁰.

The immunophenotype of the malignant cells includes expression of pan B-cell markers (CD20, CD19, CD79a, PAX-5). Some cases can have loss of CD20. EBV-DLBCL has a non-germinal center phenotype (CD10-, variable BCL-6, MUM1+). CD30 expression is more typical among the cases rich in Hodgkin-like cells. EBER ISH is invariably positive (Fig. 10)¹⁴⁰.

The differential diagnosis is between DLBCL-LT, and other systemic DLBCL with frequent cutaneous dissemination (particularly plasmablastic lymphoma). As opposed to DLBCL-LT, EBV-DLBCL shows invariable expression of EBER. Plasmablastic lymphoma can certainly be a diagnostic challenge, particularly because most cases are EBV+. However, PBL is more commonly diagnosed in patients with HIV, and is nearly always negative for the common B-cell markers (PAX-5, CD19, CD20).

The prognosis of EBV-DLBCL is very poor with a median survival of approximately 2 years. The difficulties in treatment relate to the aggressive character of the process, in addition to the consequences of systemic chemotherapeutic agents in individuals of older age with frequent comorbid conditions^{140,141,143,144}.

Plasmablastic lymphoma (PBL)

Plasmablastic lymphoma typically presents in the oral cavity of patients with HIV, and other types of immune-suppression (transplant, age related immune-senescence)^{147–151}. It can also present in children¹⁵². The cutaneous lesions are usually nodules and tumors in the trunk or extremities, and can potentially mimic DLBCL-LT; fewer than 30 cases have been reported to date^{150,153–155}.

The histologic features of PBL include the presence of sheets of blastoid cells with sometimes a vague ‘starry-sky’ pattern. The plasmablasts are medium to large cells, with moderate to abundant cytoplasm, eccentric nuclei and usually prominent, often central, nucleoli. Some cases can have a more mature appearance, hence the term ‘plasmacytic’ PBL. Multinucleated malignant plasma cells, and bizarre-appearing lymphoma cells can also be noted^{148,150,153–155}. The malignant cells typically lack the common B-cell antigens, while expressing the plasma cell markers CD38, CD138 and CD79a. CD30 and EMA are frequently expressed (Fig. 11). Variable expression of CD10 and CD56 is noted, the latter making the distinction between plasmablastic myeloma with skin involvement and PBL difficult. The proliferation index as measured by Ki67 is high, and usually in the Burkitt lymphoma range (>95%). HHV-8 is characteristically negative, which can help in the distinction from primary effusion lymphoma (PEL) and large cell lymphomas arising in the setting of Castleman disease. Rearrangement or amplification of the MYC gene occurs in 45–50% of cases^{156,157}, a finding accompanied by overexpression of the MYC protein by IHC.

As previously stated, the distinction between PBL and EBV-DLBCL can sometimes be a challenging one^{158,159}. Nonetheless, most cases of EBV-DLBCL are positive for CD20, while PBL lacks B-cell markers. The presence of CD56, CD10 and MYC rearrangements are in favor of PBL. Plasmablastic myeloma can disseminate to the skin, usually in the presence of heavy systemic involvement (>2 kg of disease)¹⁶⁰, and is not typically associated with EBV expression^{161,162}. PEL can rarely present in the skin, and is invariably associated with HIV, very poor clinical control of the disease (very low CD4 counts, marked HIV viremia) and HHV-8 expression^{163–165}. Most cases of PEL are EBV+. High-grade CD10+ B-cell lymphomas can rarely involve the skin (in the setting of systemic disease), and show double or triple hit gene rearrangements (*MYC* and *IGH-BCL-2* and/or *BCL-6* translocations)¹⁶⁶. All such cases are EBV-negative, in addition to lacking plasma cell markers.

Lymphomatoid granulomatosis (LyG)

Lymphomatoid granulomatosis is a rare angiocentric and angiodestructive EBV+ LPD with a predilection for the lungs, kidneys, central nervous system (CNS), and sometimes the skin^{167–169}. LyG typically presents in the 4th to 6th decade of life, and has a slight male predominance¹⁷⁰. Rarely LyG can present in children. Unlike other cutaneous LPD, most patients have no clear underlying immunodeficiency. LyG is linked to EBV infection, and more typically a latency type III (similar to PTLDs).

The most frequent manifestations of LyG include multiple, bilateral lung infiltrates or nodules in virtually all cases¹⁶⁷. Skin involvement occurs in 40–50% of cases^{85,171–175}. Other organs that are frequently involved include the kidneys, CNS and GI tract. Lymph nodes, spleen, liver and bone marrow are typically spared¹⁷⁶. LyG can occur in association with constitutional immune-deficiency syndromes such as Wiskott-Aldrich, myeloproliferative neoplasms and in post-transplant settings^{177–180}. In the setting of immune deficiency the differential diagnosis with other EBV+ B-LPD is challenging¹⁶⁹. B-

symptoms are present in 80% of patients. The cutaneous lesions can precede, coincide or follow the pulmonary lesions.

Skin involvement in LyG occurs in the form of dermal or sub-cutaneous nodules⁸⁵. One-third of cases show ulceration¹⁸¹. More uncommon clinical presentations include plaque-like and lichen sclerosus-like lesions (15% and 10% of cases, respectively)⁸⁵. Some cases of LyG have been reported in association with azathioprine, imatinib and methotrexate (the latter could be included under the realm of MTX-LPD)^{182–185}. The clinical course is variable, with some cases showing spontaneous self-resolution, while others progressing to DLBCL^{186,187}. Historically the survival rate was poor, an average of 2 years following the initial diagnosis, with most patients dying as a consequence of pulmonary insufficiency¹⁶⁷. The introduction of newer therapies has improved the outcome¹⁸⁸.

Histologically, cutaneous lesions of LyG differ from the pattern of involvement seen in other organs⁸⁵. In the skin, LyG shows a lymphoid or lymphohistiocytic infiltrate with or without multinucleated giant cells. Such infiltrates show a perivascular and angiocentric distribution. A lymphohistiocytic panniculitis is characteristic with poorly formed granulomas. Such lesions usually lack EBV + cells, of if present they are very few in number. A separate subset of cutaneous LyG mirrors the histologic findings present in other organs, and is characterized by an angiotropic and angiodestructive process with fibrinoid necrosis and transformed EBV + CD20 + immunoblasts that surround the vessels (Fig. 12). The background reactive T-cells are typically CD8+ cells, with expression of cytotoxic markers. Within the large cells, CD30 is positive in 50% of cases, and CD15 is characteristically negative^{85,169,175}.

The original grading scheme in cases of LyG was proposed by Lipford et al.¹⁸⁹, and was based on the number EBV+ B-cells. In most cases the EBER+ cells show a range in cell size. Grade 1 lesions have a polymorphous infiltrate with absent to rare large lymphocytes, and typically fewer than 5 EBER + cells per high power field (hpf). Grade 2 lesions contain 5–20 but invariably less than 50 EBER+ large cells/hpf. In Grade 3 the EBER cells are + greater than 50/hpf¹⁶⁷, although a T-cell rich background is still present. Sheet like growth of large EBV-positive B-cells with a paucity of T-cells favors EBV + DLBCL over LYG.

EBV is uncommonly present in cutaneous lesions. In the series from Beaty et al.⁸⁵ of cutaneous LyG only 37% of cases were EBV +, and none of the plaque lesions contain EBER + cells. Multiple cutaneous lesions in the same patient can have a different number of EBV+ cells. Since plaque and necrotic lesions do not show EBV + cells, biopsies taken from non-ulcerated papules or nodules are preferred. The pathobiology of the cutaneous lesions appears not be directly related to EBV, and therefore, grading of LyG in the skin is not encouraged^{85,169,190,191}.

LYG grade 1 has a low content of EBV-positive cells, and represents defective control of EBV, but is not neoplastic. On the other hand, grade 3 lesions are considered 'lymphoma', and require more aggressive therapy. However, grade 1 lesions can progress to grade 2 or grade 3, and grade 1 lesions can coexist with those of higher grade^{191–193}. Clonality assays are typically positive in only 25% of cases overall. However, there is a correlation between

clonality by PCR for IG gene rearrangement and grade (8% of grade 1% and 69% of grade 3 lesions are monoclonal)¹⁶⁹.

Some important factors that pathologists should consider when diagnosing LyG are: (1) is there a transplant history?; (2) is there morphology of DLBCL?; (3) when the histologic features of cutaneous LyG are seen, is there coexistent lung disease? If the answer to (1) is yes, then a diagnosis of PTLT is likely; if the answer to (2) is yes, the preferred diagnosis may be DLBCL; if the answer to (3) is no, then a diagnosis of LyG should be put into question very strongly! Only on very rare occasions has cutaneous LyG has been reported in the absence of pulmonary disease^{194,195}.

The differential diagnosis of LyG is broad and includes both neoplastic and non-neoplastic conditions. Granulomatosis with polyangiitis (Wegener granulomatosis, GPA) most typically involves the lung and skin¹⁹⁶. While both disorders can be associated with granulomatous inflammation and necrosis, GPA has a rich background of inflammatory cells that include neutrophils, plasma cells and eosinophils. The large immunoblasts present in LyG are not seen in GPA. Additionally, the most common cutaneous manifestation of GPA is leukocytoclastic vasculitis¹⁹⁷. GPA lacks the presence of EBV+ cells. EBV-MCU can also show angioinvasion and necrosis, but in contrast to LyG shows shallow ulcers with central necrosis. Hodgkin-like cells can be present in both entities. Involvement of mucosal sites appears to be less frequent in LyG^{16,137,198}, as opposed to EBV-MCU. EBV-DLBCL can potentially mimic grade 3 lesions of LyG. However, solid sheets of immunoblasts are noted, and the angiotropism appears to be a more secondary finding, rather than the primary pattern present in the biopsy, with a paucity of background T-cells. Geographic necrosis can also be present in EBV-DLBCL. Lesions of polymorphic PTLT are relatively T-cell depleted, lack angiotropism, and are accompanied by EBV viremia^{199–201}. Other LPD can also be associated with angiotropism and angiodestructions, particularly PCGDL and ENKTL. Such lymphoma subtypes show a different lineage of infection.

Cutaneous post-transplant lymphoproliferative disorders (PTLT)

Cutaneous forms of PTLT can occur in solid organ, and less frequently hematopoietic stem cell transplant patients. PTLT has been reported in 1–16% of solid transplant recipients, and the risk of development correlates very closely with the level and duration of immunosuppression required for the transplanted organ. Additionally, the age and EBV serologic status of the recipient are important risk factors^{202–205}. EBV-naïve patients who acquire a primary EBV infection after the transplant are at the highest risk for developing PTLT^{206,207}. Specific T-cell depleting agents, such as OKT3 and anti-thymocyte globulin are associated with PTLT²⁰⁸. A single center study²⁰⁹ showed that the incidence of PTLT in general was 0.8% for bone marrow transplants, 1.4% for renal, 1.8% for cardiac, 4.5% for lung, but up to 10% for combined cardiac and lung transplant recipients. Since the latter type of transplants are more frequently used in children with congenital anomalies, cutaneous PTLT have been reported with some frequency in childhood^{152,210,211}. The data about the incidence of cutaneous PTLT is sparse and a study from two transplant centers in France reported 7.5 primary cutaneous PTLT/1000 total primary cutaneous lymphomas/year, and 0.7 cutaneous PTLT/1000 solid organ transplants/year²¹².

Approximately 22% of PTLD cases show cutaneous involvement, mostly in the setting of renal transplantation²⁰⁴. Cutaneous B-cell PTLD usually presents as maculo-papular lesions, nodules or tumors, with or without associated ulceration²¹². A wide distribution of the lesions can be noted. Polymorphic PTLD, by definition, is of B-cell origin, while the term monomorphic PTLD is used for diverse forms of lymphoma, either of B-cell or T-cell derivation. Additionally, polymorphic PTLD is virtually always positive for EBV, except in so-called early lesions, whereas monomorphic PTLD can be EBV-positive or negative. An unusual form of cutaneous PTLD is EBV-positive marginal zone lymphoma, which shows some features of polymorphic PTLD²¹³. In addition, as noted earlier, mucocutaneous ulcer can present as PTLD, and has an excellent prognosis^{137,139,214}.

Among the cutaneous forms of monomorphic B-cell PTLD, the vast majority of cases are diagnosed as DLBCL or plasmacytoma, with some cases classified as plasmablastic lymphoma and LyG^{152,204,210,212}. The immunophenotype varies according to the histologic subtype presented. Plasmacytoma-like PTLD show expression of plasma cell markers (CD138, CD38, CD79a), light chain restriction, and frequent EBV expression. DLBCL cases are positive for pan B-cell markers (CD20, CD19, PAX-5, CD79a), have an activated B-cell type phenotype (MUM1+, BCL-6 +/–, CD10–). PBL are negative for the B-cell markers CD20 and CD19, but usually positive for plasma cell markers, in addition to variable expression of CD56, CD10, EMA. They have a very high Ki67 (>90%) and are diffusely EBER positive.

A variety of subtypes of T-cell lymphoma can present as monomorphic PTLD in the skin; these can be EBV-positive or negative, ranging in some series from 16% up to 60%.^{212,215,216–222} Monomorphic T-cell PTLDs mirror the immunophenotypes present in sporadically occurring cases.

Conclusion

Significant progress and changes have been incorporated into the understanding of the biology, classification, diagnosis and management of cutaneous EBV-related lymphoproliferative disorders. Such changes have been incorporated into the revised 4th edition of the WHO classification. The range in clinical behavior of EBV-positive T-cell and B-cell lymphoproliferative disorders is marked, leading to very diverse therapeutic approaches. For these reasons, correct diagnosis is critical for proper patient management.

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Fig. 1. ENKTL clinical presentation. A – A large necrotic mass is noted in the nasal area with associated septal destruction, skin involvement and significant soft tissue swelling. B – A perforation in the hard palate is noted. Courtesy of Dr. Roman Carlos.

Fig. 2.
ENKTL. A – A dense neoplastic infiltrate is noted in the dermis with extension into the subcutaneous tissue (20×). B – A distinctive grenz-zone separates the infiltrate from the surface epidermis (100×).

Fig. 3.

ENKTL. A and B – Sheets of lymphoma cells dissect through the collagen fibers, and in some areas fill the superficial papillary dermis without associated epidermotropism (100× and 200×, respectively). C and D – The lymphoma cells extend around the adnexal glands and into the adipose tissue (400× and 200×). E – The lymphoma cells are medium to large, have abundant granular cytoplasm, hyperchromasia, and have a small nucleoli (600×). F – Angiotropism is noted (200×).

Fig. 4.
ENKTL. A and B – Angiotropism without angioneclerosis (100× and 200×). C – Focal epidermotropism (400×). D – the tumor cells infiltrate skeletal muscle (200×). E – subcutaneous infiltration (200×). F– In this case, the lymphoma cells are intermediate in size (400×).

Fig. 5.
ENKTL – IHC. The lymphoma cells are positive for the polyclonal CD3 antibody, CD56, Granzyme B, TIA-1, and EBER.

Fig. 6.
HV-LPD. A - Classical HV lesions are characterized by vesicles, papules, crusts and facial edema. B – Lesions can be present at different stages in maturation and leave scars upon resolution. Courtesy of Dr. Carlos Barrionuevo (INEN, Peru).

Fig. 7.

HV-LPD. Skin biopsies from a 5-year old white female with hydroa vacciniforme-like LPD.

A. Skin from the right ankle shows a dermal lymphocytic infiltrate with marked spongiosis

and a subepidermal vesicle. B. The lesion from the right forearm contains a necrotic crust.

C. The dermal infiltrate consists of lymphocytes, some of which show cytological atypia

with variation in cell size. D. An EBER in situ hybridization shows many of the

lymphocytes to be positive, including many of the larger atypical forms. E. CD2 is positive,

including some EBER-negative lymphocytes. Clonal TCR rearrangements was positive with a weak clonal peak in a polyclonal background. The patient responded well to steroid therapy.

Fig. 8.

Mucocutaneous ulcer, skin. The lesion presented on the forearm of a 75 year old female who was otherwise well. A. There is a dense infiltrate in the dermis extending to subcutaneous tissue. B. The overlying epidermis is focally necrotic. C. The infiltrate is composed of large pleomorphic cells, some of which have a Reed-Sternberg like appearance. D. The atypical cells are weakly positive for CD20. E. EBER highlights the atypical cells, which tend to be in the superficial parts of the lesion. F. The atypical cells are strongly positive for CD30. They were also positive for CD15 (not shown).

Fig. 9.

EBV-DLBCL. A- A nodular infiltrate in the dermis is noted with areas of geographic necrosis and lack of epidermal involvement (20×). B – The infiltrate only extends superficially to the adipose tissue. C and D – Angiotropism without angionecrosis is noted (100× and 200×). E – The lymphoma cells are large and have an immunoblastic appearance (400×). F- Extensive necrosis is noted (100×).

Fig. 10.
EBV-DLBCL – IHC. The lymphoma cells are positive for CD20, PAX-5 and diffusely EBER positive. Ki67 is very high. CD30 stains a significant subset of the large cells. BCL-6 appears negative.

Fig. 11.

PBL. The lesion presented on the oral cavity of a 45 year-old man with history of HIV. A – The infiltrate expands the submucosa (40×). B – Focal areas of mucosal involvement are noted (400×). C – Necrosis is present (100×). D – The infiltrate has a vague 'starry-sky' appearance. E – The plasmablasts are medium to large cells, with abundant cytoplasm, eccentric nuclei and very large prominent nucleoli. F – CD138 is diffusely positive in the plasmablasts.

Fig. 12.

LyG. Skin lesion in a patient with lymphomatoid granulomatosis. The subcutaneous tissue contains a granulomatous infiltrate. EBER in situ hybridization was negative, and the infiltrate was composed of mainly T-cells and histiocytes.

Table 1

Classification of EBV-related lymphoproliferative disorders.

B-cell lineage

- EBV-positive mucocutaneous ulcer (EBV-MCU)
- EBV-positive diffuse large B-cell lymphoma (EBV-DLBCL)
- Plasmablastic lymphoma
- Lymphomatoid granulomatosis
- Post-transplant lymphoproliferative disorders (PTLD)
- Primary effusion lymphoma
- Burkitt lymphoma (endemic variant)

T/NK-cell lineage

- Extranodal NK/T-cell lymphoma, nasal type (ENKTL)
 - Systemic chronic active EBV infection of T-cell or NK-cell type
 - Severe mosquito bite allergy
 - Hydroa vacciniforme-like lymphoproliferative disorder (HV-LPD)
 - Aggressive NK-cell leukemia
 - Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)
 - Angioimmunoblastic T-cell lymphoma (AITL)
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